PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:
Schoen, Adam M.
BROWN RUDNICK LLP
One Financial Center
Boston, MA 02111
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference NEURE-010/01WO 35242/80	Date of mailing *(day/month/year)* 24 January 2022 (24-01-2022) **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/IB2021/000597	International filing date *(day/month/year)* 31 August 2021 (31-08-2021)
Applicant NEURENT MEDICAL LIMITED	

1. [X] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   How? Directly to the International Bureau preferably through ePCT, or on paper to:
   The International Bureau of WIPO, 34 chemin des Colombettes, 1211 Geneva 20, Switzerland

   For more detailed instructions, see the *PCT Applicant's Guide*, International Phase, paragraphs 9.004 - 9.011.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may **submit comments on an informal basis on the written opinion of the International Searching Authority** to the International Bureau. These comments will be made available to the public after international publication. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established.

   Shortly after the expiration of **18 months from the priority date, the international application will be published** by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for **entry into the national phase** before those designated Offices. In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

   Within **22 months from the priority date, the applicant may request that a supplementary international search be carried out** by a different International Searching Authority that offers this service (Rule 45*bis*.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040 Fax: (+31-70) 340-3016	Authorized officer SULIS, Elisabetta Tel: +49 (0)89 2399-7922

Form PCT/ISA/220 (revised January 2020)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
NEURE-010/01WO 35242/80		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IB2021/000597	31 August 2021 (31-08-2021)	31 August 2020 (31-08-2020)
Applicant		
NEURENT MEDICAL LIMITED		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [X] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title**,
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,
   a. the figure of the **drawings** to be published with the abstract is Figure No. 2
      [ ] as suggested by the applicant
      [X] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2021/000597

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 21-40
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims;; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2021/000597

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61N1/36 A61B18/14 A61N1/05
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61N A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2020/107882 A1 (TOWNLEY DAVID [IE] ET AL) 9 April 2020 (2020-04-09) abstract; figures 2, 14 paragraphs [0002], [0012], [0023], [0030], [0042] - [0046], [0055], [0123] paragraphs [0066] - [0074]; figure 4 -/--	1-4, 18-20, 61, 64-70, 72-74, 76-80

[x] Further documents are listed in the continuation of Box C. [x] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 January 2022	24/01/2022

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Molina Silvestre, A

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2021/000597

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Anonymous: "Flexible electronics - Wikipedia", , 8 August 2020 (2020-08-08), pages 1-9, XP55877832, Retrieved from the Internet: URL:https://en.wikipedia.org/w/index.php?title=Flexible_electronics&oldid=971874913 [retrieved on 2022-01-11] the whole document	1-20, 41-95
A	US 2013/253389 A1 (JUTO JAN-ERIK [SE] ET AL) 26 September 2013 (2013-09-26) the whole document	1-20, 41-95
A	WO 2009/154456 A1 (KERPHOS B V [NL]; DE VOS GERRIT JOHANNIS [NL]) 23 December 2009 (2009-12-23) the whole document	1-20, 41-95

1

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2021/000597

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2020107882 A1	09-04-2020	AU 2016262085 A1	04-01-2018
		AU 2021200322 A1	18-03-2021
		CA 2984207 A1	17-11-2016
		CN 107835705 A	23-03-2018
		EP 3294410 A2	21-03-2018
		HK 1252823 A1	06-06-2019
		JP 6854015 B2	07-04-2021
		JP 2018515314 A	14-06-2018
		JP 2021087861 A	10-06-2021
		US 2016331459 A1	17-11-2016
		US 2019231429 A1	01-08-2019
		US 2019239953 A1	08-08-2019
		US 2019239954 A1	08-08-2019
		US 2019239955 A1	08-08-2019
		US 2019239956 A1	08-08-2019
		US 2019239957 A1	08-08-2019
		US 2020100838 A1	02-04-2020
		US 2020107882 A1	09-04-2020
		WO 2016183337 A2	17-11-2016
US 2013253389 A1	26-09-2013	CN 104220037 A	17-12-2014
		EP 2641580 A1	25-09-2013
		JP 6175486 B2	02-08-2017
		JP 2015512279 A	27-04-2015
		US 2013253389 A1	26-09-2013
		WO 2013139644 A1	26-09-2013
WO 2009154456 A1	23-12-2009	NONE	

Information on Search Strategy - Pilot phase (see OJ 2015, A86)
The type of information contained in this sheet may change during the pilot for improving the usefulness of this new service.

Application Number
PCT/IB2021/000597

TITLE: DEVICE FOR THERAPEUTIC SINO-NASAL TREATMENT

APPLICANT: NEURENT MEDICAL LIMITED

IPC CLASSIFICATION: A61N1/36, A61B18/14, A61N1/05

EXAMINER: Molina Silvestre, A

CONSULTED DATABASES: NPL

CLASSIFICATION SYMBOLS DEFINING EXTENT OF THE SEARCH:

IPC:

CPC: A61N1/LOW, A61N1/36014, A61B18/1485, A61B2018/00327, A61B2018/00577, A61N1/0546

FI/F-TERMS:

KEYWORDS OR OTHER ELEMENTS FEATURING THE INVENTION:
Claims as filed

EPC FORM P04A62

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2021/000597	31.08.2021	31.08.2020

International Patent Classification (IPC) or both national classification and IPC
INV. A61N1/36 A61B18/14 A61N1/05

Applicant
NEURENT MEDICAL LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Molina Silvestre, A Telephone No. +49 89 2399-0

Form PCT/ISA/237 (Cover Sheet) (January 2015)

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:

      ☐ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 21-40

because:

☒ the said international application, or the said claims Nos. 21-40 relate to the following subject matter which does not require an international search *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for the whole application or for said claims Nos. 21-40

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
- ☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☒ See Supplemental Box for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-20, 41-95
	No:	Claims	
Inventive step (IS)	Yes:	Claims	5-17, 41-60, 62, 63, 71, 75, 81-95
	No:	Claims	1-4, 18-20, 61, 64-70, 72-74, 76-80
Industrial applicability (IA)	Yes:	Claims	1-20, 41-95
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

1 Reference is made to the following documents:

D1 US 2020/107882 A1 (TOWNLEY DAVID [IE] ET AL) 9 April 2020 (2020-04-09)

D2 Anonymous: "Flexible electronics - Wikipedia", , 8 August 2020 (2020-08-08), pages 1-9, XP55877832, Retrieved from the Internet: URL:https://en.wikipedia.org/w/index.php?title=Flexible_electronics&oldid=971874913 [retrieved on 2022-01-11]

2 **Re Item III**

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

3 No opinion has been established for claims 21-40 with regard to novelty, inventive step and industrial applicability because the subject-matter of these claims includes methods for treatment of the human or animal body by therapy in the sense of Rule 39.1(iv) PCT. This is because the step of treating a condition within a sino-nasal cavity constitutes such a method.

4 **Re Item V**

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

4.1 The application does not meet the requirements of Article 6 PCT, because claim 81 is not clear.

This is because the following technical feature is unclear:

F81.1: "wherein at least two of the struts are connected by a cross member"

In turn, F81.1 is unclear because the term "cross member" lacks a generally-acknowledged definition and is not defined in the claim.

For the purposes of the present document, claim 81 has been interpreted as if this unclear term had been clarified by stating that the cross member comprises a flexible PCB.

4.2 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 does not involve an inventive step in the sense of Article 33(3) PCT.

D1 is regarded as being the prior art closest to the subject-matter of claim 1, and discloses a device (fig. 14 (1402)) for treating a condition within a sino-nasal cavity of a patient, the device comprising: an end effector (fig. 14 (1412)) including one or more flexible circuit members (fig. 14 (1476)) for delivering energy to one or more target sites within the sino-nasal cavity of the patient (D1, abstract; figures 2, 14; paragraphs [0002], [0012], [0023], [0030], [0042] - [0046], [0055], [0123]).

The subject-matter of claim 1 therefore differs from this known device in that the flexible circuit member is a flexible printed circuit board (PCB) member.

D1 does not disclose in detail how the disclosed flex circuit is implemented. The problem to be solved by the present invention may therefore be regarded as filling this gap in the disclosure of D1.

The solution proposed in claim 1 of the present application cannot be considered to involve an inventive step (Article 33(3) PCT). This is because flexible PCBs are a very well-known and widely-used possibility for implementing flex circuits and is therefore a possibility that the skilled person would consider when filling this gap. This is all the more the case in view of the fact that D1 suggests creating "complex electrode arrays" (paragraph [0123]) and incorporating thermocouples and other circuitry (paragraph [0123]), aspects for which a flex PCB would be particularly well-suited.

4.3 Analogously, the present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 61 does not involve an inventive step in the sense of Article 33(3) PCT.

D1 is regarded as being the prior art closest to the subject-matter of claim 1, and discloses the provision of an end effector (balloon - fig. 14 (1470)) dimensioned to be at least partially deployed inside a sino-nasal cavity of a patient; and the attachment of a flexible circuit member (fig. 14 (1476)) to the end effector, the flexible circuit configured to deliver energy to a target site within the sino-nasal cavity (D1, abstract; figures 2, 14; paragraphs [0002], [0012], [0023], [0030], [0042] - [0046], [0055], [0123]).

The subject-matter of claim 61 therefore differs from this known method in that the flexible circuit member is a flexible printed circuit board (PCB) member.

D1 does not disclose in detail how the disclosed flex circuit is implemented. The problem to be solved by the present invention may therefore be regarded as filling this gap in the disclosure of D1.

The solution proposed in claim 61 of the present application cannot be considered to involve an inventive step (Article 33(3) PCT). This is because flexible PCBs are a very well-known and widely-used possibility for implementing flex circuits and is therefore a possibility that the skilled person would consider when filling this gap. This is all the more the case in view of the fact that D1 suggests creating "complex electrode arrays" (paragraph [0123]) and incorporating thermocouples and other circuitry (paragraph [0123]), aspects for which a flex PCB would be particularly well-suited.

4.4 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 76 does not involve an inventive step in the sense of Article 33(3) PCT.

D1 is regarded as being the prior art closest to the subject-matter of claim 76, and discloses the provision of providing a single piece of metal (each of the individual struts - fig. 4 (440)); and dimensioning the single piece of metal to form an end effector dimensioned for insertion into a sino-nasal cavity of a subject (D1, paragraphs [0066] - [0074]; figure 4)

The subject-matter of claim 76 therefore differs from this known device in that the single piece of metal is dimensioned by cutting.

D1 does not disclose in detail how the pieces of metal are dimensioned. The problem to be solved by the present invention may therefore be regarded as filling this gap in the disclosure of D1.

The solution proposed in claim 76 of the present application cannot be considered to involve an inventive step (Article 33(3) PCT). This is because cutting is a very well-known and widely-used possibility for dimensioning pieces of metal.

4.5 Dependent claims 2-4, 18-20, 64-70, 72-74, 77-80 do not appear to contain any additional features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step, the reasons being as follows:

4.5.1 In respect of each of claims 2, 4, 18, this is because its technical features are also anticipated by the disclosure of D1 (see D1 citations under 4.2 above). The subject-matter of each of these claims therefore differs from the disclosure of D1 in the same way the subject-matter of claim 1 does and hence lacks an inventive step for the same reasons. In respect of claim 4 the disclosed balloon (fig. 14 (1470)) is held to constitute a segment as per the claim.

4.5.2 In respect of claim 3, this is because its subject-matter constitutes an obvious solution to the additional, independent partial problem of filling the gap in the disclosure of D1 with respect to how to couple the disclosed electrodes to the disclosed controller. In turn, this is because D1 already hints at using electrical communication paths on or within the flex circuit (fig. 14) and because using contacts to couple a flex circuit to other system components is a well-known and widely-used design pattern in electronics.

4.5.3 In respect of each of claims 19-20, this is because its subject-matter constitutes an obvious solution to the additional, independent partial problem of providing additional functionality for the device of fig. 14 of D1. In turn, this is because D1 already hints at the possibility of detecting tissue characteristics such as the impedance and at doing so using the same electrodes used for therapy (paragraphs [0044]-[0048], [0105]-[0111]).

4.5.4 In respect of each of claims 64-68, 70, 72, this is because its respective subject-matter constitutes an obvious solution to the problem of filling the gap in the disclosure of D1 with respect to the flex circuit implementation. In turn, this is because thermal and mechanical processes as claimed are well-known possibilities in order to achieve the adhesion disclosed in D1.

4.5.5 In respect of claim 69, this is because its subject-matter constitutes an obvious solution to the problem of filling the gap in the disclosure of D1 with respect to the flex circuit implementation. In turn, this is because single-sheet PCBs are a well-known possibility for implementing flex PCBs.

4.5.6 In respect of claim 73, this is because its technical features are also anticipated by the disclosure of D1 (see D1 citations under 4.3 above). The subject-matter of each of these claims therefore differs from the disclosure of D1 in the same way the subject-matter of claim 61 does and hence lacks an inventive step for the same reasons.

In respect of claim 74, this is because its subject-matter constitutes an obvious solution to the problem of filling the gap in the disclosure of D1 with respect to the implementation of the disclosed adhesion between the flex circuit and the balloon.

4.5.7 In respect of each of claims 77-80, this is because its technical features are also anticipated by the disclosure of D1 (see D1 citations under 4.4 above). The subject-matter of each of these claims therefore differs from the disclosure of D1 in the same way the subject-matter of claim 76 does and hence lacks an inventive step for the same reasons.

4.6 The subject-matter of each of claims 5-17, 41-60, 62, 63, 71, 75, 81-95, is neither anticipated nor rendered obvious by the available prior art. The reasons are as follows:

4.7 D1 is regarded as being the prior art closest to the subject-matter of claim 5, and discloses a device for treating a condition within a sino-nasal cavity of a patient, the device comprising an end effector including a flex circuit member and one expandable segment to which the flex circuit member is operably associated with. The subject-matter of claim 5 therefore differs from this known device in that the end effector comprises a first retractable and expandable segment comprising a plurality of first support structures upon which one or more flexible PCB members are fixedly coupled and is therefore new (Article 33(2) PCT).

The problem to be solved by the present invention may be regarded as providing for an alternative design for the device of D1.

The solution to this problem proposed in claim 5 of the present application is considered as involving an inventive step (Article 33(3) PCT). This is because, while many possibilities are conceivable to this effect, no motivation can be identified in D1 or elsewhere that would lead the skilled person to solving this problem as claimed.

4.8 Similarly, D1 is regarded as being the prior art closest to the subject-matter of claim 41, and discloses a device for treating a condition in a nasal cavity, the device comprising an end effector dimensioned for insertion into a nasal cavity and a flexible circuit member. The subject-matter of claim 41 therefore differs from this known device in that the end effector comprises at least one segment that is a unitary single piece of material comprising a plurality of individual struts the flex circuit member being attached to at least one of the struts and is therefore new (Article 33(2) PCT).

The problem to be solved by the present invention may be regarded as providing for an alternative design for the device of D1.

The solution to this problem proposed in claim 41 of the present application is considered as involving an inventive step (Article 33(3) PCT). This is because, while many possibilities are conceivable to this effect, no motivation can be identified in D1 or elsewhere that would lead the skilled person to solving this problem as claimed.

4.9 An analogous reasoning applies in respect of each of claims 62, 71, 75 and 81 (assuming it can be clarified as per 4.1 above), each of which is therefore also held to meet the requirements of the PCT with respect to novelty and inventive step.

4.10 Claims 6-17 are dependent on claim 5 and as such also meet the requirements of the PCT with respect to novelty and inventive step.

4.11 Claims 42-60 are dependent on claim 41 and as such also meet the requirements of the PCT with respect to novelty and inventive step.

4.12 Claims 63 are dependent on claim 62 and as such also meet the requirements of the PCT with respect to novelty and inventive step.

4.13 Claims 82-92 are dependent on claim 81 and (assuming claim 81 can be clarified as per 4.1 above) as such also meet the requirements of the PCT with respect to novelty and inventive step.

5 **Re Item VII**

Certain defects in the international application

5.1 The features of claims 1-95 are not provided with reference signs placed in parentheses (Rule 6.2(b) PCT).

5.2 Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in D1 is not mentioned in the description, nor are these documents identified therein.

Possible steps after receipt of the international search report (ISR) and written opinion of the International Searching Authority (WO/ISA)

General information

For all international applications, the competent International Searching Authority **(ISA)** will establish an international search report **(ISR)** accompanied by a written opinion of the International Searching Authority **(WO/ISA)**. The **WO/ISA** may be responded to by

- filing informal comments with the **International Bureau of WIPO (IB)** (where no demand for international preliminary examination **(demand)** is filed)
- filing amendments under Art. 19 PCT (this can be done whether or not a **demand** is filed)
- filing amendments under Art. 34 PCT and/or formal observations in response to objections raised in the **WO/ISA** (where a **demand** *is* actually filed)

This document explains these possibilities.

Filing informal comments

After receipt of the **ISR and WO/ISA**, the applicant may file informal comments on the **WO/ISA, directly with the IB** (see International Search and Preliminary Examination Guidelines 2.15). These will be communicated to the designated/elected Offices, together with the International Preliminary Report on Patentability **(IPRP)** at 30 months from the priority date.

Amending claims under Art. 19 PCT

The applicant may file **amended claims** under Art. 19 PCT, **directly with the IB** by the later of the following dates:

- 2 months from the date of mailing of the **ISR** and the **WO/ISA**
- 16 months from the priority date

However, any such amendment received by the **IB** after the expiration of the applicable time limit shall be **considered to have been received on time** by the **IB**, if it reaches it **before** the technical preparations for international publication have been completed (the 15th day prior to the date of publication, see PCT Applicant's Guide, International Phase, 9.013).

For further information, please see Rule 46 PCT as well as form PCT/ISA/220.

Please also note that, when filing amended claims under Art. 19 PCT, such amendments shall be **accompanied by a letter** identifying the amendments made and also the basis for the amendments in the application as originally filed (Rule 46.5(b) PCT). Where a **demand** is filed, failure to comply with this requirement may result in the amendments being ignored in the International Preliminary Examination Report **(IPER)**, see Rule 70.2(c-*bis*) PCT.

BNSDOCID: <XS_____20070401OCK_I_>

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
Schoen, Adam M.
BROWN RUDNICK LLP
One Financial Center
Boston, MA 02111
ETATS-UNIS D'AMERIQUE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

	Date of mailing *(day/month/year)* 2 February 2022 (02-02-2022)
Applicant's or agent's file reference NEURE-017/01WO 35242/92	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/IB2021/000667	International filing date *(day/month/year)* 5 October 2021 (05-10-2021)

Applicant

NEURENT MEDICAL LIMITED

1. [X] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   How? Directly to the International Bureau preferably through ePCT, or on paper to:
   The International Bureau of WIPO, 34 chemin des Colombettes, 1211 Geneva 20, Switzerland

   For more detailed instructions, see the *PCT Applicant's Guide*, International Phase, paragraphs 9.004 - 9.011.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may **submit comments on an informal basis on the written opinion of the International Searching Authority** to the International Bureau. These comments will be made available to the public after international publication. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established.

   Shortly after the expiration of **18 months from the priority date, the international application will be published** by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for **entry into the national phase** before those designated Offices. In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

   Within **22 months from the priority date, the applicant may request that a supplementary international search be carried out** by a different International Searching Authority that offers this service (Rule 45*bis*.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040 Fax: (+31-70) 340-3016	Authorized officer MUSSON, Frédérique Tel: +31 (0)70 340-2490

Form PCT/ISA/220 (revised January 2020)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
NEURE-017/01WO 35242/92		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IB2021/000667	5 October 2021 (05-10-2021)	5 October 2020 (05-10-2020)
Applicant		
NEURENT MEDICAL LIMITED		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [X] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. 1b
      [X] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2021/000667

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-14
because they relate to subject matter not required to be searched by this Authority, namely:
Refer to the search opinion.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims;; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2021/000667

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B18/14 A61B5/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2018/133460 A1 (TOWNLEY DAVID [IE] ET AL) 17 May 2018 (2018-05-17) cited in the application paragraph [0031]; figure 3a paragraph [0036] - paragraph [0038] paragraph [0079] paragraph [0054] - paragraph [0068]; figure 7	15-28
E	WO 2021/260435 A1 (NEURENT MEDICAL LTD [IE]) 30 December 2021 (2021-12-30) page 50, line 10 - page 53, line 9; figure 10 page 15, line 26 - page 19, line 15; figures 1a-2 page 47, line 21 - line 31; figure 9c	15-23, 25-28

-/--

[x] Further documents are listed in the continuation of Box C.

[x] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 January 2022	02/02/2022

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Ekstrand, Vilhelm

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2021/000667

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2021/205231 A1 (NEURENT MEDICAL LTD [IE]) 14 October 2021 (2021-10-14) page 14, line 815 - page 15, line 30; figures 1,2 page 38, line 21 - page 45, line 5; figure 9a page 45, line 6 - page 51, line 16; figure 9b page 51, line 17 - page 54, line 15; figure 9c page 55, line 4 - line 13	15-23, 25-28
A	US 2017/215952 A1 (NAIR ANUJA [US]) 3 August 2017 (2017-08-03) paragraph [0093]; figure 3	21
A	US 2015/112321 A1 (CADOURI HADAR [US]) 23 April 2015 (2015-04-23) paragraph [0008] - paragraph [0009] paragraph [0059] paragraph [0082] - paragraph [0084]	22,24

2

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2021/000667

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2018133460 A1	17-05-2018	AU 2017357869 A1	06-06-2019
		CA 3041440 A1	17-05-2018
		CN 110191674 A	30-08-2019
		EP 3537954 A1	18-09-2019
		JP 2019535386 A	12-12-2019
		US 2018133460 A1	17-05-2018
		US 2020086112 A1	19-03-2020
		US 2020101283 A1	02-04-2020
		US 2020171302 A1	04-06-2020
		WO 2018087601 A1	17-05-2018
WO 2021260435 A1	30-12-2021	NONE	
WO 2021205231 A1	14-10-2021	US 2021315638 A1	14-10-2021
		WO 2021205231 A1	14-10-2021
US 2017215952 A1	03-08-2017	US 2014180273 A1	26-06-2014
		US 2017215952 A1	03-08-2017
US 2015112321 A1	23-04-2015	EP 3060150 A1	31-08-2016
		US 2015112321 A1	23-04-2015
		US 2020030029 A1	30-01-2020
		WO 2015061478 A1	30-04-2015

Information on Search Strategy - Pilot phase (see OJ 2015, A86)
The type of information contained in this sheet may change during the pilot for improving the usefulness of this new service.

Application Number
PCT/IB2021/000667

TITLE: SYSTEMS AND METHODS FOR THERAPEUTIC NASAL TREATMENT

APPLICANT: NEURENT MEDICAL LIMITED

IPC CLASSIFICATION: A61B18/14, A61B5/00

EXAMINER: Ekstrand, Vilhelm

CONSULTED DATABASES: PRESEARCH, TXT, OMBI

CLASSIFICATION SYMBOLS DEFINING EXTENT OF THE SEARCH:

IPC:

CPC: A61B2018/00327, A61B18/12, A61B2018/00577, A61B2018/00267, A61B2018/00434, A61B2018/00702, A61B2018/00761, A61B2034/101, A61B2018/0016, A61B2090/062, A61B2018/00773, A61B2018/00791, A61B2018/00875, A61B2018/1475, A61B2018/00946, A61B5/40, A61B2018/00839, A61B2018/00779, A61B2018/00714, A61B2017/00154, A61B2018/0072

FI/F-TERMS:

KEYWORDS OR OTHER ELEMENTS FEATURING THE INVENTION:
nose, nasal, sinus, cavty, nero-modulation, collateral, energy level, duration, current density.

EPO FORM P04A42

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2021/000667	05.10.2021	05.10.2020

International Patent Classification (IPC) or both national classification and IPC
INV. A61B18/14 A61B5/00

Applicant
NEURENT MEDICAL LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016	see form PCT/ISA/210	Ekstrand, Vilhelm Telephone No. +31 70 340-0

Form PCT/ISA/237 (Cover Sheet) (January 2015)

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:

      ☐ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

   see separate sheet

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 1-14

because:

☒ the said international application, or the said claims Nos. 1-14 relate to the following subject matter which does not require an international search *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for the whole application or for said claims Nos. 1-14

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☒ See Supplemental Box for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	21, 24
	No:	Claims	15-20, 22, 23, 25-28
Inventive step (IS)	Yes:	Claims	
	No:	Claims	15-28
Industrial applicability (IA)	Yes:	Claims	15-28
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Reference is made to the following documents:

D1 US 2018/133460 A1 (TOWNLEY DAVID [IE] ET AL) 17 May 2018 (2018-05-17)cited in the application

D2 WO 2021/260435 A1 (NEURENT MEDICAL LTD [IE]) 30 December 2021 (2021-12-30)

D3 WO 2021/205231 A1 (NEURENT MEDICAL LTD [IE]) 14 October 2021 (2021-10-14)

D4 US 2017/215952 A1 (NAIR ANUJA [US]) 3 August 2017 (2017-08-03)

D5 US 2015/112321 A1 (CADOURI HADAR [US]) 23 April 2015 (2015-04-23)

1 **Re Item II**

The validity of the priority claim cannot be assessed since the search authority does not have the priority document in its possession.

2 **Re Item III**

Claim 1 refer to treating a condition and includes the step of "delivering treatment energy" which in at least some embodiments is performed on the human body. Thus, claims 1-14 refer to methods of treating the human body by therapy and surgery. According to Rule 39.1 (iv) PCT and to Art 43bis.1 PCT as well as Rule 67.1 PCT, neither a search nor an international preliminary examination is required to be carried out on these claims.

3 **Re Item V**

3.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 15 is not new in the sense of Article 33(2) PCT. D1 discloses:

> A system for treating a condition within a sino-nasal cavity of a patient *(paragraph [0031]; figure 3a)*, the system comprising:
>
> a treatment device including an end effector comprising one or more electrodes *(308),(344)*; and

a controller operably associated with the treatment device and configured to control delivery of treatment energy from the one or more electrodes to one or more tissues at one or more target sites within a sino-nasal cavity of the patient at a level and for a period of time sufficient to ablate and/or modulate targeted neural tissue for the treatment of a nasal condition while minimizing or preventing collateral damage to surface tissue at the one or more target sites *(paragraph [0036] - paragraph [0038]: the claim does not specify what parameters are controlled)*

3.2 The dependent claims do not appear to contain any additional features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step, refer to the following passages:

claims 16-20: D1, paragraph [0064] - paragraph [0067]; figure 7: Tissue types and their location are identified from stimulation measurements. It is implicit that the different types of tissues have predefined characterisation data associated with them in order to be able to perform a characterisation. Paragraph [0079] discloses that the selection of the ablation pattern can be done autonomously.

claim 21: D1: automating the development of the characterisation thresholds for the different tissues cannot be considered to be inventive. Refer also to D4, paragraph [0093]; figure 3.

claim 22-24: D1, [68]: The treatment pattern could be a constant power for a predetermined period. It is thus implicit that these parameters are fed back to enable this protocol. Referring to the "predetermined current density threshold", using an impedance threshold instead of the claimed current density to detect treatment completion is considered to be a non-inventive equivalent, especially if the voltage is controlled. Refer also to D5, paragraph [0008] - paragraph [0009]; paragraph [0059]; paragraph [0082]

claims, 24 25: D1, [68]: if temperature, duration or impedance is used to control treatment completion, the act of turning off power can be a digital indicator of efficacy. Moreover, to make a ratio of the target vs current parameter values cannot be considered to be inventive. To measure and control the current density is straight forward when controlling output power and current ([68]).

claims 26-28: D1 the device is suitable for this.

4 **Re Item VI**

Certain documents cited

4.1 D2
Application: WO2021260435 A1

Publication date: 2021-12-30

Filing date: 2021-06-25

Priority date: 2020-06-26 (US202063044904P)

D2 discloses all features of claims 15-23,25-28, refer to the cited passages of the search report.

4.2 D3
Application: WO2021205231A1

Publication date: 2021-10-14

Filing date: 2021-04-08

Priority date: 2020-04-09 (US202063007639P)

D3 discloses all features of claims 15-23,25-28 refer to the cited passages of the search report.

5 **Re Item VII**

5.1 The independent claim(s) is/are not in the two-part form in accordance with Rule 6.3(b) PCT, which in the present case would be appropriate, with those features known in combination from the prior art being placed in the preamble (Rule 6.3(b)(i) PCT) and the remaining features being included in the characterising part (Rule 6.3(b)(ii) PCT).

5.2 The features of the claims are not provided with reference signs placed in parentheses (Rule 6.2(b) PCT).

5.3 Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in prior art is not mentioned in the description, nor are these documents identified therein.

6 **Re Item VIII**

Certain observations on the international application

6.1 The application does not meet the requirements of Articles 5,6 PCT, because claims 15,22,26-28 are not clear.

claim 15

The claims are formulated in terms of a result to be achieved. A treatment effect with low collateral damage can only be achieved if a plan is made and executed or if damage is detected online in both the target and sensitive tissue. These features are considered to be essential to achieve the claimed effect. Moreover, it is not clear how the treatment pattern is used during treatment. Thus, the feed-back loop must be properly described, i.e. what parameters are varied and what parameters are controlled.

claim 22

It is unclear if the "predetermined current density threshold" of the treatment pattern refers to a completion parameter or if a high/low restriction during treatment.

claims 26-28

The claims refer to use of the device or refer to planner features. However, a planner is not claimed per se.

Possible steps after receipt of the international search report (ISR) and written opinion of the International Searching Authority (WO/ISA)

General information

For all international applications, the competent International Searching Authority **(ISA)** will establish an international search report **(ISR)** accompanied by a written opinion of the International Searching Authority **(WO/ISA)**. The **WO/ISA** may be responded to by

- filing informal comments with the **International Bureau of WIPO (IB)** (where no demand for international preliminary examination **(demand)** is filed)
- filing amendments under Art. 19 PCT (this can be done whether or not a **demand** is filed)
- filing amendments under Art. 34 PCT and/or formal observations in response to objections raised in the **WO/ISA** (where a **demand** *is* actually filed)

This document explains these possibilities.

Filing informal comments

After receipt of the **ISR and WO/ISA**, the applicant may file informal comments on the **WO/ISA, directly with the IB** (see International Search and Preliminary Examination Guidelines 2.15). These will be communicated to the designated/elected Offices, together with the International Preliminary Report on Patentability **(IPRP)** at 30 months from the priority date.

Amending claims under Art. 19 PCT

The applicant may file **amended claims** under Art. 19 PCT, **directly with the IB** by the later of the following dates:

- 2 months from the date of mailing of the **ISR** and the **WO/ISA**
- 16 months from the priority date

However, any such amendment received by the **IB** after the expiration of the applicable time limit shall be **considered to have been received on time** by the **IB**, if it reaches it **before** the technical preparations for international publication have been completed (the 15th day prior to the date of publication, see PCT Applicant's Guide, International Phase, 9.013).

For further information, please see Rule 46 PCT as well as form PCT/ISA/220.

Please also note that, when filing amended claims under Art. 19 PCT, such amendments shall be **accompanied by a letter** identifying the amendments made and also the basis for the amendments in the application as originally filed (Rule 46.5(b) PCT). Where a **demand** is filed, failure to comply with this requirement may result in the amendments being ignored in the International Preliminary Examination Report **(IPER)**, see Rule 70.2(c-*bis*) PCT.

BNSDOCID: <XS_____20070401OCK_I_>

Filing a demand for international preliminary examination

In principle, the **WO/ISA** will be considered to be the written opinion of the International Preliminary Examining Authority (**IPEA**). Where the **WO/ISA** issued by the **EPO** as **ISA** gives a positive opinion on the international application and the invention to which it relates, filing a **demand** with the **EPO** as **IPEA** would normally be unnecessary, since a positive IPRP would anyway be established by the IB based on the WO/ISA (see also further below).

If the applicant wishes to file a **demand** (for example, to allow him to argue his case in international preliminary examination with regard to objections raised in a negative **WO/ISA** before the **IPEA** issues an **IPER**), this must be done before expiration of **3 months after the date of mailing of the ISR and WO/ISA** or **22 months after priority date**, whichever expires later (Rule 54*bis* PCT). Amendments under Art. 34 PCT can be filed with the IPEA, normally at the same time as filing the demand (Rule 66.1(b) PCT) or within the time limit set for reply to any written opinion issued during international preliminary examination by the **IPEA**.

If a **demand** is filed at the **EPO** as **IPEA** and no comments/amendments have been received by the time the **EPO** starts drawing up the **IPER** (Rule 66.4*bis* PCT), the **WO/ISA** will be transformed by the **IPEA** into an **IPER** (also called the **IPRP (Chapter II)** which would merely reflect the content of the **WO/ISA** (OJ 10/2011, 532). The **demand** can still be withdrawn (Art. 37 PCT).

Please also note that, when filing amendments under Art. 34 PCT, such amendments shall be accompanied by a letter which identifies the amendments made and also the basis for the amendments in the application as originally filed (Rule 66.8(a) PCT). Failure to comply with this requirement may result in the amendments being ignored in the **IPER (IPRP (Chapter II))**, see Rule 70.2(c-*bis*) PCT.

Filing a request for supplementary international search

The applicant may, with the **IB**, file a request for **supplementary international search** under Rule 45*bis*.1 PCT. The present **ISR** and **WO/ISA** may also be taken into account in the execution of that supplementary international search, provided that these are available to the Authority charged with this task before it starts the supplementary search (Rule 45*bis*.5 PCT).

This kind of request **cannot be filed specifying the ISA** who did the **international search**.

More information on this topic can be found in the **PCT Applicant's Guide**, Chapter 8 (http://www.wipo.int/pct/en/guide/ip08.html).

End of the international phase

Where no **demand** is filed, at the end of the international phase, the **IB** will transform the **WO/ISA** into the IPRP (PCT Chapter I) (Rule 44*bis* PCT), which will then be transmitted together with possible informal comments to the designated Offices. Where a demand is filed, the **WO/ISA** is not transformed into an **IPRP (Chapter I)** by the **IB**, but rather the **IPEA** will establish an **IPER**, (the IPER is the same as the IPRP (PCT Chapter II), see Rule 70.15 PCT).

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
Schoen, Adam M.
BROWN RUDNICK LLP
One Financial Center
Boston, MA 02111
ETATS-UNIS D'AMERIQUE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference NEURE-018/01WO 35242/93	Date of mailing *(day/month/year)* 4 February 2022 (04-02-2022) **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/IB2021/000699	International filing date *(day/month/year)* 5 October 2021 (05-10-2021)
Applicant NEURENT MEDICAL LIMITED	

1. [X] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   How? Directly to the International Bureau preferably through ePCT, or on paper to:
   The International Bureau of WIPO, 34 chemin des Colombettes, 1211 Geneva 20, Switzerland

   For more detailed instructions, see the *PCT Applicant's Guide,* International Phase, paragraphs 9.004 - 9.011.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may **submit comments on an informal basis on the written opinion of the International Searching Authority** to the International Bureau. These comments will be made available to the public after international publication. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established.

   Shortly after the expiration of **18 months from the priority date, the international application will be published** by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for **entry into the national phase** before those designated Offices. In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

   Within **22 months from the priority date, the applicant may request that a supplementary international search be carried out** by a different International Searching Authority that offers this service (Rule 45*bis*.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040 Fax: (+31-70) 340-3016	Authorized officer MUSSON, Frédérique Tel: +31 (0)70 340-2490

Form PCT/ISA/220 (revised January 2020)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
NEURE-018/01WO 35242/93		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IB2021/000699	5 October 2021 (05-10-2021)	6 October 2020 (06-10-2020)
Applicant		
NEURENT MEDICAL LIMITED		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of:

[X] the international application in the language in which it was filed

[ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [X] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**

[X] the text is approved as submitted by the applicant

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant

[ ] the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**

a. the figure of the **drawings** to be published with the abstract is Figure No. 1b

[X] as suggested by the applicant

[ ] as selected by this Authority, because the applicant failed to suggest a figure

[ ] as selected by this Authority, because this figure better characterizes the invention

b. [ ] none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2021/000699

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-20
because they relate to subject matter not required to be searched by this Authority, namely:
Refer to the search opinion.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims;; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2021/000699

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B18/14 A61B5/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2018/133460 A1 (TOWNLEY DAVID [IE] ET AL) 17 May 2018 (2018-05-17) cited in the application	21-33, 36-40
Y	paragraph [0031]; figure 3a paragraph [0036] - paragraph [0038] paragraph [0079] paragraph [0064] - paragraph [0068]; figure 7 paragraph [0048]; figure 3b paragraph [0051]	34,35

E	WO 2021/260435 A1 (NEURENT MEDICAL LTD [IE]) 30 December 2021 (2021-12-30) page 50, line 10 - page 53, line 9; figure 10 page 15, line 26 - page 19, line 15; figures 1a-2 page 47, line 21 - line 31; figure 9c	21-33, 36-40

	-/--	

[x] Further documents are listed in the continuation of Box C. [x] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 January 2022	04/02/2022

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Ekstrand, Vilhelm

3

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2021/205231 A1 (NEURENT MEDICAL LTD [IE]) 14 October 2021 (2021-10-14) page 14, line 815 - page 15, line 30; figures 1,2 page 38, line 21 - page 45, line 5; figure 9a page 45, line 6 - page 51, line 16; figure 9b page 51, line 17 - page 54, line 15; figure 9c page 55, line 4 - line 13	21-33, 36-40
A	US 2017/215952 A1 (NAIR ANUJA [US]) 3 August 2017 (2017-08-03) paragraph [0093]; figure 3	26
Y	US 2016/331459 A1 (TOWNLEY DAVID [IE] ET AL) 17 November 2016 (2016-11-17) cited in the application paragraph [0111]	34,35
A	US 2019/223944 A1 (COATES PAUL [US]) 25 July 2019 (2019-07-25) paragraph [0157] paragraph [0068]	21-40
A	US 2020/289185 A1 (FORSYTH BRUCE R [US] ET AL) 17 September 2020 (2020-09-17) paragraph [0083]	21-40
A	US 2015/112321 A1 (CADOURI HADAR [US]) 23 April 2015 (2015-04-23) paragraph [0008] - paragraph [0009] paragraph [0059] paragraph [0082] - paragraph [0084]	21-40

3

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2021/000699

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2018133460 A1	17-05-2018	AU 2017357869 A1	06-06-2019
		CA 3041440 A1	17-05-2018
		CN 110191674 A	30-08-2019
		EP 3537954 A1	18-09-2019
		JP 2019535386 A	12-12-2019
		US 2018133460 A1	17-05-2018
		US 2020086112 A1	19-03-2020
		US 2020101283 A1	02-04-2020
		US 2020171302 A1	04-06-2020
		WO 2018087601 A1	17-05-2018
WO 2021260435 A1	30-12-2021	NONE	
WO 2021205231 A1	14-10-2021	US 2021315638 A1	14-10-2021
		WO 2021205231 A1	14-10-2021
US 2017215952 A1	03-08-2017	US 2014180273 A1	26-06-2014
		US 2017215952 A1	03-08-2017
US 2016331459 A1	17-11-2016	AU 2016262085 A1	04-01-2018
		AU 2021200322 A1	18-03-2021
		CA 2984207 A1	17-11-2016
		CN 107835705 A	23-03-2018
		EP 3294410 A2	21-03-2018
		HK 1252823 A1	06-06-2019
		JP 6854015 B2	07-04-2021
		JP 2018515314 A	14-06-2018
		JP 2021087861 A	10-06-2021
		US 2016331459 A1	17-11-2016
		US 2019231429 A1	01-08-2019
		US 2019239953 A1	08-08-2019
		US 2019239954 A1	08-08-2019
		US 2019239955 A1	08-08-2019
		US 2019239956 A1	08-08-2019
		US 2019239957 A1	08-08-2019
		US 2020100838 A1	02-04-2020
		US 2020107882 A1	09-04-2020
		WO 2016183337 A2	17-11-2016
US 2019223944 A1	25-07-2019	CN 111867507 A	30-10-2020
		EP 3742996 A1	02-12-2020
		JP 2021516594 A	08-07-2021
		US 2019223944 A1	25-07-2019
		WO 2019147470 A1	01-08-2019
US 2020289185 A1	17-09-2020	CN 113573656 A	29-10-2021
		EP 3937812 A1	19-01-2022
		US 2020289185 A1	17-09-2020
		WO 2020190693 A1	24-09-2020
US 2015112321 A1	23-04-2015	EP 3060150 A1	31-08-2016
		US 2015112321 A1	23-04-2015
		US 2020030029 A1	30-01-2020
		WO 2015061478 A1	30-04-2015

Information on Search Strategy - Pilot phase (see OJ 2015, A86)
The type of information contained in this sheet may change during the pilot for improving the usefulness of this new service.

Application Number
PCT/IB2021/000699

TITLE: SYSTEMS AND METHODS FOR THERAPEUTIC NASAL TREATMENT

APPLICANT: NEURENT MEDICAL LIMITED

IPC CLASSIFICATION: A61B18/14, A61B5/00

EXAMINER: Ekstrand, Vilhelm

CONSULTED DATABASES: PRESEARCH, TXT, OMBI

CLASSIFICATION SYMBOLS DEFINING EXTENT OF THE SEARCH:

IPC:

CPC: A61B2018/00327, A61B18/12, A61B2018/00577, A61B2018/00267, A61B2018/00434, A61B2018/00702, A61B2018/00761, A61B2034/101, A61B2018/0016, A61B2090/062, A61B2018/00773, A61B2018/00791, A61B2018/00875, A61B2018/1475, A61B2018/00946, A61B5/40, A61B2018/00839, A61B2018/00779, A61B2018/00714, A61B2017/00154, A61B2018/0072

FI/F-TERMS:

KEYWORDS OR OTHER ELEMENTS FEATURING THE INVENTION:
nose,nasal, cavity, sinus, ablating, electrode, duration, energy, temperature range, treatment, pattern, profile,pulsed.

EPO FORM P04A62

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2021/000699	05.10.2021	06.10.2020

International Patent Classification (IPC) or both national classification and IPC
INV. A61B18/14 A61B5/00

Applicant
NEURENT MEDICAL LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016	see form PCT/ISA/210	Ekstrand, Vilhelm Telephone No. +31 70 340-0

Form PCT/ISA/237 (Cover Sheet) (January 2015)

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:

      ☐ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

   see separate sheet

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 1-20

because:

☒ the said international application, or the said claims Nos. 1-20 relate to the following subject matter which does not require an international search *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for the whole application or for said claims Nos. 1-20

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
- ☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☒ See Supplemental Box for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	26, 34, 35
	No:	Claims	21-25, 27-33, 36-40
Inventive step (IS)	Yes:	Claims	
	No:	Claims	21-40
Industrial applicability (IA)	Yes:	Claims	21-40
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Reference is made to the following documents:

D1 US 2018/133460 A1 (TOWNLEY DAVID [IE] ET AL) 17 May 2018 (2018-05-17)cited in the application

D2 WO 2021/260435 A1 (NEURENT MEDICAL LTD [IE]) 30 December 2021 (2021-12-30)

D3 WO 2021/205231 A1 (NEURENT MEDICAL LTD [IE]) 14 October 2021 (2021-10-14)

D4 US 2017/215952 A1 (NAIR ANUJA [US]) 3 August 2017 (2017-08-03)

D5 US 2016/331459 A1 (TOWNLEY DAVID [IE] ET AL) 17 November 2016 (2016-11-17)cited in the application

D6 US 2019/223944 A1 (COATES PAUL [US]) 25 July 2019 (2019-07-25)

D7 US 2020/289185 A1 (FORSYTH BRUCE R [US] ET AL) 17 September 2020 (2020-09-17)

1 **Re Item II**

The validity of the priority claim cannot be assessed since the search authority does not have the priority document in its possession.

2 **Re Item III**

Claim 1 refer to treating a condition and includes the step of "delivering treatment energy" which in at least some embodiments is performed on the human body. Thus, claims 1-20 refer to methods of treating the human body by **therapy** and **surgery**. According to Rule 39.1 (iv) PCT and to Art 43bis.1 PCT as well as Rule 67.1 PCT, neither a search nor an international preliminary examination is required to be carried out on these claims.

3 **Re Item V**

3.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 21 is not new in the sense of Article 33(2) PCT. D1 discloses:

A system for treating a condition within a sino-nasal cavity of a patient *(paragraph [0031]; figure 3a)*, the system comprising:

a treatment device including an end effector comprising one or more electrodes *(308),(344)*; and

a controller operably associated with the treatment device and configured to control delivery of treatment energy from the one or more electrodes to tissue at a target site within a sino-nasal cavity of the patient based, at least in part, on a pulsed energy treatment pattern sufficient to maintain a consistent temperature of targeted tissue receiving the treatment energy to thereby cause ablation and/ or modulation of targeted tissue for the treatment of a nasal condition *(paragraph [0036] - paragraph [0038] and [68]:pulsed. The claim does not specify what parameters are controlled. D1 provides a consistent temperature since the treatment always ends at the same temperature in some embodiments).*

3.2 The dependent claims do not appear to contain any additional features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step, refer to the following passages:

claims 22-25: D1, paragraph [0064] - paragraph [0067]; figure 7: Tissue types and their location are identified from stimulation measurements. It is implicit that the different types of tissues have predefined characterisation data associated with them in order to be able to perform a characterisation. Paragraph [0079] discloses that the selection of the ablation pattern can be done autonomously where the treatment parameters are dependent on the position of nerves and tissue type characterisation/nerve mapping.

claim 26: D1: automating the development of the characterisation thresholds for the different tissues cannot be considered to be inventive. Refer also to D4, paragraph [0093]; figure 3.

claim 27-29: D1, [68]: The treatment pattern could be a constant power for a predetermined period or a temperature threshold. It is thus implicit that these parameters are fed back to enable this protocol.

claims 30-32: D1, paragraph [0048]; figure 3b,(352)

claims: 33: D1, [68]: if temperature, duration or impedance is used to control treatment completion, the act of turning off power can be a digital indicator of efficacy. Moreover, to make a ratio of the target vs current parameter values cannot be considered to be inventive.

claims 34-35: D1, [68]: to maintain a temperature is a common alternative regimen to having a temperature threshold for treatment completion. D1 already discloses that different parameters should apply for different tissues and that 60 degree Celsius is a good treatment temperature ([51],[79]). D5, [111] discloses a similar device that maintains a temperature by temperature feed-back using a range. The tolerance will follow implicitly when wanting the specific therapeutic effect of 60 degree Celsius as taught in D1. The division is unsure if the claimed tolerance gives any surprising effects when compared to for example a tolerance of half a degree Celsius. Refer also to D6, paragraph [0157] and paragraph [0068] and D7, paragraph [0083].

claim 36: D1, [68]: last sentence

claims 37,38,39.40: D1 the device is suitable for this.

4 **Re Item VI**

Certain documents cited

4.1 D2
Application: WO2021260435 A1

Publication date: 2021-12-30

Filing date: 2021-06-25

Priority date: 2020-06-26 (US202063044904P)

D2 discloses all features of claims 21-33, 36-40, refer to the cited passages of the search report.

4.2 D3
Application: WO2021205231A1

Publication date: 2021-10-14

Filing date: 2021-04-08

Priority date: 2020-04-09 (US202063007639P)

D3 discloses all features of claims 21-33, 36-40 refer to the cited passages of the search report.

5 **Re Item VII**

5.1 The independent claim(s) is/are not in the two-part form in accordance with Rule 6.3(b) PCT, which in the present case would be appropriate, with those features known in combination from the prior art being placed in the preamble (Rule 6.3(b)(i) PCT) and the remaining features being included in the characterising part (Rule 6.3(b)(ii) PCT).

5.2 The features of the claims are not provided with reference signs placed in parentheses (Rule 6.2(b) PCT).

5.3 Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in prior art is not mentioned in the description, nor are these documents identified therein.

6 **Re Item VIII**

Certain observations on the international application

6.1 The application does not meet the requirements of Articles 5,6 PCT, because claims 21,36,37,38,40 are not clear.

claim 21

The claim is formulated in terms of a result to be achieved. A treatment effect can only be achieved if a plan is made and executed or if damage is detected online in the target tissue. These features are considered to be essential to achieve the claimed effect. Moreover, it is not clear how the treatment pattern is used during treatment. Thus, the feed-back loop must be properly described, i.e. what parameters are varied and what parameters are controlled.

claims 34,35

It seems that claim 35 cannot be dependent on claim 34 since this range is not completely within the first range.

claim 36

Refer to claim 1.

claims 37,38,40

The claims refer to use of the device or refer to planner features. However, a planner is not claimed per se.

Possible steps after receipt of the international search report (ISR) and written opinion of the International Searching Authority (WO/ISA)

General information

For all international applications, the competent International Searching Authority **(ISA)** will establish an international search report **(ISR)** accompanied by a written opinion of the International Searching Authority **(WO/ISA)**. The **WO/ISA** may be responded to by

- filing informal comments with the **International Bureau of WIPO (IB)** (where no demand for international preliminary examination **(demand)** is filed)
- filing amendments under Art. 19 PCT (this can be done whether or not a **demand** is filed)
- filing amendments under Art. 34 PCT and/or formal observations in response to objections raised in the **WO/ISA** (where a **demand** *is* actually filed)

This document explains these possibilities.

Filing informal comments

After receipt of the **ISR and WO/ISA**, the applicant may file informal comments on the **WO/ISA, directly with the IB** (see International Search and Preliminary Examination Guidelines 2.15). These will be communicated to the designated/elected Offices, together with the International Preliminary Report on Patentability **(IPRP)** at 30 months from the priority date.

Amending claims under Art. 19 PCT

The applicant may file **amended claims** under Art. 19 PCT, **directly with the IB** by the later of the following dates:

- 2 months from the date of mailing of the **ISR** and the **WO/ISA**
- 16 months from the priority date

However, any such amendment received by the **IB** after the expiration of the applicable time limit shall be **considered to have been received on time** by the **IB**, if it reaches it **before** the technical preparations for international publication have been completed (the 15th day prior to the date of publication, see PCT Applicant's Guide, International Phase, 9.013).

For further information, please see Rule 46 PCT as well as form PCT/ISA/220.

Please also note that, when filing amended claims under Art. 19 PCT, such amendments shall be **accompanied by a letter** identifying the amendments made and also the basis for the amendments in the application as originally filed (Rule 46.5(b) PCT). Where a **demand** is filed, failure to comply with this requirement may result in the amendments being ignored in the International Preliminary Examination Report **(IPER)**, see Rule 70.2(c-*bis*) PCT.

Filing a demand for international preliminary examination

In principle, the **WO/ISA** will be considered to be the written opinion of the International Preliminary Examining Authority (**IPEA**). Where the **WO/ISA** issued by the **EPO** as **ISA** gives a positive opinion on the international application and the invention to which it relates, filing a **demand** with the **EPO** as **IPEA** would normally be unnecessary, since a positive IPRP would anyway be established by the IB based on the WO/ISA (see also further below).

If the applicant wishes to file a **demand** (for example, to allow him to argue his case in international preliminary examination with regard to objections raised in a negative **WO/ISA** before the **IPEA** issues an **IPER**), this must be done before expiration of **3 months after the date of mailing of the ISR and WO/ISA** or **22 months after priority date,** whichever expires later (Rule 54*bis* PCT). Amendments under Art. 34 PCT can be filed with the IPEA, normally at the same time as filing the demand (Rule 66.1(b) PCT) or within the time limit set for reply to any written opinion issued during international preliminary examination by the **IPEA**.

If a **demand** is filed at the **EPO** as **IPEA** and no comments/amendments have been received by the time the **EPO** starts drawing up the **IPER** (Rule 66.4*bis* PCT), the **WO/ISA** will be transformed by the **IPEA** into an **IPER** (also called the **IPRP (Chapter II)** which would merely reflect the content of the **WO/ISA** (OJ 10/2011, 532). The **demand** can still be withdrawn (Art. 37 PCT).

Please also note that, when filing amendments under Art. 34 PCT, such amendments shall be accompanied by a letter which identifies the amendments made and also the basis for the amendments in the application as originally filed (Rule 66.8(a) PCT). Failure to comply with this requirement may result in the amendments being ignored in the **IPER (IPRP (Chapter II))**, see Rule 70.2(c-*bis*) PCT.

Filing a request for supplementary international search

The applicant may, with the **IB**, file a request for **supplementary international search** under Rule 45*bis*.1 PCT. The present **ISR** and **WO/ISA** may also be taken into account in the execution of that supplementary international search, provided that these are available to the Authority charged with this task before it starts the supplementary search (Rule 45*bis*.5 PCT).

This kind of request **cannot be filed specifying the ISA** who did the **international search**.

More information on this topic can be found in the **PCT Applicant's Guide**, Chapter 8 (http://www.wipo.int/pct/en/guide/ip08.html).

End of the international phase

Where no **demand** is filed, at the end of the international phase, the **IB** will transform the **WO/ISA** into the IPRP (PCT Chapter I) (Rule 44*bis* PCT), which will then be transmitted together with possible informal comments to the designated Offices. Where a demand is filed, the **WO/ISA** is not transformed into an **IPRP (Chapter I)** by the **IB**, but rather the **IPEA** will establish an **IPER**, (the IPER is the same as the IPRP (PCT Chapter II), see Rule 70.15 PCT).

BNSDOCID: <XS_____20070401OCK_I_>

US 20180133460A1

(19) **United States**

(12) **Patent Application Publication**

Townley et al.

(10) **Pub. No.: US 2018/0133460 A1**

(43) **Pub. Date: May 17, 2018**

(54) **DEVICES, SYSTEMS, AND METHODS FOR SPECIALIZING, MONITORING, AND/OR EVALUATING THERAPEUTIC NASAL NEUROMODULATION**

(71) Applicant: **National University of Ireland, Galway**, Galway (IE)

(72) Inventors: **David Townley**, County Clare (IE); **Brian Shields**, Galway (IE); **Ivan Keogh**, Galway (IE); **Peter Dockery**, Galway (IE); **Ian Stephen O'Brien**, Galway (IE); **Martin O'Halloran**, Galway (IE); **Emily Elizabeth Porter**, Galway (IE); **Marggie Jones**, Galway (IE)

(21) Appl. No.: **15/811,449**

(22) Filed: **Nov. 13, 2017**

Related U.S. Application Data

(60) Provisional application No. 62/421,135, filed on Nov. 11, 2016.

Publication Classification

(51) **Int. Cl.**

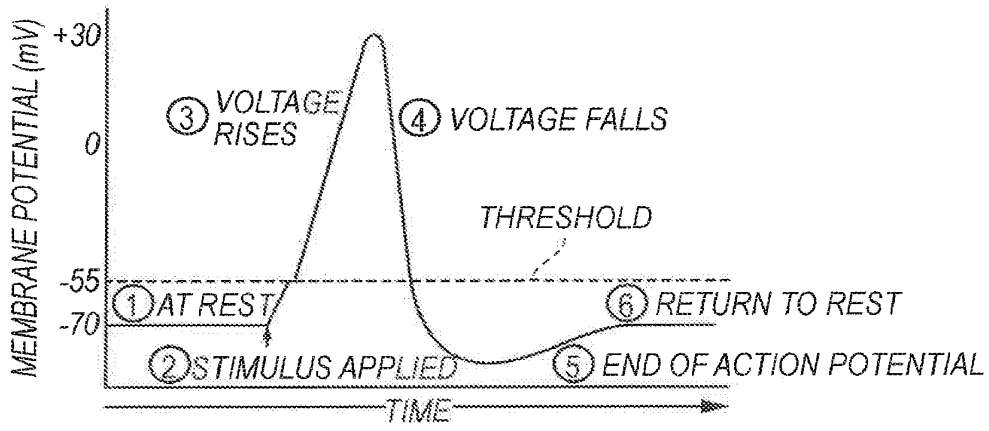
A61N 1/05	(2006.01)
A61N 1/36	(2006.01)

(52) **U.S. Cl.**

CPC *A61N 1/0546* (2013.01); *A61N 1/36075* (2013.01); *A61B 18/1492* (2013.01); *A61N 1/3603* (2017.08); *A61N 1/36021* (2013.01); *A61N 1/36135* (2013.01)

(57) **ABSTRACT**

Devices, systems, and methods for specializing, monitoring, and/or evaluating therapeutic nasal neuromodulation are disclosed herein. A targeted neuromodulation system configured in accordance with embodiments of the present technology can include, for example, an evaluation/modulation assembly at a distal portion of a shaft and including a plurality of electrodes. The electrodes are configured to emit stimulating energy at frequencies for identifying and locating target neural structures and detect the resultant bioelectric properties of the tissue. The system can also include a console that maps locations of the target neural structures. The evaluation/modulation assembly can then apply therapeutic neuromodulation energy in a highly tailored neuromodulation pattern based on the mapped locations of the target neural structures. Accordingly, the system provides therapeutic neuromodulation to highly specific target structures while avoiding non-target structures to reduce collateral effects.



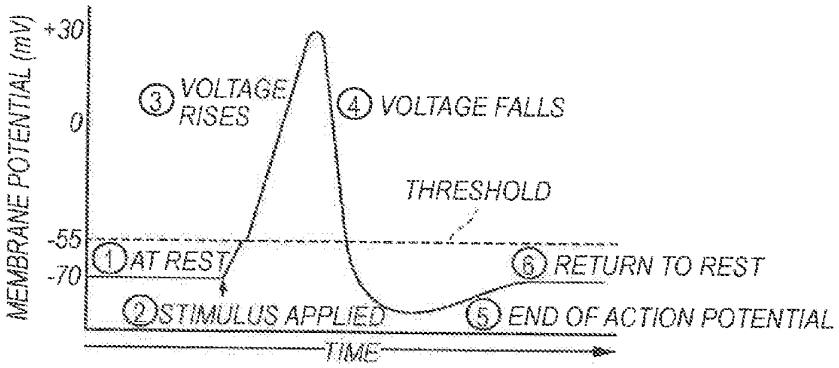


Fig. 1

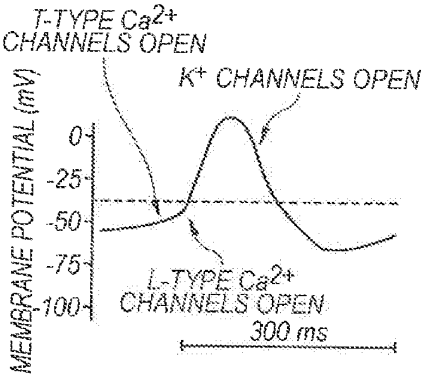


Fig. 2A

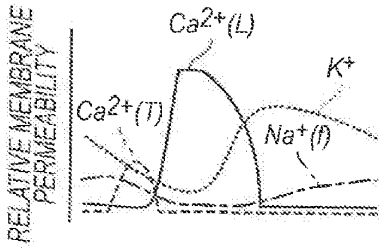


Fig. 2B

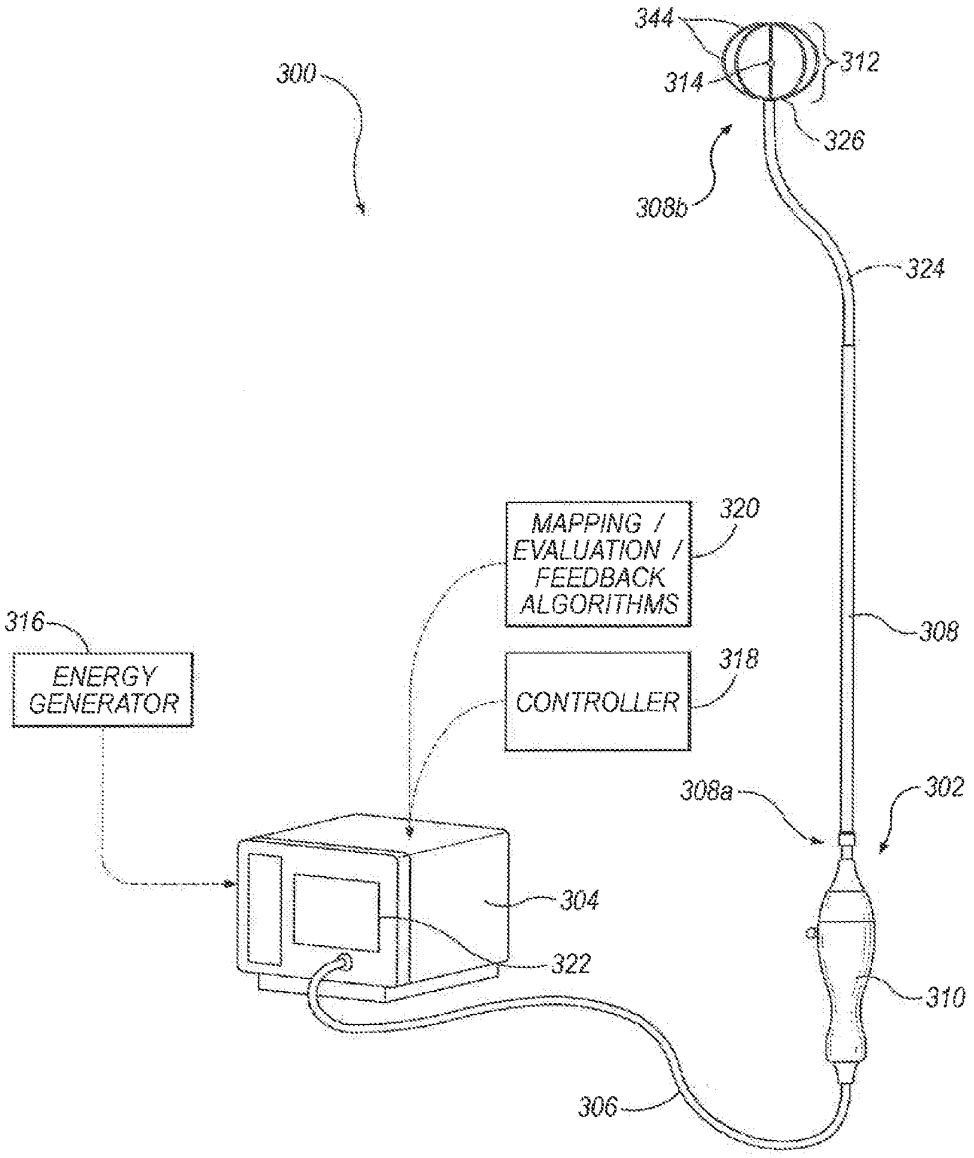


Fig. 3A

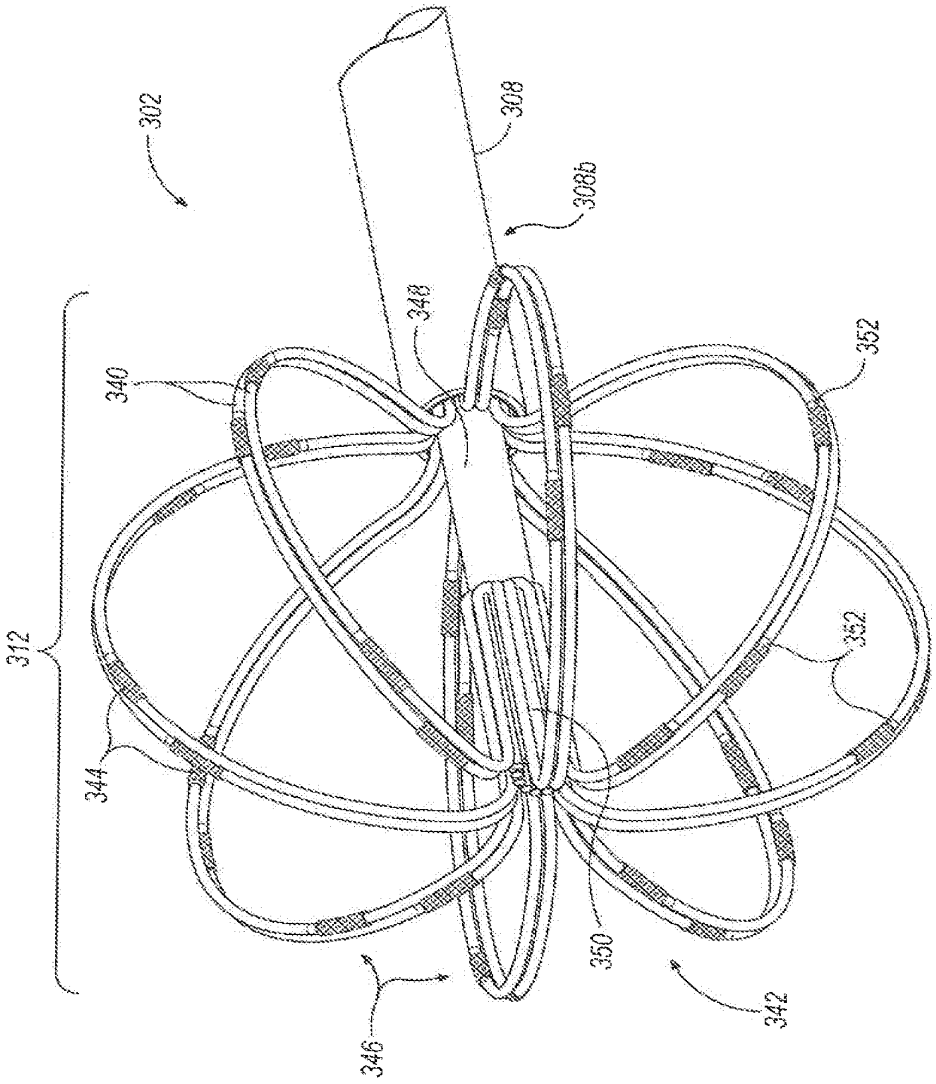


Fig. 3B

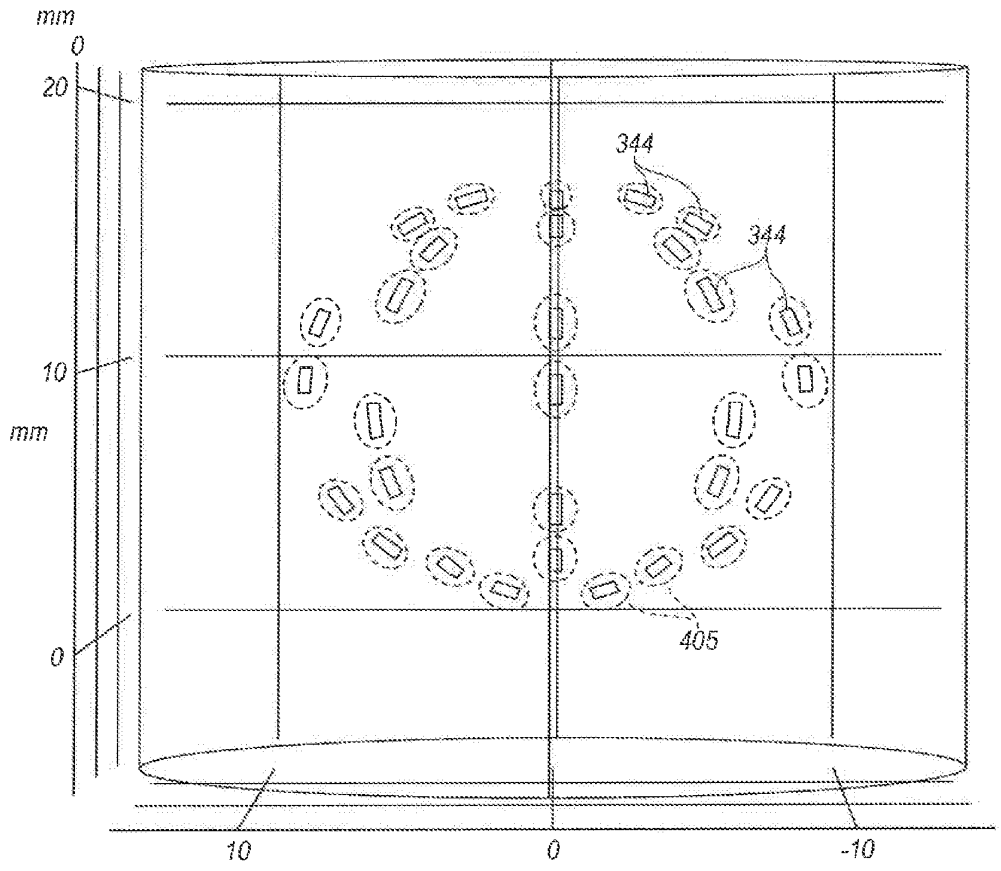


Fig. 4A

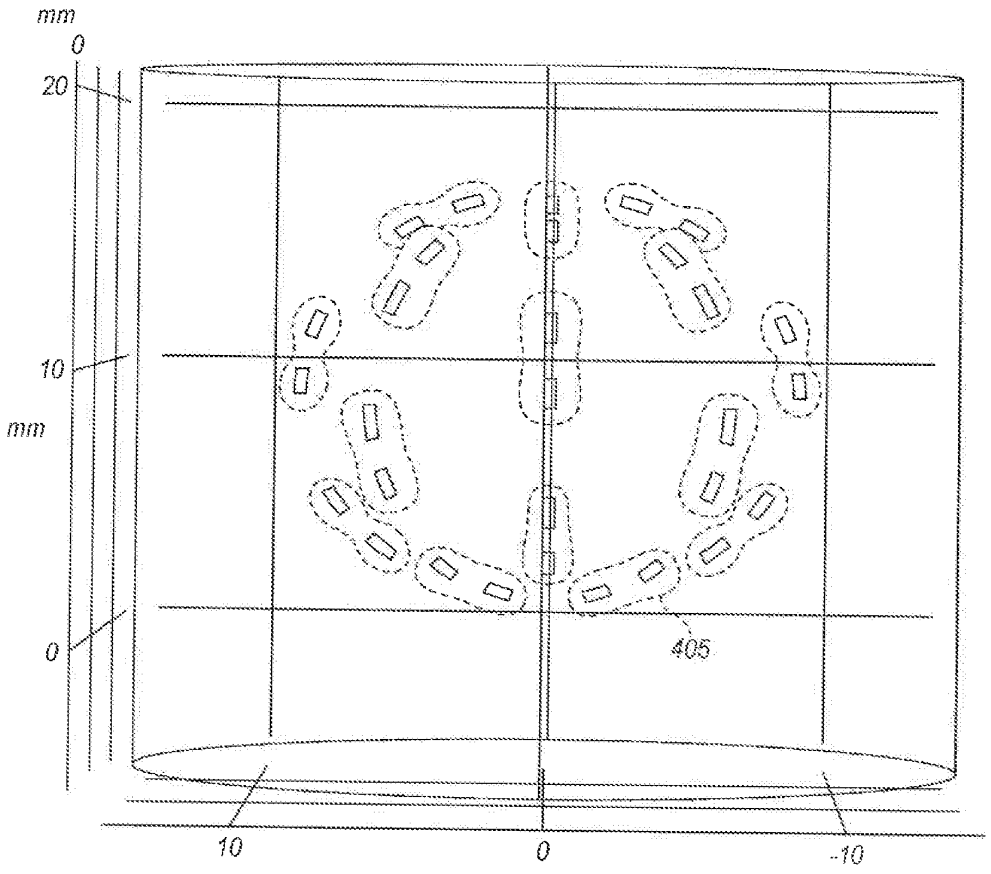


Fig. 4B

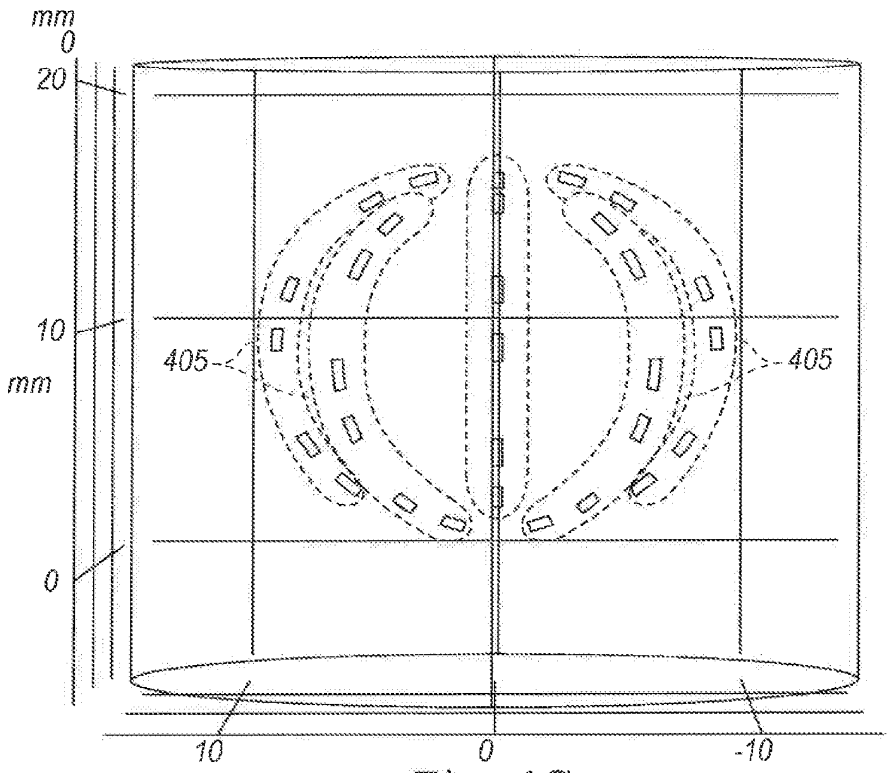


Fig. 4C

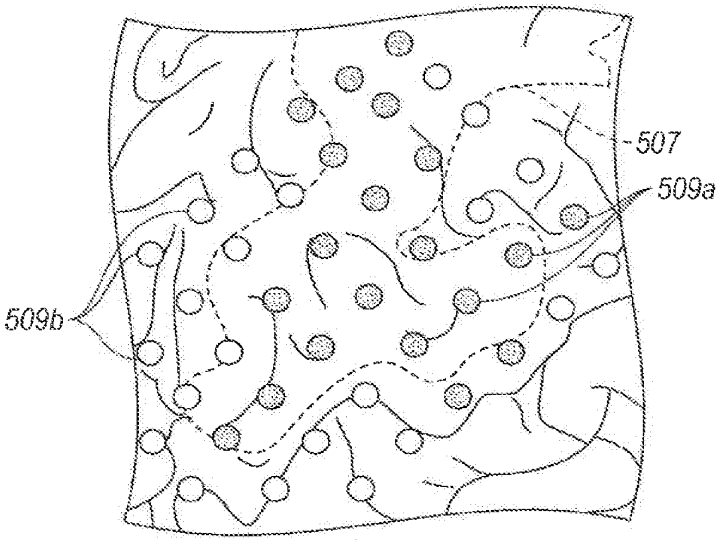


Fig. 5

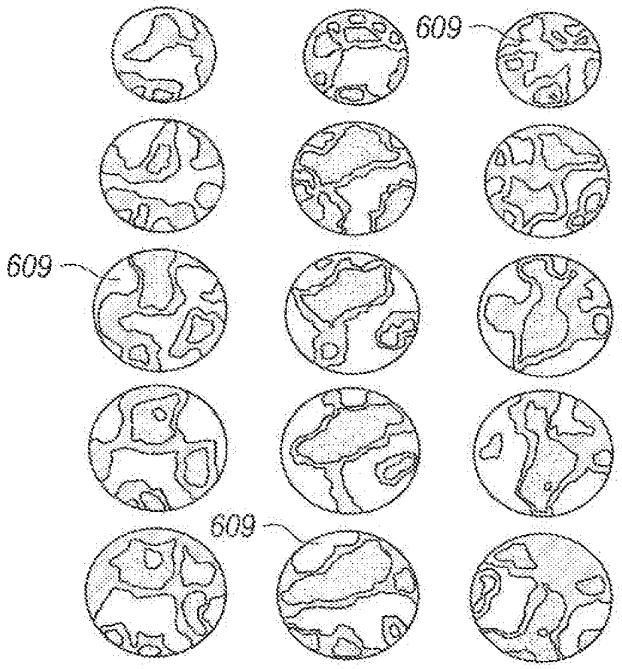


Fig. 6

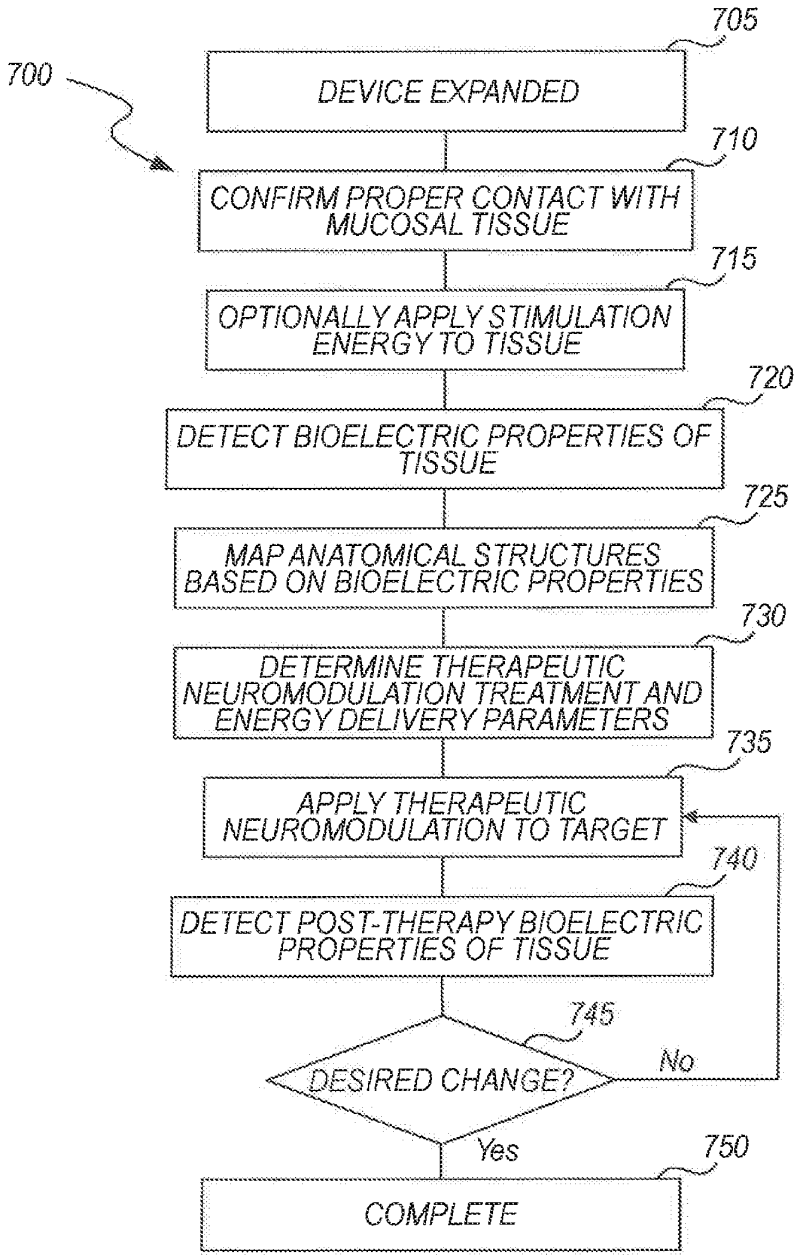


Fig. 7

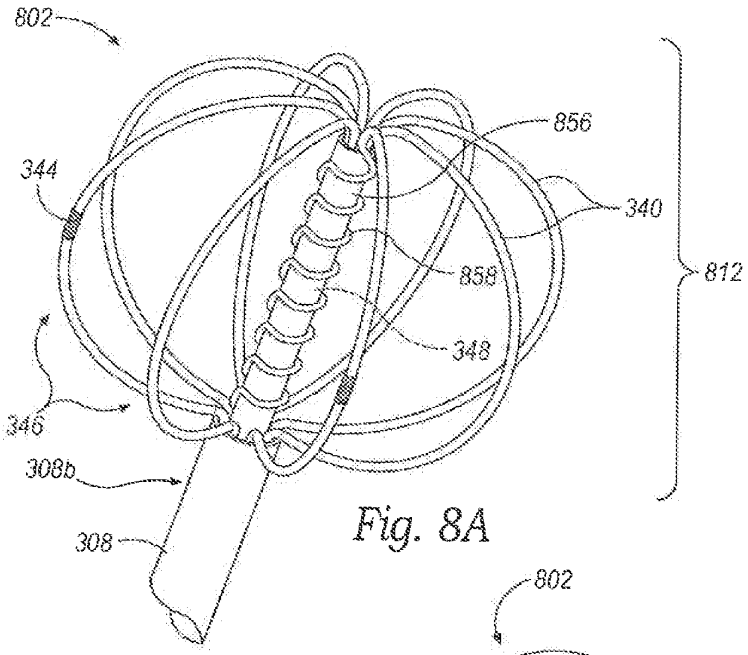


Fig. 8A

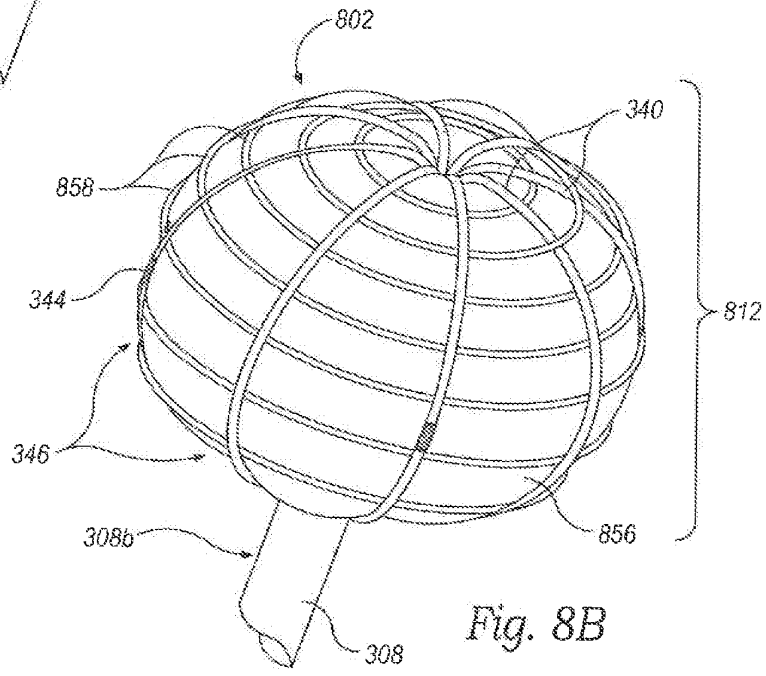


Fig. 8B

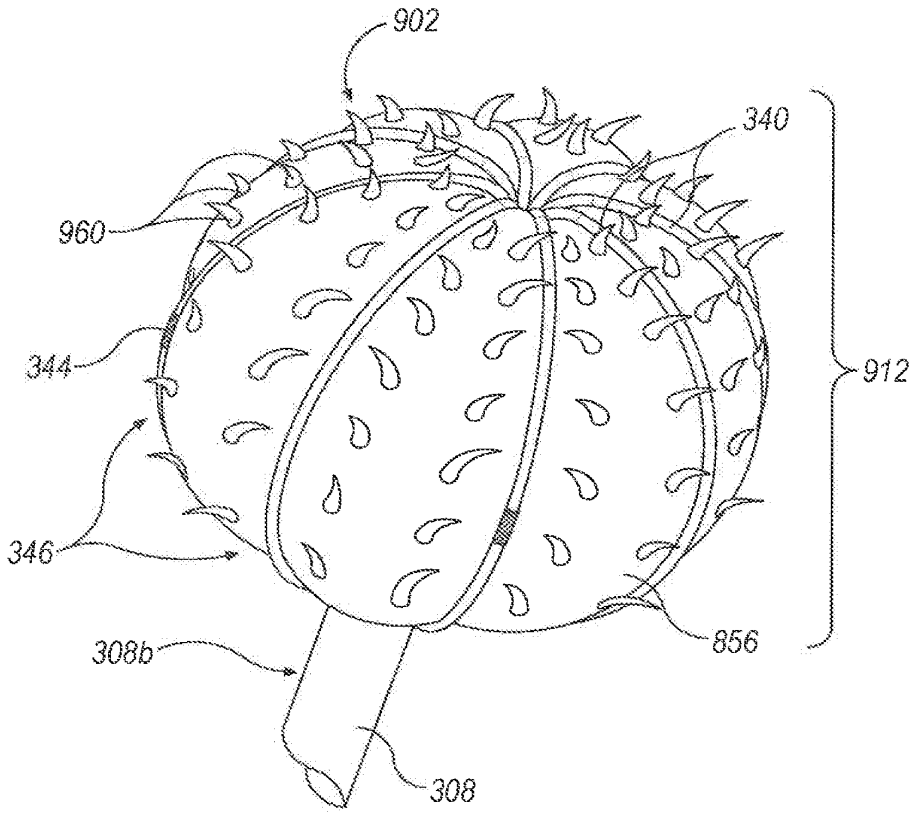


Fig. 9

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:
Schoen, Adam M.
BROWN RUDNICK LLP
One Financial Center
Boston, MA 02111
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference NEURE-011/01WO 35242/85	Date of mailing *(day/month/year)* 4 April 2022 (04-04-2022) **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/IB2021/000700	International filing date *(day/month/year)* 6 October 2021 (06-10-2021)
Applicant NEURENT MEDICAL LIMITED	

1. [X] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   How? Directly to the International Bureau preferably through ePCT, or on paper to:
   The International Bureau of WIPO, 34 chemin des Colombettes, 1211 Geneva 20, Switzerland

   For more detailed instructions, see the *PCT Applicant's Guide*, International Phase, paragraphs 9.004 - 9.011.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may **submit comments on an informal basis on the written opinion of the International Searching Authority** to the International Bureau. These comments will be made available to the public after international publication. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established.

   Shortly after the expiration of **18 months from the priority date, the international application will be published** by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for **entry into the national phase** before those designated Offices. In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

   Within **22 months from the priority date, the applicant may request that a supplementary international search be carried out** by a different International Searching Authority that offers this service (Rule 45*bis*.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040 Fax: (+31-70) 340-3016	Authorized officer WACH, Patrick Tel: +31 (0)70 340-3325

Form PCT/ISA/220 (revised January 2020)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
NEURE-011/01WO 35242/85		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IB2021/000700	6 October 2021 (06-10-2021)	6 October 2020 (06-10-2020)
Applicant		
NEURENT MEDICAL LIMITED		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 6 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of:

☒ the international application in the language in which it was filed

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (See Box No. II)

3. ☒ **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**

☒ the text is approved as submitted by the applicant

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

☒ the text is approved as submitted by the applicant

☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**

a. the figure of the **drawings** to be published with the abstract is Figure No. _____

☐ as suggested by the applicant

☐ as selected by this Authority, because the applicant failed to suggest a figure

☐ as selected by this Authority, because this figure better characterizes the invention

b. ☒ none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2021/000700

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims;; it is covered by claims Nos.:
1-20

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2021/000700

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B18/12 A61B18/14 A61B90/90 A61B18/00 A61B90/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US 2020/129223 A1 (ANGELES MICHAEL [CA] ET AL) 30 April 2020 (2020-04-30) paragraphs [0003], [0028], [0033] - [0040]; figures 1, 4,5	1-8, 11-18 1-20
Y	US 2020/078134 A1 (LOYD RODNEY B [US] ET AL) 12 March 2020 (2020-03-12) paragraphs [0002], [0026], [0029] - [0035], [0039], [0043], [0046] - [0049]; figures 1-4	1-20
Y A	WO 01/17450 A1 (CURON MEDICAL INC [US]) 15 March 2001 (2001-03-15) page 13, line 24 - page 14, line 21; figures 7,8,12 page 20, lines 6-19	8-10,19, 20 2-7, 11-18

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[x] Further documents are listed in the continuation of Box C. [x] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 February 2022	04/04/2022

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Husselin, Stephane

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2021/000700

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94/10921 A1 (EP TECHNOLOGIES [US]) 26 May 1994 (1994-05-26) pages 12-18; figures 4,5	1-7, 11-18

1

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2021/000700

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2020129223 A1	30-04-2020	NONE	
US 2020078134 A1	12-03-2020	EP 3847663 A1	14-07-2021
		US 10350025 B1	16-07-2019
		US 2020078134 A1	12-03-2020
		WO 2020051279 A1	12-03-2020
WO 0117450 A1	15-03-2001	AU 7118000 A	10-04-2001
		CA 2384410 A1	15-03-2001
		EP 1211998 A1	12-06-2002
		JP 2003525659 A	02-09-2003
		US 6464689 B1	15-10-2002
		WO 0117450 A1	15-03-2001
WO 9410921 A1	26-05-1994	CA 2148714 A1	26-05-1994
		EP 0746249 A1	11-12-1996
		JP H08506738 A	23-07-1996
		US 5383874 A	24-01-1995
		US 5651780 A	29-07-1997
		WO 9410921 A1	26-05-1994

Form PCT/ISA/210 (patent family annex) (April 2005)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-20

A system for treating a condition within a sino-nasal cavity of a patient, comprising a console unit configured to be operably associated with a treatment device. The system being configured to determine authenticity of the treatment device.

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2. claims: 21-40

A system for treating a condition within a sino-nasal cavity of a patient, comprising a treatment device including an end effector comprising one or more electrodes. The system being configured to determined availability of the one or electrodes based on impedance assessment.

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3. claims: 41-60

A system for treating a condition within a sino-nasal cavity of a patient, the system comprising a treatment device including a multi-segment end effector comprising a plurality of sets of support structures. The system being configured to determine a status of each of the plurality of support structures with respect to the treatment pattern.

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4. claims: 61-95

A system for treating a condition within a sino-nasal cavity of a patient, the system comprising a treatment device. The system being configured to provide, via an interactive interface associated with the console unit, one or more post-procedure inputs for controlling subsequent use of the end effector.

Information on Search Strategy - Pilot phase (see OJ 2015, A86)
The type of information contained in this sheet may change during the pilot for improving the usefulness of this new service.

Application Number
PCT/IB2021/000700

TITLE: SYSTEMS AND METHODS FOR THERAPEUTIC NASAL TREATMENT

APPLICANT: NEURENT MEDICAL LIMITED

IPC CLASSIFICATION: A61B18/12, A61B18/14, A61B90/90, A61B18/00, A61B90/00

EXAMINER: Husselin, Stephane

CONSULTED DATABASES: WPI

CLASSIFICATION SYMBOLS DEFINING EXTENT OF THE SEARCH:

IPC:

CPC: A61B2018/00327, A61B2018/00577, A61B2018/00595, A61B18/12, A61B18/1485, A61B2018/00267, A61B2018/1475, A61B2090/0803, A61B2090/0808, A61B2090/0814, A61B90/90, A61B2560/028, A61B2560/0285

FI/F-TERMS:

KEYWORDS OR OTHER ELEMENTS FEATURING THE INVENTION:
IDENTIFICATION
EAR, NOSE, THROAT
RETRACTABLE ELECTRODES
BASKET SHAPE
COUNT USE
INDICATING CORRECT ASSEMBLING
PREVENTING RE-USE
ID?, identif+, authenti+
(pr[é,e]vent+, avoid+, emp#ch+, #vite+) 5d (use?, r[é,e]_use+)
display+, indicat+, affich+, GUI?, screen?, #cran?
(nose, nasal, sino-nasal, nez, Sinus) 5d (micro_debrid+, d#brid+)
(alert+, info+, messag+, signal+, suggest+, indicat+) 5d (user?, utilisateur?, physician?, op#rateur?,op#rator?, surg+, chirug+)

EPO FORM P04A42

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2021/000700	06.10.2021	06.10.2020

International Patent Classification (IPC) or both national classification and IPC
INV. A61B18/12 A61B18/14 A61B90/90 A61B18/00 A61B90/00

Applicant
NEURENT MEDICAL LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016	see form PCT/ISA/210	Husselin, Stephane Telephone No. +31 70 340-0

Form PCT/ISA/237 (Cover Sheet) (January 2015)

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:

      ☐ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 21-95

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for the whole application or for said claims Nos. 21-95

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
- ☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☐ See Supplemental Box for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:

   ☐ paid additional fees

   ☐ paid additional fees under protest and, where applicable, the protest fee

   ☐ paid additional fees under protest but the applicable protest fee was not paid

   ☒ not paid additional fees

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-20

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	9, 10, 19, 20
	No:	Claims	1-8, 11-18
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-20
Industrial applicability (IA)	Yes:	Claims	1-20
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item IV

Lack of unity of invention

This Authority considers that the application does not meet the requirements of unity of invention and that there are four inventions. The following separate inventions are not so linked as to form a single general inventive concept:

I. Claims: 1-20

A system for treating a condition within a sino-nasal cavity of a patient, comprising a console unit configured to be operably associated with a treatment device. The system being configured to determine authenticity of the treatment device.

II. Claims: 21-40

A system for treating a condition within a sino-nasal cavity of a patient, comprising a treatment device including an end effector comprising one or more electrodes. The system being configured to determined availability of the one or electrodes based on impedance assessment.

III. Claims: 41-60

A system for treating a condition within a sino-nasal cavity of a patient, the system comprising a treatment device including a multi-segment end effector comprising a plurality of sets of support structures. The system being configured to determine a status of each of the plurality of support structures with respect to the treatment pattern.

IV. Claims: 61-95

A system for treating a condition within a sino-nasal cavity of a patient, the system comprising a treatment device. The system being configured to provide, via an interactive interface associated with the console unit, one or more post-procedure inputs for controlling subsequent use of the end effector.

The reasons, for which the inventions are not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT, are as follows:

The common matter linking together the independent claims 1, 21, 41 and 61 is "*A system for treating a condition within a sino-nasal cavity of a patient, the system comprising: a console unit configured to be operably associated with a treatment device and control operation thereof*". This common matter does not comprise a single general

inventive concept, based on same or corresponding special technical features within the meaning of Rule 13.2 PCT, because at least documents D1 and D2 anticipate the common matter, see D1 (FIG.1 and [0003]) and D2 (FIG.1, [0002]).

Additional features of claim 1, representing the difference over the non-inventive common matter, provide the technical effect of determining the authenticity of the treatment device and solve the objective technical problem of preventing the use of non-authorized treatment devices.

Additional features of claim 21, representing the difference over the non-inventive common matter, provide the technical effect of determining the availability of the one or more electrodes of the treatment device and solve the objective technical problem of providing the user with an indication as to when the device is primed and ready to perform treatment in the selected location.

Additional features of claim 41, representing the difference over the non-inventive common matter, provide the technical effect of determining a status of each of the plurality of support structures with respect to a treatment pattern and solve the objective technical problem of ensuring successful ablation/modulation of the targeted tissue while minimizing and/or preventing collateral damage to surrounding or adjacent non-targeted tissue at the target site.

Additional features of claim 61, representing the difference over the non-inventive common matter, provide the technical effect of providing, via an interactive interface associated with the console unit, one or more post-procedure inputs for controlling subsequent use of the end effector and solve the objective technical problem of ensuring that the overall procedure (i.e., treatment of rhinosinusitis) is completed by ensuring that all portions of targeted tissue undergo treatment.

The above mentioned features representing the difference over the non-inventive common matter are therefore not corresponding because they solve different problems.

Hence, the claims comprise neither the same, nor corresponding special technical features, so the technical relationship between the subject matter of the claims required by Rule 13.2 PCT is lacking and the claims are not so linked as to form a single general inventive concept as required by Rule 13.1 PCT.

Consequently the application does not meet the requirement for unity of invention.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1 US 2020/129223 A1 (ANGELES MICHAEL [CA] ET AL) 30 April 2020 (2020-04-30)

D2 US 2020/078134 A1 (LOYD RODNEY B [US] ET AL) 12 March 2020 (2020-03-12)

D3 WO 01/17450 A1 (CURON MEDICAL INC [US]) 15 March 2001 (2001-03-15)

D4 WO 94/10921 A1 (EP TECHNOLOGIES [US]) 26 May 1994 (1994-05-26)

1 Independent claim 1 not new

The present application does not meet the criteria of Article 33(2) PCT, because the subject-matter of independent claim 1 is not new.

Document D1 discloses:

A system (FIG.1) *for treating a condition within a sino-nasal cavity of a patient* (see [0003]: "the treatments may address any of a wide variety of conditions, just two examples of which are nasal valve insufficiency (which may cause difficulty breathing through the nose) and chronic rhinitis (runny nose)"), *the system comprising:*

a console unit (102) *configured to be operably associated with a treatment device* (104) *and control operation thereof, the console unit configured to:*

analyze identifying data associated with a treatment device upon connection of the treatment device to the console unit (see [0028]: "In some embodiments, electronics inside the console 102 may include a stylus identification safety feature that identifies the stylus 104 when it is plugged into the stylus connection port 110");

determine authenticity of the treatment device based on the analysis of the identifying data (see [0028]: "The stylus connection port 110 can be configured to accept only the connection end of the stylus 104 and can be configured to not accept or work with counterfeit or other devices"); *and*

output, via an interactive interface associated with the console unit, an alert to a user indicating at least the authenticity determination (see "the stylus type indicator 506" in FIG.5 and [0040]: "If such an alternative type of stylus 104 is inserted, the console 102 will identify the stylus type and

indicate the type via the stylus type indicator 506". See also [0037]: "FIG. 5 shows the default image 500 displayed on the display 108 of the console 102, once a valid stylus 104 is connected.").

Subject-matter of claim 1 is therefore known from D1.

2 Independent claim 1 not inventive

The present application does not meet the criteria of Article 33(3) PCT, because the subject-matter of independent claim 1 does not involve an inventive step.

Document D2 discloses:

A system (FIG.1) *for treating a condition within a sino-nasal cavity of a patient* (see [0002], [0043]: "The device unit 200 may be a microdebrider or a sinus debrider [...]"), *the system comprising:*

a console unit (100) *configured to be operably associated with a treatment device* (200) *and control operation thereof, the console unit configured to:*

analyze identifying data associated with a treatment device upon connection of the treatment device to the console unit (see [0031]: "In certain embodiments, the query is a request or software command to the device unit 200 to respond with a message containing, for example, device unit 200 identifying information and device status information");

determine authenticity of the treatment device based on the analysis of the identifying data (see [0031]: "The identifying information can be information such as a unique and serialized device ID number such that no other connected device (either the same or a different model of the connected device) can have the same device ID number"); *and*

The subject-matter of claim 1 therefore differs from this known system in that the console unit is further configured to *output, via an interactive interface associated with the console unit, an alert to a user indicating at least the authenticity determination*

The problem to be solved by the present invention may therefore be regarded as to ensure that the user is made aware of the result of the authenticity determination. A skilled person in the art would consider documents D1 or D4 that provide user interfaces which are used for outputting messages related to the identification of a treatment device upon connection to a console (see in D1 "the stylus type indicator 506" in FIG.5 and [0040]: "If such an alternative type of stylus 104 is inserted, the console 102 will identify the stylus type and indicate the type via the stylus type indicator 506" . See also D4 79 or 84 in FIG.4: "[...] the first control signal 78 preferably generates a confirming,

user discernible "Use Permitted" message 79." and "the second control signal 80 generates a user discernible "Use Not Permitted" alarm message 84 [...]"). By applying the teachings of either D1 or D4 to the system of D2, the skilled person would arrive at the invention, without the exercise of inventive skills.

The solution proposed in claim 1 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT).

3 Dependent claims

Dependent claims do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step.

Claims 2-4	See D1 ([0028], [0033-0034]). See also D2 ("unique and serialized device ID number" in [0029], [0031]); D3 ("identification codes") or D4 ("catheter identification means 88 [...] programmed with a digital value representing the catheter identification code").
Claims 5-7	See D1 ([0028]: "Such a safety feature may, for example, automatically shut down (or disable powering on) the console 102, if a user tries to plug in a device other than the stylus 104."). See also D2 ([0035]: " In certain embodiments, the unlocking circuit 201 may be a locking or unlocking mechanism or circuit which may comprise an electronically controllable component that has the capability to prevent or allow the transmission of power or drive signals to the motor unit in a way that prevents operation of the drive unit 202"); D3 (FIG.8 and p.13, ln.24 - p.14, ln.21) or D4 (p.12, ln.19 - p.13, ln.19).
Claim 8	See D1 ("the stylus type indicator 506" in FIG.5 and [0040]: "If such an alternative type of stylus 104 is inserted, the console 102 will identify the stylus type and indicate the type via the stylus type indicator 506").

See also D3 (FIG.12 and p.20, ln 6-19) or D4 (79 or 84 in FIG.4: "[...] the first control signal 78 preferably generates a confirming, user discernible "Use Permitted" message 79." and "the second control signal 80 generates a user discernible "Use Not Permitted" alarm message 84 [...]").

Adding an audible alert to the visual alert is not considered inventive.

Claims 9, 10, 19, 20

The GUI in D3 provides one or more suggested actions (see p.20, ln 6-19: "When the identification code 214 is not valid, the REGISTRATION function 514 commands the display microprocessor 474 to generate an EXCHANGE prompt 516 on the graphics display monitor 420. Fig. 12 shows a representative EXCHANGE prompt 516. When graphically implemented, as shown in Fig. 12, the EXCHANGE prompt 516 leads the operator in a step-wise fashion through the tasks of replacing the previously used device 26 and its key card 202 with a new device 26 and its associated key card 202.").

Claims 11-18

See D1 ([0033-0034]: " In some embodiments, the console 102 may permanently deactivate the stylus 104 when it has reached its maximum number of uses.").

See also D2 ([FIG.2-4 and [0032]: "The MCU 103 is also configured to process the message received from the query command by, for example, analyzing the usage status of the device unit 200 to determine if the device unit 200 has been used previously, and then accordingly whether the device unit 200 should be locked or unlocked."); D3 (p.13, ln.24 - p.14, ln.21: "The presence of a match between the instant identification code and any registered identification code indicates the usage key card 202 has been previously read by the module 48, which reflects a prior use of the device 26 or another device not packaged with the card 202.") or D4 (FIG.5 and p.17, ln.20: "As Fig. 5 shows, the identification means 76 can also serve to monitor the use of the catheter 14.").

Possible steps after receipt of the international search report (ISR) and written opinion of the International Searching Authority (WO/ISA)

General information

For all international applications, the competent International Searching Authority **(ISA)** will establish an international search report **(ISR)** accompanied by a written opinion of the International Searching Authority **(WO/ISA)**. The **WO/ISA** may be responded to by

- filing informal comments with the **International Bureau of WIPO (IB)** (where no demand for international preliminary examination **(demand)** is filed)
- filing amendments under Art. 19 PCT (this can be done whether or not a **demand** is filed)
- filing amendments under Art. 34 PCT and/or formal observations in response to objections raised in the **WO/ISA** (where a **demand** *is* actually filed)

This document explains these possibilities.

Filing informal comments

After receipt of the **ISR and WO/ISA**, the applicant may file informal comments on the **WO/ISA, directly with the IB** (see International Search and Preliminary Examination Guidelines 2.15). These will be communicated to the designated/elected Offices, together with the International Preliminary Report on Patentability **(IPRP)** at 30 months from the priority date.

Amending claims under Art. 19 PCT

The applicant may file **amended claims** under Art. 19 PCT, **directly with the IB** by the later of the following dates:

- 2 months from the date of mailing of the **ISR** and the **WO/ISA**
- 16 months from the priority date

However, any such amendment received by the **IB** after the expiration of the applicable time limit shall be **considered to have been received on time** by the **IB**, if it reaches it **before** the technical preparations for international publication have been completed (the 15th day prior to the date of publication, see PCT Applicant's Guide, International Phase, 9.013).

For further information, please see Rule 46 PCT as well as form PCT/ISA/220.

Please also note that, when filing amended claims under Art. 19 PCT, such amendments shall be **accompanied by a letter** identifying the amendments made and also the basis for the amendments in the application as originally filed (Rule 46.5(b) PCT). Where a **demand** is filed, failure to comply with this requirement may result in the amendments being ignored in the International Preliminary Examination Report **(IPER)**, see Rule 70.2(c-*bis*) PCT.

Filing a demand for international preliminary examination

In principle, the **WO/ISA** will be considered to be the written opinion of the International Preliminary Examining Authority (**IPEA**). Where the **WO/ISA** issued by the **EPO** as **ISA** gives a positive opinion on the international application and the invention to which it relates, filing a **demand** with the **EPO** as **IPEA** would normally be unnecessary, since a positive IPRP would anyway be established by the IB based on the WO/ISA (see also further below).

If the applicant wishes to file a **demand** (for example, to allow him to argue his case in international preliminary examination with regard to objections raised in a negative **WO/ISA** before the **IPEA** issues an **IPER**), this must be done before expiration of **3 months after the date of mailing of the ISR and WO/ISA** or **22 months after priority date,** whichever expires later (Rule 54*bis* PCT). Amendments under Art. 34 PCT can be filed with the IPEA, normally at the same time as filing the demand (Rule 66.1(b) PCT) or within the time limit set for reply to any written opinion issued during international preliminary examination by the **IPEA**.

If a **demand** is filed at the **EPO** as **IPEA** and no comments/amendments have been received by the time the **EPO** starts drawing up the **IPER** (Rule 66.4*bis* PCT), the **WO/ISA** will be transformed by the **IPEA** into an **IPER** (also called the **IPRP (Chapter II)** which would merely reflect the content of the **WO/ISA** (OJ 10/2011, 532). The **demand** can still be withdrawn (Art. 37 PCT).

Please also note that, when filing amendments under Art. 34 PCT, such amendments shall be accompanied by a letter which identifies the amendments made and also the basis for the amendments in the application as originally filed (Rule 66.8(a) PCT). Failure to comply with this requirement may result in the amendments being ignored in the **IPER (IPRP (Chapter II))**, see Rule 70.2(c-*bis*) PCT.

Filing a request for supplementary international search

The applicant may, with the **IB**, file a request for **supplementary international search** under Rule 45*bis*.1 PCT. The present **ISR** and **WO/ISA** may also be taken into account in the execution of that supplementary international search, provided that these are available to the Authority charged with this task before it starts the supplementary search (Rule 45*bis*.5 PCT).

This kind of request **cannot be filed specifying the ISA** who did the **international search**.

More information on this topic can be found in the **PCT Applicant's Guide**, Chapter 8 (http://www.wipo.int/pct/en/guide/ip08.html).

End of the international phase

Where no **demand** is filed, at the end of the international phase, the **IB** will transform the **WO/ISA** into the IPRP (PCT Chapter I) (Rule 44*bis* PCT), which will then be transmitted together with possible informal comments to the designated Offices. Where a demand is filed, the **WO/ISA** is not transformed into an **IPRP (Chapter I)** by the **IB**, but rather the **IPEA** will establish an **IPER**, (the IPER is the same as the IPRP (PCT Chapter II), see Rule 70.15 PCT).

Electronic Acknowledgement Receipt

EFS ID:	45867099
Application Number:	17225560
International Application Number:	
Confirmation Number:	9752
Title of Invention:	SYSTEMS AND METHODS FOR IMPROVING SLEEP WITH THERAPEUTIC NASAL TREATMENT
First Named Inventor/Applicant Name:	David Townley
Customer Number:	21710
Filer:	Adam M Schoen/Kelley Warren
Filer Authorized By:	Adam M Schoen
Attorney Docket Number:	NEURE-008/01US 35242/69
Receipt Date:	03-JUN-2022
Filing Date:	08-APR-2021
Time Stamp:	15:56:40
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Form (SB08)	35242_69US_-_Information_Disclosure_Statement_Fillable_PDF.pdf	1265383 2ff68b34b9cd905c003508e218c18b193534da15	no	10
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Information:					
2	Foreign Reference	35242_11US_-_JP2007537784A.pdf	3541990 8f557a3f59803830c0afa0249cf420e7972511ce	no	71
Warnings:					
Information:					
3	Foreign Reference	35242_11US_-_Translation_of_JP2007537784A.pdf	637285 5dd681c2462060570e8ff0127682b643eb412196	no	61
Warnings:					
Information:					
4	Foreign Reference	35242_85WO_-_WO0117450A1.pdf	1290939 9d922de383ff21d28e7788fda20698b889af4938	no	39
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Information:					
5	Foreign Reference	35242_80WO_-_WO2009154456A1.pdf	1305516 0112efea85fe8cf683bc11496aa2b8401c4b9bc9	no	31
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Information:					
6	Foreign Reference	35242_82US_-_WO2021205230A1.pdf	5366640 d43cde361713437229 92bee1ebf429c5394cdc5a	no	108
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Information:					
7	Foreign Reference	35242_79US_-_WO2021205231A1.pdf	6192616 da39513e403acd7971f803c3a9af0bb8f1edac5f	no	129
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8	Foreign Reference	35242_93WO_-_WO2021260435A1.pdf	6821780 f3ec5488d975e1e81672f4e4c4d99592cebfa546	no	133
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9	Foreign Reference	35242_85WO_-_WO9410921A1.pdf	1290690 f92d1331024576c983d6ee7788d5ff8e0062c543	no	33
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Information:					
10	Non Patent Literature	35242_31US_-_Annotated_Perfler_Figure.pdf	20025 0fb57233b56f7e57351b14670623a0015229f792	no	1
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Information:					
11	Non Patent Literature	35242_80WO_-_Flexible_electronics_-_Wikipedia.pdf	1014071 d7cec9d2a2984c565e0904223131d859ec692fca	no	9
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Information:					
12	Non Patent Literature	35242_10US_-_FOA_US_16382845.pdf	733391 3410c293ae81a20d349823d1bb8c11715c47a836	no	20
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Information:					
13	Non Patent Literature	35242_31US_-_Final_OA_16701855.pdf	670131 36727feca11630306a7db0c394f469dba52268ec	no	22
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Information:					
14	Non Patent Literature	35242_80WO_-_ISR__WO_PCTIB2021000597.pdf	1018058 35860e0dfe929229e48c5ce1ab7c1adcc0c66637	no	18
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Information:					
15	Non Patent Literature	35242_92WO_-_ISR__WO_PCTIB2021000667.pdf	1062880 2f9708feaf81bd6d2296ad934107f7eabad379e7	no	17
Warnings:					
Information:					

16	Non Patent Literature	35242_93WO_-_ISR__WO_PCTIB2021000699.pdf	1563060 e802032ad6386f31dd342f390d0a11592f916ad2	no	28
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Information:					
17	Non Patent Literature	35242_85WO_-_ISR__WO_PCTIB2021000700.pdf	1267938 c8979b2a204e9b5d461c3ee2594272baa718f67f	no	20
Warnings:					
Information:					
18	Non Patent Literature	35242_11US_-_JP_OA_2021-035965.pdf	442958 3835f4b6e17b2f30b85becc6738b8bf0c81b14b5	no	7
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Information:					
19	Non Patent Literature	35242_31US_-_NFOA_16701808.pdf	768895 90fb99f72131a233fa555ff46eea82179a69cdf3	no	20
Warnings:					
Information:					
20	Non Patent Literature	35242_31US_-_NFOA_16701835.pdf	404751 8b22ee5dd85180a5ca57c32cd99ef8f4a5603108	no	13
Warnings:					
Information:					
21	Non Patent Literature	35242_31US_-_OA_US16701843.pdf	340972 569970539db90b04299efcf3f2ac62dd54a6d2bd	no	9
Warnings:					
Information:					
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Warnings:					
Information:					

23	Non Patent Literature	35242_31US_-_NOA_US16701820.pdf	473926 240a6f898550dfd88bea5590bfe91996df558414	no	10
Warnings:					
Information:					
			Total Files Size (in bytes):	37799426	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	17225560
Filing Date	2021-04-08
First Named Inventor	David Townley
Art Unit	N/A
Examiner Name	Not Yet Assigned
Attorney Docket Number	NEURE-008/01US 35242/69

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20070173760	A1	2007-07-26	Fedenia et al.	
	2	20150202003	A1	2015-07-23	WOLF et al.	

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							

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NON-PATENT LITERATURE DOCUMENTS Remove

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17225560
	Filing Date	2021-04-08
	First Named Inventor	David Townley
	Art Unit	N/A
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	NEURE-008/01US 35242/69

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	Non-Final Office Action issued in U.S. Application No. 16/701,855, date of mailing: November 15, 2021, 18 pages	
	2	Non-Final Office Action issued n U.S. Application No. 16/382,865, date of mailing: November 11, 2021, 16 pages	

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17225560
	Filing Date	2021-04-08
	First Named Inventor	David Townley
	Art Unit	N/A
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	NEURE-008/01US 35242/69

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Adam M. Schoen/	Date (YYYY-MM-DD)	2021-11-24
Name/Print	Adam M. Schoen	Registration Number	58,576

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt

EFS ID:	44366001
Application Number:	17225560
International Application Number:	
Confirmation Number:	9752
Title of Invention:	SYSTEMS AND METHODS FOR IMPROVING SLEEP WITH THERAPEUTIC NASAL TREATMENT
First Named Inventor/Applicant Name:	David Townley
Customer Number:	21710
Filer:	Adam M Schoen/Kelley Warren
Filer Authorized By:	Adam M Schoen
Attorney Docket Number:	NEURE-008/01US 35242/69
Receipt Date:	24-NOV-2021
Filing Date:	08-APR-2021
Time Stamp:	15:05:44
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Form (SB08)	35242_69US_-_Information_Disclosure_Statement_Fillable_PDF.pdf	1034340 735233394b7173163ddd0a6bbb9c27e748f68b54	no	4
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Information:					
2	Non Patent Literature	35242_27US_-_NFOA_US16701855.pdf	591550 51622fb69233c84f3b5cbce4c42291933b85f955	no	18
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Information:					
3	Non Patent Literature	35242_11US_-_NFOA_US16382865.pdf	577610 f712cd0af71a4a8de5c7c68d8a19b12d112b59be	no	16
Warnings:					
Information:					
			Total Files Size (in bytes):	2203500	

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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United States Patent and Trademark Office
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
17/225,560	04/08/2021	David Townley	NEURE-008/01US 35242/69

CONFIRMATION NO. 9752

21710
BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

PUBLICATION NOTICE

OC000000129100855

Title:SYSTEMS AND METHODS FOR IMPROVING SLEEP WITH THERAPEUTIC NASAL TREATMENT

Publication No.US-2021-0315634-A1
Publication Date:10/14/2021

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Public Records Division. The Public Records Division can be reached by telephone at (571) 272-3150 or (800) 972-6382, by facsimile at (571) 273-3250, by mail addressed to the United States Patent and Trademark Office, Public Records Division, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently https://portal.uspto.gov/pair/PublicPair. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	17225560
Filing Date	2021-04-08
First Named Inventor	David Townley
Art Unit	N/A
Examiner Name	Not Yet Assigned
Attorney Docket Number	NEURE-008/01US 35242/69

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	5184625		1993-02-09	Cottone, Jr. et al.	
	2	5697536		1997-12-16	Eggers et al.	
	3	5697882		1997-12-16	Eggers et al.	
	4	5746224		1998-05-05	Edwards	
	5	5836947		1998-11-17	Fleischman et al.	
	6	5843026		1998-12-01	Edwards et al.	
	7	6063079		2000-05-16	Hovda et al.	
	8	6106518		2000-08-22	Wittenberger et al.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17225560
	Filing Date	2021-04-08
	First Named Inventor	David Townley
	Art Unit	N/A
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	NEURE-008/01US 35242/69

	9	6139527		2000-10-31	Laufer et al.	
	10	6352533		2002-03-05	Ellman et al.	
	11	6529756		2003-03-04	Phan et al.	
	12	6595988		2003-07-22	Wittenberger et al.	
	13	6626899		2003-09-30	Houser et al.	
	14	6746474		2004-06-08	Saadat	
	15	7232458		2007-06-19	Saadat	
	16	7500985		2009-03-10	Saadat	
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See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

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Signature	/Adam M. Schoen/	Date (YYYY-MM-DD)	2021-10-13
Name/Print	Adam M. Schoen	Registration Number	58,576

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Applicant(s): HOLAIRA INC [US] ± (HOLAIRA, INC)

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An apparatus and method for pulmonary treatment by denervation is provided. The apparatus includes an elongate member configured for insertion into the trachea to a positions adjacent a pulmonary plexus. The apparatus further includes at least one energy delivery element disposed on the elongate member. The energy delivery element is positionable to target at least one nerve in the tracheal wall when the elongate member is positioned in the trachea. Energy from the energy delivery element is delivered to the at least one nerve to treat pulmonary

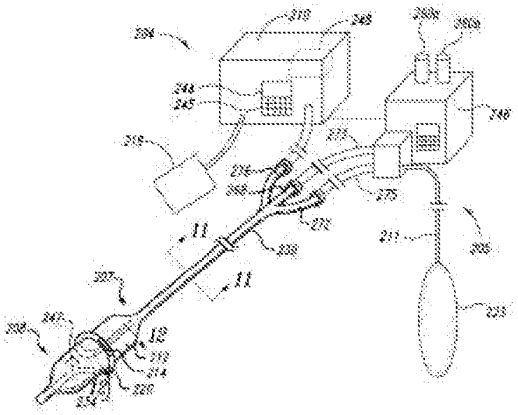

FIG. 10

symptoms, conditions, and/or diseases, such as asthma, COPD, obstructive lung diseases, or other pulmonary diseases.

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(71) Applicant: **Holaira, Inc.**
Plymouth, MN 55447 (US)

(72) Inventors:
- **Deem, Mark**
Mountain View, CA California 94041 (US)
- **Shenoy, Vivek**
Redwood City, CA California 94062 (US)
- **Mayse, Martin L.**
Wayzata, MN Minnesota 55391 (US)

(74) Representative: **Grünecker Patent- und Rechtsanwälte**
PartG mbB
Leopoldstraße 4
80802 München (DE)

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(54) SYSTEM FOR PULMONARY TREATMENT

(57) An apparatus and method for pulmonary treatment by denervation is provided. The apparatus includes an elongate member configured for insertion into the trachea to a positions adjacent a pulmonary plexus. The apparatus further includes at least one energy delivery element disposed on the elongate member. The energy delivery element is positionable to target at least one nerve in the tracheal wall when the elongate member is positioned in the trachea. Energy from the energy delivery element is delivered to the at least one nerve to treat pulmonary symptoms, conditions, and/or diseases, such as asthma, COPD, obstructive lung diseases, or other pulmonary diseases.

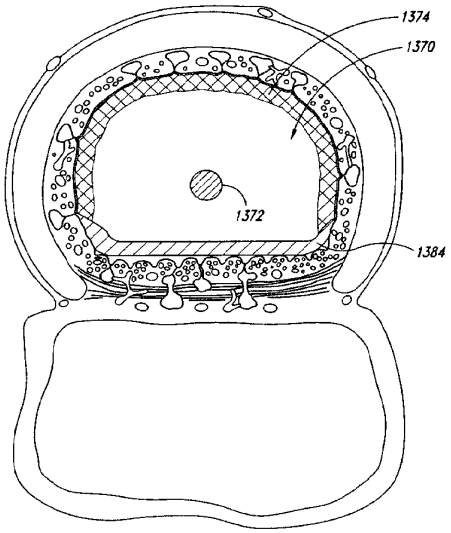

FIG. 53

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Description

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit under 35 U.S.C. § 119(e) of U.S. Provisional Patent Application No. 61/321,346 filed April 6, 2010. This provisional application is incorporated herein by reference in its entirety.

BACKGROUND

Technical Field

[0002] The present invention generally relates to the field of pulmonary treatments.

Description of the Related Art

[0003] One treatment for asthma which was performed in the 1930's to 1950's, prior to the advent of effective asthma medications, was surgical sympathectomy of the posterior pulmonary nerve plexus. Although the surgery was very morbid, typically requiring severing large muscle groups and manipulating the ribs, pleura and lungs, it was in some cases effective. As an alternative for patients for whom medications and other conventional treatments are ineffective, it would be desirable to achieve the benefits of a pulmonary sympathectomy, but without the high morbidity rates typically associated with such a procedure in the past.

[0004] There exists, in addition to the posterior pulmonary nerve plexus, an anterior pulmonary nerve plexus. The anterior pulmonary nerve plexus was never approached surgically due to its proximity to the heart and the great vessels. It is possible that these nerves also are involved in airway constriction associated with asthma and other pulmonary diseases.

[0005] There are several complicating factors to performing a denervation of these nerves from within the body. The nerves of interest run along the outside of the anterior trachea and bronchi, and the posterior plexus runs along the posterior, along and within the junction between the trachea and the esophagus. As a result of such difficulties there has been minimal interest in such approaches to the treatment of asthma.

BRIEF SUMMARY

[0006] At least some embodiments include a treatment system that can be used to perform pulmonary treatments to address a wide range of pulmonary symptoms, conditions, and/or diseases, including, without limitation, asthma, chronic obstructive pulmonary disease ("COPD"), obstructive lung diseases, or other diseases that lead to an unwanted (e.g., increased) resistance to airflow in the lungs.

[0007] In some embodiments, an apparatus for pulmonary treatment by select denervation includes an elongate member configured for insertion into the trachea to a position adjacent target nerve tissue, such as a pulmonary plexus. The apparatus further includes at least one energy delivery element disposed on the elongate member in a position corresponding to the anatomical location of at least one nerve in or adjacent the tracheal wall when the elongate member is positioned in the trachea. In certain embodiments, energy from a single energy delivery element ablates the at least one nerve. In other embodiments, a plurality of energy delivery elements cooperate to ablate or otherwise alter the nerve or other targeted tissue.

[0008] A pulmonary treatment method, in some embodiments, includes positioning at least one energy delivery element in a trachea or airway of the bronchial tree adjacent a nerve site to be treated. In some embodiments, energy from the element is delivered to a portion of the circumference of the trachea at the treatment site. Tissue adjacent the treatment site is cooled to prevent tissue damage outside the treatment site.

[0009] To cool the tissue, a cooling medium can be delivered through a device positioned along a lumen of the esophagus. The device can have one or more cooling balloons configured to contact the wall of the esophagus to absorb heat, thereby cooling non-targeted tissue. Additionally or alternatively, an apparatus in the trachea combined with or separate from the at least one energy delivery element can include one or more cooling devices (*e.g.,* cooling balloons).

[0010] Some embodiments include an apparatus and method for targeting one or more target sites positioned between the lumens of the trachea and the esophagus. In certain embodiments, one or more devices are placed on the lumens of the trachea and/or esophagus to deliver energy so as to damage or otherwise alter one or more target sites located between the lumens of the trachea and the esophagus. The target sites can include nerve tissue. Preferably, such target sites are damaged while tissue closer to the lumens of the trachea and/or esophagus are protected from damage.

[0011] In some embodiments, a system for pulmonary treatment includes a pulmonary treatment device and a protection device. The pulmonary treatment device has one or more energy delivery elements positionable through at least

a portion of a trachea into in an airway. The one or more energy delivery elements are configured to deliver energy to a wall of the airway to alter nerve tissue located in or proximate to the wall of the airway. The protection device has a protection member positionable in an esophagus even when the pulmonary treatment device is positioned in the airway. The protection member is configured to absorb heat from a wall of the esophagus to inhibit damage to esophageal tissue. In some procedures, the system is used to ablate nerve tissue of nerve trunks travelling along the airway. Additionally or alternatively, nerve tissue within the airway wall can be ablated.

[0012] A cooling apparatus can be associated with the energy delivery element to limit tissue damage adjacent select denervation sites. The cooling apparatus can include one or more pumps, blowers, conduits, facemasks, valves, or the like. Media from the cooling apparatus can flow through the subject to cool internal tissue. In some embodiments, the cooling apparatus includes a pump that delivers chilled air through a conduit into a lumen of the esophagus. The chilled air circulates within the lumen to cool the esophageal tissue.

[0013] A method for pulmonary treatment includes positioning at least one energy delivery element through at least a portion of the trachea into an airway adjacent a treatment site to be treated. In certain procedures, the airway is part of the trachea. In other procedures, the at least one energy delivery element is delivered through and out of the trachea and into the bronchial tree.

[0014] The method can further include delivering energy from the element to a portion of the circumference of the airway. The temperature of tissues can be adjusted to prevent or limited damaged to non-target tissue. In some procedures, tissues of an esophagus are cooled to prevent damage of the esophageal tissues while the energy is delivered. The esophageal tissues can also be cooled before and/or after delivering the energy.

[0015] The energy delivery element can be repositioned any number of times. In certain embodiments, the energy delivery element can be positioned in close proximity to the previous position. Energy is delivered to an adjacent treatment site. The adjacent site can barely overlap with the previous site. Alternatively, a small gap can be between the two treatment sites. The apparatus can be moved (*e.g.,* rotated, translated, or both) to reposition the energy delivery element to provide a slight overlap or a slight gap circumferentially with respect to an already treated site.

[0016] In some embodiments, a pulmonary treatment apparatus includes an elongate member and a microwave antenna. The elongate member is insertable through at least a portion of a trachea into an airway. The microwave antenna is coupled to the elongate member and positionable in the airway at a treatment location proximate nerve tissue in a wall thereof. The microwave antenna is configured to deliver microwave energy so as to alter the nerve tissue in a manner which disrupts transmission of nerve signals therein while non-target tissue (*e.g.,* tissue disposed between the microwave antenna and the nerve tissue) is not permanently injured. An active electrode can be non-inflatably (*e.g.,* balloonlessly) expandable from a contracted configuration to an expanded configuration. Thus, the activate electrode can be moved without the use of a balloon or other type of expansion device.

[0017] A system for pulmonary treatment can include at least one pulmonary treatment device capable of damaging nerve tissue such that the destroyed nerve tissue impedes or stops the transmission of nervous system signals to nerves more distal along the bronchial tree. The nerve tissue can be temporarily or permanently damaged by delivering different types of energy to the nerve tissue. For example, the nerve tissue can be thermally damaged by increasing a temperature of the nerve tissue to a first temperature (*e.g.,* an ablation temperature) while the wall of the airway is at a second temperature that is less than the first temperature. In some embodiments, a portion of the airway wall positioned radially inward from the nerve tissue can be at the first temperature so as to prevent permanent damage to the portion of the airway wall. The first temperature can be sufficiently high to cause permanent destruction of the nerve tissue. In some embodiments, the nerve tissue is part of a nerve trunk located in connective tissue outside of the airway wall. The smooth muscle and nerve tissue in the airway wall can remain functional to maintain a desired level of smooth muscle tone. The airway can constrict/dilate in response to stimulation (*e.g.,* stimulation caused by inhaled irritants, the local nervous system, or systemic hormones). In other embodiments, the nerve tissue is part of a nerve branch or nerve fibers in the airway wall. In yet other embodiments, both nerve tissue of the nerve trunk and nerve tissue of nerve branches/fibers are simultaneously or sequentially damaged. Various types of activatable elements, such as ablation elements in the form of microwave antenna, RF electrodes, heating elements, or the like, can be utilized to output the energy.

[0018] At least some methods of pulmonary treatment include positioning an elongate member through at least a portion of the trachea. The elongate member has a treatment element and a sensor coupled thereto. A first tissue characteristic is sensed using the sensor with the treatment element at a first airway location. The first tissue characteristic is compared to a reference value to evaluate the location of the treatment element in the airway. The treatment element is activated to treat an airway.

[0019] In certain embodiments, an apparatus for pulmonary treatment includes an elongate member insertable through a trachea into an airway and an active electrode coupled to the elongate member. The active electrode is configured to deliver energy to target tissue in a wall of the airway. A return electrode is positionable in the airway or the esophagus and configured to receive the energy from the target tissue. A protection member is configured to cool non-target tissue proximate to the target tissue. The non-target tissue can be surrounded or can be spaced apart from the target tissue.

[0020] The active electrode is expandable from a contracted configuration to an expanded configuration without the

use of a balloon. The device can be self-expanding. For example, the device can include a self-expanding basket, a cage, a wire mesh, or other type of component capable of assuming a helical, spiral, corkscrew, or similar configuration. As such the active electrode can be non-inflatably expanded or actuated.

[0021] A method of pulmonary treatment includes delivering energy at a first power level from an active portion of an energy delivery element to create a first lesion covering a first portion of a circumference of an airway. Energy is delivered at a second power level from the active portion of the energy delivery element to create a second lesion covering a second portion of the circumference of the airway displaced from the first portion. The first power level is substantially greater than the second power level. In certain embodiments, the second portion is circumferentially or axially displaced from the first portion relative to a lumen of the airway. For example, the second portion can be both circumferentially displaced and axially displaced from the first portion.

[0022] Another method of pulmonary treatment includes delivering a first amount of energy from an energy delivery device to a first portion of a wall of an airway and delivering a second amount of energy from the energy delivery device to a second portion of the airway wall. The first portion of the wall and the second portion of the wall are spaced apart from one another or can partially overlap one another. For example, most of the first and second portions by area or volume can overlap one another.

[0023] A method of pulmonary treatment includes positioning an energy delivery element in an airway of a subject. The energy delivery element is non-inflatably actuated. The energy delivery element can be moved into engagement with a wall of the airway without using a balloon or other type of inflation device. The energy delivery element can be self-expanding. For example, the energy delivery element can be a self-expandable cage. The non-inflatably expandable cage can move one or more electrodes proximate to or in contact with the airway wall.

[0024] Energy can be delivered from the energy delivery element to the wall of the airway to alter target nerve tissue therein or proximate thereto. A cooling medium is passed into the airway into direct contact with the wall to absorb heat from the wall while delivering the energy. Alternatively, a protection device can be used to cool the airway wall.

[0025] The energy delivery element can comprise a first electrode. The first electrode is positioned within a first space between a first pair of adjacent cartilage rings of the airway. A second electrode is placed in a second space between a second pair of adjacent cartilage rings of the airway. The electrode can be part of a helical or corkscrew shaped device.

[0026] A protection device can be positioned in the esophagus to absorb heat from esophageal tissue while delivering the energy. Energy can be received by the protection device with or delivering energy from a second electrode coupled to the protection device.

[0027] A surface layer of tissue of the wall (*e.g.*, a wall of the trachea, a wall of the esophagus, etc.) can be protected from permanent injury while a lesion of permanently injured tissue is created at a depth below the surface layer. The surface layer is at least about 2 mm in thickness. At least a portion of the lesion contains nerve tissue. In certain procedures, the nerve tissue is altered sufficiently to reduce airway constriction in the subject.

[0028] The cooling medium can include one or more gas or other type of media. The energy delivery element is coupled to an elongate member such that the cooling medium is introduced into the airway through a channel in the elongate member. The cooling medium flows through a channel in the energy delivery element to absorb heat therefrom.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

[0029] For the purpose of illustrating the invention, the drawings show aspects of one or more embodiments of the invention. However, it should be understood that the present invention is not limited to the precise arrangements and instrumentalities shown in the drawings, wherein:

Figure 1 shows a cross section of the trachea and esophagus, and approximate locations of the anterior and posterior plexus nerves.
Figure 2 shows the cartilaginous rings of the trachea. The connective tissue sheath is shown cut away.
Figure 3 shows the trachea in cross section, illustrating a target region in the pulmonary plexus for treatment in embodiments of the present invention.
Figure 4 is a lateral view illustrating the length of a potential target region corresponding to the cross section in Figure 3.
Figure 4A is an anatomical drawing showing details of the posterior pulmonary plexus.
Figure 5 is a lateral view of a treatment system positioned in the trachea and the esophagus.
Figure 6 is a detailed view of a treatment device in the trachea and an esophageal device in the esophagus.
Figure 7 is cutaway view of a trachea and a distal tip of the treatment device.
Figure 8A is a cross-sectional view of the trachea and isotherms in tissue of the trachea and the esophagus.
Figure 8B is a cross-sectional view of the trachea and isotherms in tissue of the trachea and the esophagus.
Figure 9 illustrates a tracheal treatment device and an esophageal treatment device.
Figure 10 is an isometric view of a treatment system.
Figure 11 is a cross-sectional view of a tracheal catheter taken along a line 11-11.

Figure 12 is a cross-sectional view of the tracheal catheter taken along a line 12-12.
Figure 13 is an isometric view of an electrode assembly.
Figure 14 is a cross-sectional view of the electrode assembly of Figure 13 taken along a line 14-14.
Figure 15 is a partial cross-sectional view of a treatment system with a catheter extending out of a delivery apparatus.
Figure 16 is a side elevational view of a deployed energy delivery assembly with fluid flowing through an energy emitter assembly.
Figure 17 is a cross-sectional view of the deployed energy delivery assembly with fluid flowing through an expandable member.
Figure 18 is a cross-sectional view of the energy delivery assembly with fluid flowing into the expandable member.
Figure 19 is an elevational view of the ablation assembly with fluid flowing through the energy emitter assembly.
Figure 20 is a side elevational view of an electrode adjacent a cartilaginous ring.
Figure 21 is a side elevational view of electrodes positioned between cartilaginous rings.
Figure 22 is an isometric view of an ablation assembly with a pair of electrodes.
Figure 23 is an isometric view of an ablation assembly with three electrodes.
Figure 24A is a schematic view of a treatment system employing monopolar electrodes for pulmonary treatment and an esophageal device in a subject.
Figure 24B is a schematic view of an embodiment of the present invention employing monopolar electrodes for treatment.
Figure 25A is a schematic view of a tracheal device and an esophageal device in a subject.
Figure 25B is a schematic view of an embodiment employing trachea-to-esophagus circumferential bipolar electrodes.
Figure 26 illustrates a circumferential bipolar energy distribution possible with the embodiment of Figures 25A and 25B.
Figure 27 is a schematic view of an embodiment employing trachea-to-esophagus bipolar, anterior esophageal return electrodes.
Figure 28 illustrates a bipolar energy density distribution possible with the embodiment of Figure 27.
Figure 29 is a schematic view of an embodiment of the present invention employing trachea-to-esophagus bipolar, posterior isolated electrodes.
Figure 30 illustrates a bipolar energy distribution possible with the embodiment of Figure 29.
Figures 31A and 32B are schematic views of an embodiment of the present invention employing trachea-to-esophagus bipolar electrodes with no balloon support.
Figure 32 is an elevational view of an exemplary basket embodiment according to the present invention.
Figures 33A and 33B are schematic views of an embodiment employing a bipolar wire cage with circumferential electrode bands.
Figures 34A and 34B are schematic views of an embodiment of the present invention employing bipolar balloons with circumferential electrode bands.
Figure 35 is a schematic view of an embodiment of the present invention employing tracheal bipolar electrodes with a single tracheal protection zone.
Figure 36A is a schematic view of an embodiment of the present invention in an airway and employing tracheal bipolar electrodes with a dual tracheal protection zone.
Figure 36B is a schematic view of the tracheal device of Figure 36A.
Figure 36C is a top plan view of the tracheal device of Figure 36A.
Figures 37A-37C are schematic views of an embodiment of the present invention employing inter-cartilage electrodes in a stacked ring configuration.
Figures 38A and 38B are schematic views of an embodiment of the present invention employing inter-cartilage electrodes in a coiled configuration.
Figures 39A and 39B are schematic views of an embodiment of the present invention employing inter-cartilage electrodes with a winding adjustment element.
Figures 40A and 40B are schematic views of an embodiment of the present invention employing inter-cartilage electrodes with adjustable D-shaped rings in a bipolar configuration.
Figures 41A and 41B are schematic views of an embodiment of the present invention employing inter-cartilage electrodes with adjustable D-shaped rings in a bipolar configuration with cooling means.
Figure 42 is a schematic view of an embodiment of the present invention employing an esophageal protection device.
Figure 43 is a schematic view of an embodiment of the present invention employing esophageal protection with conductive elements.
Figure 44 is a schematic view of an embodiment of the present invention employing a distal occlusion device with a gas protectant.
Figure 45 is a schematic view of an embodiment of the present invention employing a distal occlusion device with

a gas protectant and conductive elements.
Figure 46 is a schematic view of an embodiment of the present invention employing a distal occlusion device with a gas protectant and conductive elements showing the protective gas flow.
Figure 47 is a schematic view of an embodiment of the present invention employing a multi-slot coaxial microwave antenna.
Figure 48A is a schematic side view of a tracheal device employing a single antenna microwave system.
Figure 48B is a schematic view of the tracheal device of Figure 48A.
Figure 49 is a side view of a tracheal device.
Figure 50A is a schematic side view of a tracheal device with a dual antenna microwave system.
Figure 50B is a schematic front view of the tracheal device of Figure 53A.
Figure 51A is a schematic side view of a tracheal device with a dual antenna microwave system and an esophageal reflector/protector.
Figure 51B is a schematic front view of the tracheal device and esophageal reflector/protector device of Figure 51A.
Figure 52A is a schematic side view of a tracheal device with a microwave device with a cooling or coupling jacket.
Figure 52B is a schematic front view of the tracheal device of Figure 55A.
Figure 53 is a cross-sectional view of a tracheal device positioned within the trachea.
Figure 54A is a schematic view of an alternative embodiment of the present invention employing a microwave device with a cooling/coupling element.
Figure 54B illustrates a specific absorption rate profile generated by the treatment system of Figure 54A.
Figure 54C is a graph of an axial profile along a specific absorption rate observation line.

DETAILED DESCRIPTION

[0030] Throughout this disclosure, the words disrupt, ablate, modulate, denervate will be used. It should be understood that these globally refer to any manipulation of the nerve that changes the action of that nerve. This can be a total cessation of signals, as in ablation or severing, or it can be a modulation, as is done by partial or temporary disruption, pacing, etc.

[0031] Similarly, trachea is often used to describe a segment wherein the devices and methods will be used. It should be understood that this is shorthand and can be meant to encompass the trachea itself, as well as the right and left main bronchi and other portions of the pulmonary tree as necessary.

[0032] It should be noted that the pulmonary nerves referred to in the disclosure not only include nerves that innervate the pulmonary system but also any neural structures that can influence pulmonary behavior. For example, elements of the cardiac plexus, or the nerves that innervate the esophagus, also interact with the airways and may contribute to asthmatic conditions. The nerves can include nerve trunks along the outer walls of hollow vessels, nerve fibers within the walls of hollow vessels (*e.g.,* the wall of the trachea and/or esophagus), nerves within a bridge between the trachea and esophagus, or at other locations. The left and right vagus nerves originate in the brainstem, pass through the neck, and descend through the chest on either side of the trachea. These nerves can be targeted. The vagus nerves spread out into nerve trunks that include the anterior and posterior pulmonary plexuses that wrap around the trachea, the left main bronchus, and the right main bronchus. The nerve trunks also extend along and outside of the branching airways of the bronchial tree. Nerve trunks are the main stem of a nerve comprising a bundle of nerve fibers bound together by a tough sheath of connective tissue. The vagus nerves, including their nerve trunks, along the trachea or other nerve tissue along, proximate to, or in the bronchial tree can be targeted. A treatment device in the form of a tracheal device can be positioned at different locations within an airway (*e.g.,* the trachea, one of the main stem bronchi, or other structures of the bronchial tree).

[0033] The pulmonary branches of the vagus nerve along the left and right main stem bronchus intermedius are particularly preferred targets. The nerve trunks of the pulmonary branches extend along and outside of the left and right main stem bronchus and distal airways of the bronchial tree. Nerve trunks of the main stem nerve comprise a bundle of nerve fibers bound together by a tough sheath of connective tissue. Any number of procedures can be performed on one or more nerve trunks to affect the portion of the lung associated with those nerve trunks. Because some of the nerve tissue in the network of nerve trunks coalesce into other nerves (*e.g.,* nerves connected to the esophagus, nerves though the chest and into the abdomen, and the like), specific sites can be targeted to minimize, limit, or substantially eliminate unwanted damage of those other nerves.

[0034] Some fibers of anterior and posterior pulmonary plexuses coalesce into small nerve trunks which extend along the outer surfaces of the trachea and the branching bronchi and bronchioles as they travel outward into the lungs. Along the branching bronchi, these small nerve trunks continually ramify with each other and send fibers into the walls of the airways. Any of those nerve trunks or nerve tissue in walls can be targeted. Various procedures that may be performed with at least some of the devices and methods of embodiments of the present invention are described in copending application Serial No. 12/463,304 filed on May 8, 2009, which is incorporated herein by reference in its entirety.

[0035] As illustrated in Figure 1, the C-shaped structure 10 that separates the inner elements of the airway-the smooth muscle 12, goblet cells 16, mucosa, anterior plexus nerves 22, posterior plexus nerves 23, epithelium 24, nerves 25, arteries 26, etc.,-from the nerves are thick bands of cartilage 10. These bands 10 cover the majority of the circumference of the trachea and larger bronchi, with a discontinuity only along the posterior segment where the trachea and esophagus are coincident. As further shown in Figure 2, these bands 10a, 10b, 10c (collectively "10") are discrete elements, arranged longitudinally along the length of the trachea 18 and large bronchi, with thinner areas of connective tissue between them. The anterior plexus runs outside of these bands. So it can be seen that any modality designed to sever or disrupt these nerves will be heavily guarded against by these rings.

[0036] A different complication exists along the posterior border where the discontinuity in the cartilage bands exists. Here, the trachea and esophagus are coincident, connected to one another by an area of connective tissue. Here the problem is the opposite of that on the posterior side. The esophagus can be easily damaged by devices operating from within the lung to disrupt or modulate the nerves running between the two lumens. A rare but fatal complication of cardiac ablation for the treatment of atrial fibrillation occurs when ablations performed within the heart create a weakness along the esophagus (the posterior left atrium is also adjacent the esophagus). In some cases, this weakness turns into a fistula, causing atrial rupture, massive hemorrhage and death. So it is critical to protect these ancillary structures or to direct the means for disruption or modulation away from them.

[0037] It can be seen from these descriptions of the anatomy of the trachea 18 and esophagus 30 that (as shown in Figure 3) energy or treatment means directed at or through the posterior wall 31 of the trachea 18, or the anterior wall 32 of the esophagus 30, would have direct access to the posterior pulmonary plexus 23.

[0038] A potential region of interest for pulmonary nerve therapy is further described with reference to Figure 4A. Nerves which supply the pulmonary plexus arise from multiple levels of the thoracic spine 38 as well as multiple levels of the vagus nerve. Treatment and/or therapy delivery may occur anywhere within this potential target region 40, as a single treatment or as a plurality of treatments, administered in a single treatment session or staged over multiple sessions.

[0039] To modulate or disable the pulmonary nerves, it can be seen from the above anatomical descriptions that protection and or therapy can be delivered via the trachea 18, main stem bronchii or other airways further distally in the bronchial tree, the esophagus 30, or combinations of these. Following are brief descriptions of a number of different embodiments wherein energy is delivered to the targeted nerves through combinations of devices, or in some embodiments, through a single device. The targeted nerves can run along the trachea 18 and the esophagus 30, between the trachea 18 and the esophagus 30, or other suitable locations. For example, nerve tissue within walls of the trachea 18 and/or the esophagus 30 can be destroyed or otherwise altered. Alternatively or additionally, nerve trunks running along the outer wall of the trachea 18 and/or the esophagus 30 can be altered or destroyed.

[0040] In addition to the potential access to the pulmonary plexus 23 from the area of the trachea 18 and the correlated area in the esophagus 30, it can be seen from Figure 4A that a good number of branches from the thoracic ganglia 40 converge in the area of the carina, and the areas of the upper right bronchi 42 and upper left bronchi 44. Thus, the esophagus 30 may still need to be protected if tissue modification is to be done in the area of the carina, but as the target area moves more distally down the right and left bronchi, the need for esophageal protection diminishes.

[0041] Another reason that it may be beneficial to focus the treatment area more towards the individual right and left bronchi 42, 44 is that the recurrent laryngeal nerve may in some cases be collocated with nerves supplying the pulmonary plexus as they travel down the tracheal/esophageal interface to the lower areas of the plexus. Damage to the laryngeal nerve was shown in the surgical literature for pulmonary sympathectomy to be associated with complications of speech and swallowing, so preserving its function is critical.

[0042] Of note, as the treatment zone is located farther down the bronchial tree, past the carina and away from the trachea, the cartilaginous rings become completely circumferential-the area of non-coverage which was available for exploitation by a treatment device is no longer present. With this in mind, devices targeting regions of full cartilaginous coverage may have the requirement that they need to traverse and deliver therapy around, between or through these rings in order to reach the target nerves.

[0043] According to certain embodiments of the invention, devices may be configured for the delivery of radio frequency energy to modulate or disable the pulmonary plexus. While embodiments shown are configured for delivery of RF energy, many of the configurations can also be adapted to accommodate a catheter based microwave antenna, high energy pulse electroporation, or similar energy modalities.

[0044] The RF energy can be delivered in a traditional conductive mode RF, where the energy is directly applied to the tissue through a direct contact electrode, or it can be delivered through the use of capacitive coupling to the tissue. In capacitive coupling, a slightly higher frequency signal is typically used compared to traditional RF, and the energy is delivered to the tissue across a dielectric, which is often a cooling element. In one example of capacitive coupling, energy may be delivered across a cooling plate that keeps the surface of tissue contacted from being harmed as energy is delivered deeper into the target tissue.

[0045] The RF energy can be delivered to different target regions, which can include, without limitation, nerve tissue (*e.g.,* tissue of the vagus nerves, nerve trunks, etc.), fibrous tissue, diseased or abnormal tissues (*e.g.,* cancerous tissue,

inflamed tissue, and the like), cardiac tissue, muscle tissue, blood, blood vessels, anatomical features (*e.g.,* membranes, glands, cilia, and the like), or other sites of interest. In RF ablation, heat is generated due to the tissue resistance as RF electrical current travels through the tissue. The tissue resistance results in power dissipation that is equal to the current flow squared times the tissue resistance. To ablate deep tissues, tissue between an RF electrode and the deep tissue can become heated if active cooling is not employed using a cooling device, such as a cooling plate or cooling balloon. The cooling device can be used to keep tissue near the electrode below a temperature that results in cell death or damage, thereby protecting tissue. For example, cooling can prevent or limit overheating at the electrode-tissue interface. Overheating (*e.g.,* tissue at temperatures above 95°C to about 110°C) can lead to the formation of coagulum, tissue desiccation, tissue charring, and explosive outgassing of steam. These effects can result in increased tissue resistance and reduced RF energy transfer into the tissue, thereby limiting the effective RF ablation lesion depth. Active cooling can be used to produce significantly deeper tissue lesions. The temperature of coolant for active cooling can be about 0°C to about 24°C. In some embodiments, the coolant and electrode produce a lesion at a therapeutic depth of at least about 3 mm while protecting tissue at shallower depths from lethal injury. In some embodiments, the lesions can be formed at a depth of about 3 mm to about 5 mm to damage nerve tissue. Other temperatures and depths can be achieved.

[0046] Figure 5 shows a system 204 including a pulmonary treatment device in the form of a tracheal catheter 207 positioned in the trachea 18 and a protection device 205, or temperature control device, positioned in the esophagus 30. An energy delivery assembly 208 is positioned to deliver energy to ablate targeted tissue between the trachea 18 and esophagus 30 while protecting non-targeted tissue. The temperature control device 205 includes a protection member 212 that absorbs heat to cool and protect tissue of the esophagus 30, thereby inhibiting damage to esophageal tissue. The tracheal catheter 207 can deliver a sufficient amount of energy to the trachea wall to heat and damage target tissue while the temperature control device 205 absorbs a sufficient amount of heat from the esophagus wall to inhibit damage to esophageal tissue while the target tissue is damaged. The tracheal device 204 and the temperature control device 205 can cooperate to ablate or otherwise alter targeted tissue, such as the pulmonary plexus 32.

[0047] It will be understood that, with regard to any of the embodiments described herein, while described here for use in the trachea, the devices and methods of the invention may be used for treatment in more distal airways including the mainstem bronchii, broncus intermedius, and more distal branches of the bronchial tree. Thus the terms "tracheal device" and the like are not intended to be limited to devices used in the trachea and may be interpreted to mean devices for use in any location in the trachea or bronchial tree where nerve tissue may be targeted to treat asthma and other pulmonary diseases using the techniques described herein.

[0048] Referring to Figures 6 and 7, if the energy delivery assembly 208 includes an energy delivery element in the form of an RF electrode 214, the electrode 214 can be brought into contact with or proximate to an inner surface of the trachea 18. The RF electrode 214 can output RF energy which travels through the tissue and is converted into heat. The heat causes formation of a lesion. The RF energy can be directed radially outward towards the targeted tissue without causing appreciable damage to non-targeted tissue (*e.g.,* tissue of the esophagus 30, inner tissue of the trachea 18, anterior tissue of the trachea 18) using coolant (represented by arrows 201). A wide range of different procedures, such as, for example, denervation of a portion of the trachea 18, an entire circumference of the trachea 18, target nerve trunks travelling to one lung or both lungs, or the like. Nerve tissue is damaged to relax the muscle tissue in the bronchial tree to dilate the airway to reduce air flow resistance in one or both lungs, thereby allowing more air to reach the alveolar sacs for the gas exchange process. Decreases in airway resistance may indicate that passageways of airways are opening, for example in response to attenuation of nervous system input to those airways. The balloon 212 can absorb heat to cool the anterior region 203 (shown removed in Figure 7) of the trachea 18. Emitter assembly 220 wraps around the balloon 212 to contact the posterior region 202 of the trachea 18, as shown in Figure 6. The emitter assembly 220 extends along the balloon 212 to a distal tip 197.

[0049] A physician can select and ablate or otherwise alter appropriate nerve tissue to achieve a desired decrease in airway resistance, which can be measured at a subject's mouth, a bronchial branch that is proximate to the treatment site, a trachea, or any other suitable location. The airway resistance can be measured before performing the therapy, during the therapy, and/or after the therapy. In some embodiments, airway resistance is measured at a location within the bronchial tree by, for example, using a vented treatment system that allows for respiration from areas that are more distal to the treatment site. Any number of procedures can be used to treat asthma, COPD, and other diseases, conditions, or symptoms.

[0050] The temperature control device 205 of Figure 6 includes an elongate member 211 connected to the inflatable member 223. Media, such as chilled saline, flows through an input lumen 213 and circulates through a chamber 215. The media absorbs heat and exits the chamber 215 through an outlet 217. The media flows proximally through an output tube 216. The longitudinal length of the inflatable member 223 can be longer than a longitudinal length of the energy delivery assembly 208 to ensure that a longitudinal section of tissue extending distally and proximally of the targeted tissue is cooled to avoid unwanted tissue alteration, for example, tissue damage.

[0051] Figures 8A and 8B show isotherms. By adjusting the rate of power delivery to an electrode 214, the rate at which media is passed into the energy delivery assembly 208, the rate at which media is passed into the inflatable

member 212, the temperatures of the media, the sizes and configuration of energy delivery assembly 208/inflatable member 212, and the exact contour and temperature of the individual isotherms can be modified. An energy distribution can be produced which results in isotherm A being warmest and, moving radially outward from isotherm A, each successive isotherm becomes cooler, with isotherm F being coolest. At minimum, the temperature at isotherm A will be high enough to produce cell death in the target tissue. In at least some preferred embodiments, isotherm A will be in a range of about 50°C to about 90°C, more preferably about 60°C to about 85°C, and most preferably about 70°C to about 80°C. Isotherm F will be at or around body temperature, and the intervening isotherms will be at intervals between body temperature and the temperature at isotherm A. For example, by selecting the proper temperature and flow rate of saline and the rate of power delivery to the electrode, it is possible to achieve temperatures in which isotherm A = 70°C, B = 55°C, C = 50°C, D = 45°C, E = 40°C, and F = 37°C. In some tissues, a lethal temperature may be greater than or equal to about 70°C. For example, the A isotherm can be about 75°C to about 80°C to form lesions in nerve tissue. Different isotherms and temperature profiles can be generated for different types of tissue because different types of tissue can be affected at different temperatures. Further adjustments make it possible to achieve temperatures where isotherm A = 50°C, B = 47.5°C, C = 45°C, D = 42.5°C, E = 40°C, and F = 37°C. Alternative adjustments make it possible to achieve temperatures where isotherm A is equal to or greater than 90°C, B = 80°C, C = 70°C, D = 60°C, E = 50°C, and F = 40°C. Only those areas contained within the A and B isotherms will be heated enough to induce cell death for certain types of tissue. Other temperature ranges are also possible depending on the lethal temperature of the target tissue. In some procedures, tissue at a depth of about 2 mm to about 8 mm in the airway wall can be ablated while other non-targeted tissues at a depth of less than 2 mm in the airway wall are kept at a temperature below a temperature that would cause cell death. The isotherms of Figure 8A can be generated without cooling using the temperature control device 205. By cooling tissue using the temperature control device 205, the isotherms generate bands, as illustrated in Figure 8B. Advantageously, the interior tissues of the trachea 18 and the esophagus 30 can be undamaged while deep tissue, including nerve tissue 23, is damaged.

[0052] The RF electrode 214 can be positioned at other locations. Figure 9 shows the RF electrode 214 positioned to target the right anterior plexus 22. After each application of energy, the energy delivery assembly 208 can be angularly rotated to treat a different section of the trachea wall. In some procedures, an entire circumference of the trachea wall 18 can be treated. In other embodiments, circumferential segments of the trachea wall 18 are treated to target specific tissue while minimizing tissue damage of adjacent sections of the trachea wall. Throughout the procedure, the temperature control device 205 can cool the esophageal tissue.

[0053] Different amounts of energy can be delivered to different sections of the trachea 18. Energy delivered at a first power level from the electrode 214 can create a first lesion covering a first portion of a circumference of the airway. Energy delivered at a second power level from the electrode 214 can create a second lesion covering a second portion of the circumference of the airway displaced from the first portion. The first power level is substantially different (*e.g.,* greater) than the second power level. For example, the second power level can be about 40% to about 90% of the first power level, more preferably about 50%-80% of the first power level. The second power level can be selected to avoid permanent injury to non-target tissue proximate to the treatment site. The second portion can be circumferentially or axially displaced from the first portion relative to lumen of the airway. The first portion of the circumference can be on an anterior aspect of the airway, and the second portion can be on a posterior aspect of the airway.

[0054] Because the anterior region of the trachea 18 is spaced well apart from the esophagus 30, a higher amount of energy can be used to ablate the pulmonary plexus 22. As the electrode 214 is rotated towards the esophagus 30, the amount of emitted energy can be reduced. This can help minimize, limit, or substantially eliminate tissue damage to the esophageal tissue. Different amounts of energy can be delivered to different regions (*e.g.,* circumferential locations) of the trachea 18. A relatively high amount of energy can be delivered to the anterior region of the trachea 18 as compared to the amount of energy delivered to the posterior region of trachea 18. A lower amount of energy can be delivered to the posterior tissue of the trachea 18 to avoid damage to esophagus tissue. In some protocols, about 20 watts of energy is delivered to electrode 214 to ablate tissue located at the anterior region of the trachea 18. The electrode 214 can emit no more than about 15 watts of energy when it is positioned to contact the posterior region of the trachea 18. In various procedures, the amount of energy delivered to the electrode 214 can be at least about 40% but less than 90% of the energy delivered to the electrode 214 at a different region of the trachea 18. In certain embodiments, the amount of energy emitted by the electrode 214 positioned along the posterior portion of the trachea 18 is in a range of about 50% to about 80% of the energy delivered to the electrode 214 positioned at the anterior portion of the trachea 18. In other embodiments, the amount of energy emitted by the electrode 214 positioned along the posterior portion of the trachea 18 is in a range of about 60% to about 90% of the energy delivered to the electrode 214 positioned at the anterior portion of the trachea 18. Other relative percentages are also possible.

[0055] As the mainstem bronchi pass from the lung root at the main carina out towards the lungs, a variety of external structures lie in close proximity to their outer surfaces. Anteriorly, these external structures are the pulmonary arteries and veins, aorta and superior vena cava; medially they are the soft tissues of the mediastinum and the heart; laterally the external structure is the lung parenchyma; posteriorly on the right it is again lung parenchyma; proximally on the left

it is the esophagus; and distally it is the lung. Additionally, the continuation of the left main vagus nerve as it passes inferiorly to innervate the abdomen and pelvis is interposed between the esophagus and the left main bronchi.

[0056] Due to the high rate of blood flow through the blood vessels and the heart, these structures are effective heat sinks and much of the heat generated during treatment is removed from their walls during treatment. Thus, the walls of the blood vessels and of the heart are relatively unaffected by the treatment. The mediastinal soft tissues and the lung lack the heat sinking effect seen in the blood vessels and heart, but they may tolerate thermal injury without untoward clinical consequences. However, the esophagus and interposed vagus nerve lack significant blood flow and may be susceptible to thermal injury during treatment in the left mainstem bronchus.

[0057] In one procedure, the treatment site to which RF energy is applied is the most distal centimeter of the left mainstem bronchus. Because the esophagus 30 runs along the posterior aspect of the proximal potion of the left mainstem bronchus, at this most distal aspect of the bronchus, the posterior wall is in contact with lung parenchyma only. Thus, the RF energy can be delivered to the most distal centimeter of the left mainstem bronchus to avoid injury to the esophagus 30. Other types of energy can also be delivered to this location.

[0058] In another procedure, the posterior wall of the left mainstem bronchus is either not treated or is treated with a lower dose of energy, while the remainder of the airway's circumference is treated with a higher dose of energy. When the balloon 212 of Figures 5 and 6 has a longitudinal length of about 8 mm to about 12 mm, the electrode 214 can be cooled with either room temperature water or iced water coolant passing through the electrode 214 and balloon 212. In certain procedures, the rate of flow of the water or coolant through the balloon 212 and the electrode 214 can be maintained at about 100 ml per minute for a treatment duration of about 120 seconds, while power levels are maintained at less than 15 W applied on the posterior wall of the mainstem bronchus to cause substantially no injury to the esophagus 30 or the interposed vagus nerve. Other combinations of electrode size, coolant, coolant temperature, coolant flow, treatment duration and power could be used to achieve the same results.

[0059] Referring to Figure 10, the treatment system 204 includes a media delivery system 246 and a control module 210 coupled to an elongate member in the form of a shaft 230 of the catheter 207. The temperature control device 205 is coupled to the media delivery system 246. An electrode pad 219 for placement against the patient is connected to the control module 210. Energy delivery assembly 208 comprises an emitter assembly 220 extending from the elongate shaft 230 and wrapping around a balloon 212. The balloon 212 can be inflated from a collapsed state (see Figure 15) to the expanded state shown in Figure 10. As the balloon 212 inflates, the electrode 214 can be moved towards the airway wall. The fully inflated balloon 212 can hold the electrode 214 near (*e.g.,* proximate or in contact with) tissue through which energy is delivered. The coolant can absorb thermal energy to cool the balloon 212 or the energy emitter assembly 220, or both. This in turn cools the outer surface of the airway wall.

[0060] The control module 210 can include, without limitation, one or more computers, processors, microprocessors, digital signal processors (DSPs), field programmable gate arrays (FPGA), computing devices, and/or application-specific integrated circuits (ASICs), memory devices, buses, power sources, and the like. For example, the control module 210 can include a processor in communication with one or more memory devices. Buses can link an internal or external power supply to the processor. The memories may take a variety of forms, including, for example, one or more buffers, registers, random access memories (RAMs), and/or read-only memories (ROMs). Programs, databases, values, or other information can be stored in memory. For example, in some embodiments, the control module 210 includes information associated with tissue characteristics. A comparison can be performed between sensed tissue characteristics and stored tissue characteristics. Operation of the catheter 207 can be adjusted based, at least in part, on the comparison. Different types of reference values (*e.g.,* reference values for non-treated tissue, reference values for treated tissues, impedance values, etc.) corresponding to tissue characteristics can be utilized in such a protocol. The control module 210 may also include a display 244, such as a screen, and an input device 245. The input device 245 can include one or more dials, knobs, touchpads, or a keyboard and can be operated by a user to control the catheter 207. Optionally, the input device 245 can also be used to control operation of the temperature control device 205.

[0061] The control module 210 can store different programs. A user can select a program that accounts for the characteristics of the tissue and desired target region. For example, an air-filled lung can have relatively high impedance, lymph nodes have medium impedance, and blood vessels have relatively low impedance. The control module 210 can determine an appropriate program based on the impedance. A differential cooling program can be executed to deliver different temperature coolants through the balloon 212 and the emitter assembly 220. The temperature difference can be at least 10°C. Performance can be optimized based on feedback from sensors that detect temperatures, tissue impedance, or the like. For example, operation of the energy delivery assembly 208 can be controlled based on a surface temperature of the tissue to which energy is delivered. If the surface temperature becomes excessively high, cooling can be increased and/or electrode power decreased in order to produce deep lesions while protecting surface tissues.

[0062] The control module 210 can function as an energy generator, such as a radio frequency (RF) electrical generator. RF energy can be outputted at a desired frequency. Example frequencies include, without limitation, frequencies in a range of about 50 KHZ to about 1,000 MHZ. When the RF energy is directed into tissue, the energy is converted within the tissue into heat causing the temperature of the tissue to be in the range of about 40°C to about 99°C. The RF energy

can be applied for about 1 second to about 120 seconds. In some embodiments, the RF generator has a single channel and delivers approximately 1 to 25 watts of RF energy and possesses continuous flow capability. Other ranges of frequencies, time intervals, and power outputs can also be used. An internal power supply 248 can be an energy storage device, such as one or more batteries. Electrical energy can be delivered to the energy emitter assembly 220, which converts the electrical energy to RF energy or another suitable form of energy. Other forms of energy that may be delivered include, without limitation, microwave, ultrasound, direct current, or laser energy. Alternatively, cryogenic ablation may be utilized wherein a fluid at cryogenic temperatures is delivered through the shaft 230 to cool a cryogenic heat exchanger on the assembly 208.

[0063] Referring again to Figures 5 and 10, the control module 210 can have one or more communication devices to wirelessly, optically, or otherwise communicate with the media delivery system 246. Pumps of the media delivery system 246 can be operated based on the signals. In other embodiments, the control module 210 can include the media delivery system 246. A single unit can therefore control operation of the catheter 207 and the temperature control device 205.

[0064] The media delivery system 246 can pump cooling media through the pulmonary treatment device 207 and the temperature control device 205 and includes a media container 260a coupled to a supply line 268 and a media container 260b coupled to a return line 272. Luer connectors or other types of connectors can couple the lines 268, 272 to lines 273, 275. The media container 260a can include a container (*e.g.,* a bottle, a canister, a tank, a bag, or other type of vessel for holding fluid or other media). In pressurizable embodiments, the media container 260a includes one or more pressurization devices *(e.g.,* one or more pumps, compressors, or the like) that pressurize coolant. Temperature control devices (*e.g.,* Peltier devices, heat exchangers, or the like) can cool or recondition the fluid. The media can be a coolant including saline, deionized water, refrigerant, cryogenic fluid, gas, mixtures thereof, or the like.

[0065] In other embodiments, the media container 260a can be an insulated container that holds and delivers a chilled coolant to the supply line 268. In embodiments, the media container 260a is bag, such as an IV type bag, configured to be held on a pole.

[0066] The balloon 212 optionally has a sensor 247 (illustrated in dashed line in Figure 10) that is communicatively coupled to the control module 210. The control module 210 can command the catheter 207 based on signals from the sensor 247 (*e.g.,* a pressure sensor, a temperature sensor, a thermocouple, a pressure sensor, a contact sensor, an impedance sensor, or the like). Sensors can also be positioned on energy emitter assembly 220, along the elongate shaft 230, or at any other location. In a closed loop system, the electrical energy is delivered to the electrode 214 based upon feedback signals from one or more sensors configured to transmit (or send) one or more signals indicative of one or more tissue characteristics, energy distribution, tissue temperatures, or any other measurable parameters of interest. Based on those readings, the control module 210 adjusts operation of the electrode 214. Alternatively, in an open loop system, the operation of the electrode 214 is set by user input. For example, the user can observe tissue temperature or impedance readings and manually adjust the power level delivered to the electrode 214. Alternatively, the power can be set to a fixed power mode. In yet other embodiments, a user can repeatedly switch between a closed loop system and an open loop system.

[0067] In certain procedures, the sensor 247 can sense one or more tissue characteristics. The control module 210 can analyze the sensed tissue characteristics. For example, the control module 210 compares at least one sensed tissue characteristic to at least one stored reference value to, for example, evaluate the location of the electrode 214 relative to the airway. The evaluation can include, without limitation, determining the position of the electrode 214 relative to a reference location. The control unit 210 can estimate the location of at least one non-target structure or tissue based on impedance and/or other measurable characteristic. After estimating the location of the non-target structure or tissue, the electrode 214 can be repositioned before delivering energy so as to avoid injury to the non-target structures or tissue. Previously treated tissue can be detected based on impedance and/or other measurable characteristics. The electrode 214 can be activated to treat the airway when it is determined that the electrode 214 is located in the desired position.

[0068] Media flowing through the conduit 234 cools the electrode 214. Alternatively, flow diverters within the balloon 212 can direct some or all of the coolant in the balloon 212 towards the electrode 214 or a balloon sidewall and may provide a separate cooling channel for the electrode 214. In some embodiments, one or more cooling channels extend through the electrode 214 (*e.g.,* electrode 214 may be tubular so that coolant can flow through it). In other embodiments, the coolant flows around or adjacent the electrode 214. For example, an outer member, illustrated as the conduit 234 in Figure 10, can surround the electrode 214 such that fluid can flow between the electrode 214 and the conduit 234. Additionally or alternatively, the energy delivery assembly 208 can be actively cooled or heated using one or more thermal devices (*e.g.,* Peltier devices), cooling/heating channels, or the like.

[0069] Referring to Figures 10 and 11, the elongate shaft 230 extends from the control module 210 to the energy delivery assembly 208 and includes a power line lumen 320, a delivery lumen 324, and a return lumen 326. A power line 280 extends through the power line lumen 320 and couples the control module 210 to the electrode 214. The delivery lumen 324 provides fluid communication between the media container 260a and the energy emitter assembly 220 and balloon 212. The return lumen 326 provides fluid communication between the balloon 212 and/or electrode 214 and the fluid receptacle 260b. The elongate shaft 230 can be made, in whole or in part, of one or more metals, alloys (*e.g.,* steel

alloys such as stainless steel), plastics, polymers, and combinations thereof, as well as other biocompatible materials, and can be flexible to pass conveniently along highly branched airways. Sensors can be embedded in the elongate shaft 230 to detect the temperature of the fluids flowing therethrough.

[0070] Figure 12 shows the electrode 214 positioned in a channel 330 of the conduit 234 and includes a coolant channel 340. The electrode main body 350 can be a rigid tube made, in whole or in part, of metal (*e.g.,* titanium, stainless steel, or the like). In some embodiments, conduit 234 does not extend over the entire electrode 214, leaving a central portion of the tubular electrode exposed for direct contact with the airway wall. In other embodiments, the electrode main body 350 is made, in whole or in part, of a shape memory material. Shape memory materials include, for example, shape memory metals or alloys (*e.g.,* Nitinol), shape memory polymers, ferromagnetic materials, combinations thereof, and the like. These materials can assume predefined shapes when released from a constrained condition or different configurations when activated with heat. In some embodiments, the shape memory material can be transformed from a first preset configuration to a second preset configuration when activated (*e.g.,* thermally activated).

[0071] As shown in Figures 13 and 14, sensors 360a, 360b (collectively "360") are coupled to the electrode main body 350. A pair of lines 370a, 370b (collectively "370") pass through the channel 340 and are coupled to the sensors 360a, 360b, respectively. In some embodiments, the sensor 360a is a contact sensor, and the sensor 360b is a temperature sensor, impedance sensor, and/or a pressure sensor. The number, positions, and types of sensors can be selected based on the treatment to be performed.

[0072] In multilayer embodiments, the electrode main body 350 can include at least one tube (*e.g.,* a non-metal tube, a plastic tube, etc.) with one or more films or coatings. The films or coatings can be made of metal, conductive polymers, or other suitable materials formed by a deposition process *(e.g.,* a metal deposition process), coating process, etc., and can comprise, in whole or in part, silver ink, silver epoxy, combinations thereof, or the like.

[0073] Radio-opaque markers or other types of visualization features can be used to position the main body 350. To increase visibility of the electrode 214 itself, the electrode 214 may be made, in whole or in part, of radiographically opaque material.

[0074] Figures 15-17 show one exemplary method of using a treatment system 200. A physician can visually inspect the airway 100 using a delivery apparatus 206 to locate and evaluate the treatment site(s) and non-targeted tissues before, during, and/or after performing a therapy. The airway 100 can be part of the trachea, main stem bronchi, or any other airway of the bronchial tree. A delivery apparatus 206 can be a bronchoscope, a guide tube, a delivery sheath, or an endoscope and can include one or more viewing devices, such as optical viewing devices (*e.g.,* cameras), optical trains (*e.g.,* a set of lenses), and the like. For example, the delivery apparatus 206 can be a bronchoscope having one or more lights for illumination and optical fibers for transmitting images. The catheter 207 may be adapted to be delivered over a guidewire (not shown) that passes between the balloon 212 and the energy emitter assembly 220. This provides for rapid exchange capabilities.

[0075] When the delivery apparatus 206 of Figure 15 is moved along a body lumen 101 (*e.g.,* an airway), the collapsed energy delivery assembly 208 is held within a working channel 386 of the delivery apparatus 206. The conduit 234 can form a loop 221 such that the electrode 214 is almost parallel to a long axis 373 when the catheter 207 is in a substantially straight configuration. In the illustrated embodiment of Figure 15, an angle β is defined between the direction of the long axis 373 of the catheter 207 and a long axis 374 of the electrode 214. The angle β can be in a range of about 0 degrees to about 30 degrees. In some embodiments, the angle β is in a range of about 0 degrees to about 20 degrees. The electrode 214, being curved, can also nest with and partially encircle the elongate shaft 230. In certain embodiments, at least a portion of the elongate shaft 230 is disposed within an arc of the electrode 214 for a further reduced profile. As such, the shaft 230 can be positioned between the ends of the electrode 214. Electrode 214 may have various lengths, depending on the desired length of the lesion to be created in each electrode position. In preferred embodiments, electrode 214 has a length of at least about 1 mm to about 4 mm. In certain embodiments, the length of the electrode 214 is about 2 mm up to about 3 mm. The electrode can have a width (or diameter if cylindrical) no larger than the width of the spaces between the cartilage rings, in some embodiments being about 0.1 mm to about 3 mm.

[0076] With continued reference to Figure 15, the diameter D_L of the working channel 386 can be less than about 8 mm. The diameter D_B of the deflated balloon 212 can be relatively small. For example, a minimum diameter $D_{B\ min}$ can be in a range of about 2 mm to about 3 mm, and a maximum diameter $D_{B\ max}$ in a range of about 5 mm to about 6 mm when the balloon 212 is fully collapsed. If the electrode 214 is collapsible, the diameter D_{max} of the assembly 208 can be less than about 3 mm. In ultra low-profile configurations, the maximum diameter D_{max} can be less than about 2.8 mm.

[0077] The balloon 212 can be inflated to move the energy emitter assembly 220 near (*e.g.,* proximate to or in contact with) the airway 100. The angle P can be increased between 70 degrees and about 110 degrees when the balloon 212 is fully inflated. Figure 16 shows the energy delivery assembly 208 deployed, wherein the electrode 214 can be about perpendicular to the long axis 373. There can be play between the energy emitter assembly 220 and the balloon 212 such that the angle β is in a range of about 60 degrees to about 120 degrees in order to accommodate variations of anatomical structures, misalignment (*e.g.,* misalignment of the catheter shaft 230), or the like. In some embodiments, the electrode 214 moves towards a circumferentially extending orientation as it moves from a delivery orientation to the

deployed orientation. The electrode 214 in the deployed orientation extends substantially circumferentially along the wall of the airway 100. In certain embodiments, the electrode 214 will be configured to be positioned entirely within the spaces 375 between cartilage rings 376 along the airway wall when the energy delivery assembly 208 is in the fully deployed configuration.

[0078] Figures 16 and 17 show the energy emitter assembly 220 fluidically coupled to both the elongate shaft 230 and the balloon 212. Generally, coolant cools the tissue-contacting portion of the energy emitter assembly 220. The cooling section 209 of the energy delivery assembly 208 contacts the airway wall 100 so as to cool tissue adjacent to the tissue-contacting portion while energy is outputted by the electrode 214. The cooling section 209 can be formed by the portions of the energy emitting assembly 220 and the balloon 212 that contact the airway wall 100. If the electrode 214 faces an anterior region of the trachea 18, the assembly 208 can seat between cartilage rings 376 to avoid or limit movement of the electrode 214 along the length of the airway 100. If the energy delivery assembly 208 is positioned in the bronchial tree, especially in the main stem bronchi, the electrode 214 can be seated between spaced apart cartilage rings 376.

[0079] As the balloon 212 inflates, the electrode 214 moves (*e.g.,* pivots, rotates, displaces, etc.) from a first orientation of Figure 15 in which the electrode 214 extends axially along the airway 100 and a second orientation of Figure 16 in which the entire electrode 214 is disposed in a space 375 between adjacent cartilage rings 376a, 376b. The balloon 212 can both cool the airway 100 and cause the electrode 214 to seat in the space 375.

[0080] Figure 16 shows the energy emitter assembly 220 positioned to locate the electrode 214 in the space 375. In certain embodiments, the electrode 214, in the first orientation, extends a distance with respect to a longitudinal axis 373 (see Figure 15) that can be greater than the distance the electrode 214, in the second orientation, extends with respect to the longitudinal axis 373.

[0081] To deploy the energy emitting assembly 208, coolant from the elongate shaft 230 flows through the energy emitter assembly 220 and into the balloon 212. The electrode 214 can output a sufficient amount of energy to ablate a target region. The electrode 214 can be at a position corresponding to the anatomical location of at least one nerve in or proximate to the airway wall 100. The electrode 214 outputs energy to ablate the targeted nerve tissue. The coolant absorbs thermal energy from electrode 214 and the airway wall 100.

[0082] To treat tissue along the trachea, the diameter D_E of the electrode 214 and conduit 234 can be in a range of about 1.5 cm to about 2 cm when pressurized with coolant. In some embodiments, the diameter D_E of the electrode 214 and conduit 234 can be in a range of about 2 cm to about 2.5 cm to treat an average sized adult human. To treat tissue along one of the main stem bronchi, the diameter D_E can be in a range of about 1.5 mm to about 2.5 mm. Such embodiments are well suited to treat tissue outside the lung along the main bronchi. In certain embodiments, the diameter D_E is about 2 mm. In yet other embodiments, the diameter D_E can be in a range of about 0.1 mm to about 3 mm. The diameter D_E of the deflated conduit 234 and electrode 214 can be about 0.1 mm to about 1 mm. For example, to treat a bronchial tree of a human, the diameter of the inflated balloon 212 can be in a range of about 12 mm to about 18 mm. For enhanced treatment flexibility of the bronchial tree, the inflated balloon diameter may be in a range of about 7 mm to about 25 mm. Of course, the balloon 212 can be other sizes to treat other organs or tissue of other animals.

[0083] The energy delivery assembly 208 provides differential cooling because the coolant in the energy emitter assembly 220 is at a lower temperature and a higher velocity than the coolant in the balloon 212. Coolant, represented by arrows, flows out of the elongate shaft 230 and into the energy emitter assembly 220. The coolant proceeds through the energy emitter assembly 220 and the coolant channel 340 (Figure 14) of the electrode 214. The coolant absorbs thermal energy from the electrode 214. The heated coolant flows into the tip 240 and proceeds proximally through a lumen 400, as shown in Figure 18. The coolant flows through a valve 420 (*e.g.,* a throttle) and passes through a port 424. The valve 420 is disposed along a fluid path connecting the energy emitting assembly 220 and the portion of the balloon 212 defining the cooling section 209. The coolant circulates in a chamber 426 and absorbs heat from the tissue. This helps keep shallow tissue below a temperature that would cause cell death or tissue damage.

[0084] The coolant flows through a port 430, a lumen 432, and a throttle 434. The throttles 420, 434 can cooperate to maintain a desired pressure. The throttle 420 is configured to maintain a first flow rate of the coolant through the energy emitting assembly 220 and a second flow rate of the coolant through the cooling section 209. The first flow rate can be significantly different from the second flow rate.

[0085] The conduit 324 can assume a preset shape when pressurized. The valves 420, 434 can cooperate to maintain the desired pressure within the balloon 212 within a range of about 5 psig to about 15 psig. Such pressures are well suited to help push the electrode 214 between cartilaginous rings. Other pressures can be selected based on the treatment to be performed. The valves 420, 434 can be throttle valves, butterfly valves, check valves, duck bill valves, one-way valves, or other suitable valves.

[0086] When RF energy is transmitted to the electrode 214, the electrode 214 outputs RF energy that travels through tissue. The RF energy can heat tissue (*e.g.,* superficial and deep tissue) of the airway wall while the coolant cools the tissue (*e.g.,* superficial tissues). The net effect of this superficial and deep heating by RF energy and superficial cooling by the circulating coolant is the concentration of heat in the outer layers of the airway wall 100. Tissue structures can

vary between different types of airways. In the bronchial tree, the temperature of the connective tissue can be higher than the temperatures of the epithelium, stroma, and/or smooth muscle. By example, the temperature of the connective tissue can be sufficiently high to cause damage to the nerve trunk tissue or other deep tissue while other non-targeted tissues of the airway are kept at a lower temperature to prevent or limit damage to the non-targeted tissues.

[0087] Heat can be concentrated in one or more of the internal layers (*e.g.,* the stroma) of the airway wall or in the inner lining (*e.g.,* the epithelium) of the airway wall. Furthermore, one or more of the vessels (*e.g.,* vessels of the bronchial artery) may be within the lesion. The heat generated using the electrode 214 can be controlled such that blood flowing through the bronchial artery branches protects those branches from thermal injury while nerve trunk tissue is damaged, even if the nerve tissue is next to the artery branches. The catheter 207 can produce relatively small regions of cell death. For example, a 2 mm to 3 mm section of tissue in the middle of the airway wall 100, along the outer surface of the airway wall 100, or between the airway wall 100 and other body tissue (*e.g.,* tissue of the esophagus) can be destroyed. By the appropriate application of power and the appropriate cooling, lesions can be created at any desired depth.

[0088] A circumferential lesion can be formed around all or most of the circumference of the airway wall 100 by ablating tissue while slowly rotating the energy delivery assembly 208 or by positioning the energy delivery assembly 208 in a series of rotational positions at each of which energy is delivered for a desired time period. Some procedures form adjacent lesions that become contiguous and form a circumferential band all the way around the airway wall 100. In some embodiments, the entire loop 221 (Figure 16) can be an electrode. The loop 221 can be coated with a conductive material and can carry the electrode. A single procedure can produce a circumferential lesion. After forming the lesion, coolant flowing into the balloon 212 can be stopped. The balloon 212 is deflated causing the energy emitter assembly 220 to recoil away from the airway wall 100. The catheter 207 may be repositioned to treat other locations or removed from the subject entirely.

[0089] If the user wants the coolant in the balloon 212 to be at a lower temperature than the coolant in the energy emitter assembly 220, chilled coolant can be delivered into the balloon 212 and then into the energy emitter assembly 220. Figures 18 and 19 show such a coolant flow. Low temperature coolant flowing through the elongate body 230 passes through the valve 434 and the port 430. The coolant circulates in the chamber 426 and absorbs heat. The heated coolant flows through the valve 420 and proceeds through the energy emitter assembly 220 to cool the electrode 214.

[0090] Airway cartilage rings or cartilage layers typically have a significantly larger electrical resistance than airway soft tissue (*e.g.,* smooth muscle or connective tissue). Airway cartilage impedes energy flow (*e.g.,* electrical radio frequency current flow) and makes the formation of therapeutic lesions with radio frequency electrical energy to affect airway nerve trunk(s) challenging when the electrode is next to cartilage.

[0091] Positioners can facilitate positioning of the electrodes. Such positioners include, without limitation, bumps, bulges, protrusions, ribs or other features that help preferentially seat the electrode 214 at a desired location, thus making it easy to perform the treatment or to verify correct positioning. Figures 20 and 21 show the energy emitter assembly capable of serving as an intercartilaginous positioner. When the balloon 212 presses against the airway 100, the loop 221 moves along the balloon 212 to preferentially position the electrodes 214 between cartilage rings 452a, 452b. The loop 221 protrudes outwardly from the balloon 212 a sufficient distance to ensure that the energy delivery assembly 208 applies sufficient pressure to the airway wall to cause self-seating. The catheter 207 can be moved back and forth to help position the electrodes 214 next to soft compliant tissue 453 in the space 453. The energy emitter assembly 220 can be configured to displace a distance D_o (*e.g.,* measured along a long axis 310), which is at least half of the distance D between the cartilage rings 452a, 452b. This ensures that the electrodes 214 can be positioned generally midway between the cartilage rings 452a, 452b.

[0092] The plurality of electrodes 214 can reduce both treatment time and procedure complexity as compared to a catheter with a single electrode. This is because the multi-electrode catheter may have to be positioned a smaller number of times within a bronchial tree (or other hollow organ) as compared to single electrode catheters to produce a number of lesions of a desired therapeutic size. Multi-electrode catheters can thus precisely and accurately treat a user's respiratory system.

[0093] Figure 22 shows an energy emitter assembly 500 that includes two energy delivery elements including electrodes 510a, 510b spaced apart from one another about a circumference of a balloon 520. The electrodes 510a, 510b can be about 45 degrees to 210 degrees from another with respect to a long axis 511 of an ablation assembly 501. Other electrode positions are possible. Figure 23 shows an energy emitter assembly 530 with three energy delivery elements 540a, 540b, 540c positioned about 60 degrees from one another. In these embodiments, each electrode may be coupled to separate power lines to allow for independent control of each, or all electrodes may be coupled to the same power line so as to be operated together. Further, a pair of electrodes may be operated in a bipolar manner, wherein one electrode is positive and the other negative, with RF power being transmitted from one to the other through the tissue.

[0094] Figures 24A and 24B illustrate a portion of a treatment apparatus in the form of a tracheal device 639 in a delivered configuration for treating the trachea 18 in a monopolar fashion. The tracheal device 639 includes a basket 638 with a positioning member 640 and electrode members 642a, 642b, 642c (collectively "642"). The electrode members

642 can cooperate to treat the posterior plexus nerves 23. In this instance, an active device is placed in the trachea, with a ground pad placed on the patient's skin, typically in the thigh area. In order to prevent damage to the esophagus 30, a cooling or protection device is inserted into the esophagus 30. This device can be inserted through the mouth, or preferably, trans-nasally. The trans-nasal placement keeps the device separated from the manipulations of the device, to be placed in the trachea.

[0095] The basket 638 can be a cage or other type of self-expanding device. Advantageously, the basket 638 can be moved from a low profile (or collapsed configuration) to deployed state (or an expanded configuration) without the use of a balloon. Such non-inflatably expandable embodiments can be made of one or more shape memory materials (*e.g.,* Nitinol) capable of assuming different configurations. Additionally or alternatively, the basket 638 can be actuated using one or more pull wires or similar components.

[0096] A protection device in the form of a catheter 643 has a cooling balloon 644. In order for such an embodiment to efficiently circulate cooling media, the protection catheter 643 can include an inlet and an outlet to allow circulation of media (e.g., cooling media) through the balloon 644. The protective or cooling media is introduced through one lumen, allowed to inflate and circulate within the balloon 644, and exit through a second lumen. Additionally, the cooling media can be either gas or liquid, and can be chosen from a number of different varieties of either. Example gasses include room temperature or cooled air, nitrogen, cryogenic media, or the like. Example liquids include room temperature or cooled water, saline, ringer's solution, glucose solutions or the like.

[0097] Whereas Figures 24A, 24B referred to above describe a monopolar device with esophageal protection, Figures 25A and 25B illustrate one of a group of embodiments which will be called the trachea-to-esophagus, or T:E devices. In these embodiments, devices 666, 662 are inserted into the trachea 18 and esophagus 30, respectively. The devices 666, 662 cooperate to form a therapy and protection system encompassing the use of both devices to send and receive energy to the targeted tissue, and to protect the non-target tissue as well, as desired and required.

[0098] The protection or cooling media in the two different devices 666, 662 can be set up to maintain the same level of protection in both devices and both structures, or they may be set to provide differential cooling to one structure over another. For example, it may be desirable to cool the esophagus 30 more than the trachea 18, in order to provide greater protection to the esophagus 30, and in order to locate the lesion within the tissue bridge between the structures biased toward the trachea side of the bridge. This might better target the neural plexus specifically, while providing greater safety to the esophagus 30.

[0099] In Figures 25A and 25B, two devices 666, 662, which may be essentially the same in design, are inserted into each of the lumens (trachea and esophagus). The devices 666, 662 have an optional central lumen for guide wire guidance, a balloon with inflation lumens, and optionally, a second lumen for circulation of protective cooling media, and outer electrodes 667, 668. In the embodiments of Figures 25A and 25B, the outer electrodes 667, 668 are comprised of a cage of wires surrounding balloons 676, 678. Each cage can be deployed by the respective balloon 676, 678 directly, or they can be made of a suitable shape memory alloy to allow them to expand to contact the tissue independent of balloon action. The electrodes 667, 668 can be comprised of any suitable conductive material, including stainless steel, chromium cobalt, nickel titanium, metal-loaded conductive polymers, or the like. One of the devices can be attached to the energy delivery aspect of a delivery control box, and one acts as the return electrode. Depending on the specific energy density desired, the active device can placed in either the trachea 18 or the esophagus 30, and the return in the other. A cooled fluid may be circulated through balloons 676, 678 to absorb heat from energy delivery elements including electrodes 667, 668 and from the tissue of the esophageal and tracheal wall. During treatment, the balloons 676, 678 can be inflated to physically contact the inner surfaces of the trachea 18 and esophagus 30, respectively. The balloons 676, 678 have a generally circular shape as viewed along the lumen of the trachea 18, similar to the embodiments shown in Figure 24B. The balloons 676, 678 can have transverse cross-sections that are substantially circular, elliptical, polygonal, or combinations thereof and can have a smoother exterior surface, roughened exterior surface, undulating or wavy exterior surface, or the like. The electrodes 667, 668 deliver energy directly to the tissue. In other treatments, the balloons 676, 678 can be smaller than the lumens of the trachea 18 and the esophagus 30.

[0100] Figure 26 shows the energy distribution around the esophagus 30 and trachea 18 as may be produced by a system as described in Figures 25A and 25B. An area of high energy density 680 (shown hatched) exists in the tissue bridge 682 between the two structures, with relatively lower energy density 684, 686 (shown non-hatched) in other tissues around the perimeter of each of the individual structures. Without cooling, the tissue of the high energy density region 680 is ablated or otherwise altered (*e.g.,* damaged, destroyed, etc.) and preferably includes the posterior plexus nerves 23. In certain treatments, all of the posterior plexus nerves 23 between lumens of the trachea 18 and the esophagus 30 are damaged. In other treatments, targeted posterior plexus nerves 23 are damaged. If cooling media is circulated through one or both balloons, 676, 678, the tissue near the inner surface of the tracheal wall, as well as the tissue of the esophagus, can be protected from injury, while ablating target nerve tissues. Energy delivery and cooling may be adjusted to produce the isotherms of Figures 8A and 8B which are well suited for targeting damage to the interior tissue, such as the posterior plexus nerves 23, without damaging other tissue of the trachea 18, esophagus 30, and bridge 682.

[0101] An embodiment designed to optimize energy density around the trachea 18 is shown in Figure 27. In this

embodiment, the active electrodes 700 of a device 702 are arranged around the entire circumference in the trachea 18, and the return electrodes 714 are disposed only on the anterior aspect of the esophageal device 712. In this case, the anteriorly oriented support electrodes 714 are conductive, while the posterior and optionally the posterior-lateral elements 716 are non-conductive. To render them non-conductive, they could simply be insulated from the return leads at the points of connection at the distal and proximal ends of the balloon, insulated over the length of the members via insulating shrink tubing, polymer coextrusion or coating, or made of completely non-conductive materials, such as an extruded polymer.

[0102] Figure 28 illustrates a resultant energy density distribution that may be created by the system of Figure 27. A relatively high energy density 720 (shown hatched) develops between the trachea 18 and esophagus 30, in the area of the posterior plexus 23, with a slightly lower density 721 developing around the lateral and anterior aspects of the trachea 18 (still sufficient to ablate the anterior plexus), and almost no field develops around the majority of the circumference of the esophagus 30. By circulating cooling media through the balloon of the esophageal device, the tissue of the esophagus may be protected from injury. Further, by circulating cooling fluid through the balloon of the tracheal device, the surface tissue on the inner wall of the trachea may be protected.

[0103] A further localization of the energy field may be achieved through alternative embodiments, for example, as shown in Figure 29. In this embodiment, the active electrodes 730, 732 are confined to the posterior aspect of the tracheal device 740 and the anterior aspect of the esophageal device 742. The opposing arms 750, 752 of the devices 740, 742 can be passive (*e.g.,* ground electrodes). All of the aforementioned alternatives for achieving this electrode localization apply, as well as those describing the potential differential cooling/protection options.

[0104] Figure 30 illustrates an energy density localization as may be achieved by the embodiment of Figure 29. Such embodiments localize the energy density in the region 760 between the trachea 18 and the esophagus 30, and target more specifically the posterior plexus. Again, esophageal cooling may be applied to minimize damage to esophageal tissue.

[0105] It should also be appreciated that any of the above balloon supported embodiments (Figures 25A through 30) can be made with the electrode and support elements only without the use of balloons, and can be made to create the same ablation patterns seen in all of the above balloon supported embodiments. For example, Figures 31A and 31B illustrate an alternative embodiment similar to the embodiment described in connection with Figures 29 and 30, but in a non-balloon-supported embodiment. An energy density distribution pattern such as shown in Figure 30 also may be produced by the embodiment of Figures 31A and 31B.

[0106] Figure 32 illustrates an embodiment of the present invention in side elevation that may correspond to the types of device described in the previous embodiments. Note that in Figure 32, the device 799 includes a balloon 800 shown in conjunction with the basket electrode array 810. In some embodiments, as described, the balloon 800 is eliminated and the basket array 810 is carried directly on a central shaft 820. The basket array 810 includes a plurality of flexible, resilient, elongated electrode struts 813 oriented in a longitudinal direction and arranged around the circumference of shaft 820. Electrode struts 813 bow outwardly into an expanded, arcuate shape either under the expansion force of balloon 800, or by pulling on the distal ends thereof in a proximal direction, whereby electrode struts 813 bow outwardly under compression. The device 799 includes in inflow conduit 822 and an outflow conduit 824 used to circulate media through the balloon 800.

[0107] Other variations of the embodiments described so far are shown in Figures 33A and 33B. In Figures 33A and 33B, a tracheal device 840 includes a support cage 844 which carries on its periphery a circumferential band 845 that can be selectively insulated and energized to create any of a variety of energy density patterns, including those shown in Figures 26, 28 or 30. The band 845 can be a conductive flexible member that is in the form of a conductive strip, tubular band, or the like. The band may have one or more discontinuities or a sinusoidal or other shape to allow it to expand circumferentially. The band 845 can be movable from a contracted configuration to an expanded configuration. Spaced apart struts of the support cage 844 extend radially outward to the circumferential band 845. Any number of bands of different sizes and configurations can be carried by the cage 844.

[0108] The esophageal device 850 includes a support cage 854 that may also carry on its periphery a circumferential band 855 that can be selectively insulated and energized to create any of the energy density patterns shown in Figures 26, 28 or 30 or a variety of other patterns. Similarly, the support structures 844, 854 for the circumferential band of Figures 33A and 33B could be replaced by a balloon 846, as shown in Figure 34A and 34B. Figure 34B also show one possible energy density pattern, including high energy density region 849 (shown hatched), achieved by the embodiments in either Figures 33A-33B or Figures 34A-34B.

[0109] A tracheal device 862 of Figures 34A and 34B can include a band 864 with an active electrode. In some embodiments, the entire band 864 is an electrode. In other embodiments, one or more portions of the band 864 can be electrodes while other portions are insulated. A device 872 includes a band 874 with an active portion 876 and a passive portion 878. The active portion 876 can be an electrode that cooperates with the band 864 to target the posterior pulmonary plexus or other target region. The bands 864, 874 can be portions of a balloon or other type of inflatable or expandable member. In some embodiments, the walls of the balloons include electrodes mounted or adhered thereto.

The balloon (wire basket or cage) can be an actuable device movable between a delivery configuration and a deployed configuration to move the band 874.

[0110] Eliminating the balloon in the longitudinal support structure embodiments described above may require different means for providing cooling or protection. Further description of such alternative embodiments are provided later in the present disclosure.

[0111] Embodiments described to this point have either shown monopolar devices within the trachea, or bipolar devices which energize from trachea to esophagus, or vice versa. Figure 35 illustrates a further embodiment whereby bipolar energy can be delivered from within the trachea 18 alone, in order to concentrate the energy density around the circumference of the trachea 18 and target both the anterior plexus 22 and posterior plexus 23, with potentially higher energy density than would be achievable by monopolar energy alone.

[0112] In the embodiment of Figure 35, a device 900 includes an electrode array 902 that is divided into two distinct sections, wherein one section serves as the active electrodes 910 and the other section serves as return electrodes 912 (*e.g.,* ground electrodes). In this way energy may be delivered from active electrodes 910 to return electrodes 912 via the tissue in the tracheal wall to produce the desired energy density pattern. Other aspects of electrode design and material selection previously described apply to this embodiment as well.

[0113] Figures 36A-36C show a variation of the bipolar system in Figure 35. The system includes a basket-type electrode array as described in previous embodiments having a plurality of electrode bands. The electrode array is disposed around a balloon 922. The balloon 922 is divided into different sections by a septum 925 within the balloon 922. The septum 925 divides chambers 927, 929. Fluid at different temperatures can be delivered to the chambers 927, 929 to provide differential cooling between opposing surfaces of the balloon 922. In a further alternative, there would be a dual balloon system having one balloon facing the anterior and one balloon facing the posterior portion of the trachea 18. Different temperatures or different flow rates of media can be introduced into the different cooling/protection zones in order to provide greater protection for one area than the other. This differential in temperature profiles can also be used to direct the area of ablation more deeply into the wall of the trachea 18, directing it more towards the nerves. For example, if the nerves 23 on the posterior side are more deeply embedded in the bridge tissue between the trachea 18 and esophagus 30, more cooling might be desired here than on the anterior side. Another scenario is one in which the user only wants to protect the superficial mucosa on the anterior side, and so a comparatively low level of protection is required. On the posterior side, on the other hand, more protection may be required to preserve the integrity and function of the esophagus 30, and to prevent fistulas from occurring. A wide range of different types of split or multi-chambered inflatable members can be used.

[0114] It can also be appreciated that embodiments disclosed herein, such as the embodiment of Figures 36A-36C, which occlude the lung during treatment, can be deployed and retracted in order to allow for ventilation. Alternatively (not shown), any of these occlusive devices can be designed with a lumen or lumens which provide flow through the devices, allowing for ventilation of the lung distal to the occlusion site. Room air, oxygen or the like can be supplied to the distal lung.

[0115] The following family of designs shares a common attribute in that they take advantage of the cartilaginous rings which surround the upper airways to actually locate the delivery portions between the insulating rings, directing the energy directly into the only weakness in the wall of the airway from which the energy can reach the nerves on the anterior side.

[0116] Figures 37A-37C illustrate an embodiment with a device 1000 that includes a stack of a plurality of ring electrodes 1002 attached to a central or offset shaft 1010 which lends support and provides electrical connection to the control box of the system. The illustrated ring electrodes 1002 extend circumferentially about the inner wall of the trachea. The shaft 1010 extends vertically from the rings along a lumen of the trachea. The diameter and width of the ring material is chosen such that it fits entirely or substantially within the gap between two adjacent cartilaginous rings.

[0117] The diameter of the rings 1002 can be set to slightly oversize or to roughly match the diameter of the airway 1016, as shown in Figure 37A. The rings 1002 themselves may be resilient and expandable similar to a self-expanding vascular stent such that, regardless of airway diameter, they expand to fill the airway circumference. Various designs and methods to vary the diameter of the rings 1002 can be employed in these designs. For example, one end of a given ring may be fixed to the longitudinal spine of the device, and the other formed to engage another longitudinal element which winds the ring down into a smaller diameter for more distal placement (not shown).

[0118] The impedance sensors 1003 (shown in dashed line) of Figure 37B detect the impedance of the tissue of the airway wall and any external structures that may be in contact with the airway wall, such as the pulmonary artery or esophagus. Each of the various tissues and fluids in and surrounding the airway, such as smooth muscle, cartilage, nerves, blood vessels, mucous, air, and blood, has a different impedance. Moreover, previously treated (ablated) tissue will have different impedance than untreated tissue. Thus, the longitudinal and rotational position of the sensor (and hence the electrode) may be detected by measuring the impedance at the location and comparing it to a reference value or to the impedance of tissue at other locations. In this way, the power level or degree of cooling or both may selected based upon the location of the electrode to ensure target nerve structures are ablated without damaging other critical

structures such as the esophagus. In addition, the presence of previously created lesions may be detected so that overlapping such lesions and over-treating tissue can be avoided.

[0119] Impedance sensors 1003 may be adapted to be manually activated by the user at any particular electrode location. Alternatively, the system may be configured to run the sensors continuously or automatically trigger them prior to or simultaneous with energy delivery through the electrode at each treatment location. Prior to energy delivery, the system may provide an indication of the impedance to the user so that power or coolant delivery may be adjusted, or the system may automatically adjust the power delivered through the electrode based on the measured impedance.

[0120] Impedance may also be detected using the electrodes themselves without a separate sensor. The RF generator may be equipped with an impedance detection system which calculates the impedance seen by the electrode when power is delivered. In this way prior to lesion creation at any particular location a very low power signal may be delivered from the electrode and impedance then calculated to ensure proper positioning and power settings.

[0121] In use, the rings 1002 are deployed within the desired treatment area. They can be delivered within a sheath or tubular cannula in a compressed state and released when in position to expand into contact with the airway wall. Once deployed, the system is withdrawn proximally, or pushed distally by a small amount. Tactile feedback lets the physician know when the rings have slipped into place. In some embodiments, an active electrode is configured to fit between a first pair of adjacent cartilage rings of the airway in the expanded configuration. Return electrodes arc configured to fit between a second pair of adjacent cartilage rings of the airway while the active electrode is positioned between the first pair of adjacent cartilage rings. Alternatively, tissue impedance can be measured, with lower impedance signaling the electrodes are between rings, and in position to access the nerves.

[0122] As an alternative to the stacked ring design, a coil could be formed to provide the same inter-cartilaginous locking functionality as the stacked ring design. Figure 38A shows a device 1040 that includes a coiled or corkscrew-shaped ring 1044. The pitch of the coils 1044 is set such that adjacent turns of the coil lock into separate neighboring inter-cartilaginous regions. In one version of the coiled ring design, a length of resilient coil is provided straightened out inside of a delivery catheter or capture sheath. When the distal tip of the capture sheath is in place at the distal end of the treatment region, a distal tip 1045 and the coils 1044 are delivered to the distal end of the treatment region. The capture sheath is withdrawn until the entire treatment area of interest is covered by the coiled elements. Again, tactile feedback confirms that the rings are locked into place, or impedance is measured. A shaft 1046 extends from the coiled ring 1044 along the lumen of the trachea.

[0123] Figures 39A and 39B show another embodiment of the coiled ring system 1060 wherein the distal and proximal ends of the coils are both attached to longitudinal members. Coil diameter can be varied by twisting the two elements relative to one another in order to tighten or loosen the diameter of the coils. The coils can seat between the cartilage rings. The system 1060 includes a winding arm 1061 and a proximal electrode 1063.

[0124] The locking ring electrode concept can be incorporated into a number of the previously described tracheal-esophageal embodiments in order to recreate the energy density distributions shown in Figures 26, 28, and 30. A ring-type device in the lung could be used in combination with any of the previously described esophageal devices to provide esophageal cooling, or to provide esophageal electrodes for a bipolar delivery system.

[0125] Another variation of the locking ring embodiment is shown in Figures 40A and 40B. In this case, a device 1070 includes an anterior portion 1072 defined by a resilient member 1074 formed into a roughly "D" or kidney-shaped or rabbit ear-shaped member or ring. The ends of member 1074 may be wrapped around two independently rotatable longitudinal members 1075a, 1075b, so that the size and shape of the "D" can be modified by rotating the longitudinal members 1075a, 1075b to wrap or unwrap the resilient member. For example, rotating the left longitudinal member 1075a counterclockwise and the right one 1075b clockwise in Figure 40B would result in the D ring reducing in size (as shown by the dashed lines).

[0126] A plurality of these D-rings can be attached above or below one another in a configuration similar to the one shown in Figure 37A, and if desired can all be made expandable and contractible as described above. If a bipolar energy pattern is desired, a second set of D-rings can be positioned to contact the posterior wall of the trachea as well (not shown). The anterior and posterior rings can be alternated, or interleaved, such that each subsequent ring faces the opposite direction, or a series of rings can face one direction, and then a separate series of rings faces the opposite direction. The latter configuration provides longitudinal separation of the active and return electrode as well as the anterior/posterior separation provided by the interleaved design.

[0127] Alternatively, as shown in Figures 40A and 40B, a non-ring electrode 1082 can be used along the posterior aspect of the trachea 18. Since there are no cartilaginous rings on the posterior aspect, an electrode 1082 can be in the form of a mesh electrode, arrays of longitudinal spine electrodes, or any other suitable electrode design can be used in conjunction with the ring or D-ring electrodes described above to allow bipolar energy delivery.

[0128] Figures 41A and 41B illustrate a further alternative device 1090 that includes holes or vents for introduction of cooling media, and a plurality of spaced apart ring electrodes 1092a, 1092b. Cooling vents may be disposed in the shaft 1095 to which the electrodes 1092a, 1092b are attached. Through these vents cooling or protectant media (represented by arrows) can be directly applied to the electrodes and/or to the tissue adjacent to the electrodes. The media can be

any of the aforementioned media. Alternatively, any of the vented designs described in this disclosure can use a liquefied gas wherein the gas flows into the system liquefied and cools via an endothermic phase transition.

[0129] In another exemplary embodiment, shown in Figure 42, the esophagus is protected by an esophageal device 1100 in the situation where the tracheal device (not shown) alone is involved in the modification or ablation of the nerves. The tracheal device can be monopolar RF, bipolar RF with both leads in the trachea, or microwave.

[0130] The embodiment of Figure 42 is shown to cover a substantial portion of the entire zone of the esophagus 1141 which could potentially suffer tissue damage from a delivery device positioned within the trachea. This affords protection of the entire exposed esophageal territory with a single device placement. Alternatively, the esophageal device could be made shorter, and moved either in concert with, or at appropriate intervals to the movement of the tracheal device. Such an embodiment may include features such as an elongate shaft to insert the balloon and circulate cooling fluid through a balloon 1142, multiple lumens to effectively circulate protectant, and/or an optional guide wire lumen to aid in placement of the device.

[0131] Although there is an area of the trachea shown in crosshatch Figure 42 as the treatment area of the trachea, it should be noted in this and all figures that show exemplary treatment areas that this area is not the only potential treatment area. It is shown merely to point out that in some embodiments the esophageal device covers substantially the entire potential intended treatment zone.

[0132] A catheter shaft 1113 of Figure 42 is connected to a generator/pump unit and can be a multi-lumen shaft to allow bidirectional fluid flow. In certain embodiments, the catheter shaft 1113 has two lumens coupled to side holes. Fluid can be delivered into a proximal balloon end 1142 through one lumen. Media can be circulated within the balloon 1142 to cool the tissue surrounding the esophagus. The media can flow out of the balloon 1142 using the other lumen.

[0133] The catheter shaft 1113 can have a sealed tip 1130. A fluid can be delivered through the chamber of the balloon 1142 and returned via the body 1110. One or more conductive elements 1140 can be positioned to be adjacent to or to contact the potential ablative zone. During ablation, the conductive element can help conduct heat between the tissue and the cooling media circulating within the expandable balloon 1142 covering the potential ablative zone 1141.

[0134] The exemplary embodiment illustrated in Figure 43 is a variation of the embodiment of Figure 42, in which conductive means are added to the basic protection system to allow for bipolar trachea-to-esophagus treatment options. All of the previously mentioned features and benefits apply the embodiment of Figure 43 as well. While Figure 43 shows a circumferential conductive zone, such as a wire mesh 1160 on the device, it should be appreciated that any of the conductive elements described herein (wire cages, ring electrodes, etc.) could be configured onto the protective device 1100. In the case where the protective device is long enough to cover substantially all of the potential treatment area, the conductive elements of the protective device will also cover substantially the entire potential treatment zone.

[0135] Figure 44 illustrates another alternative embodiment including means for protecting the esophagus during nerve modification. In this case, a relatively short occlusion device 1180 is delivered to the esophagus distal to the most likely termination of the potential treatment zone. Behind this occlusion device 1180, protectant media is circulated freely in the esophagus. In this embodiment, cooled gasses are most likely to be used. Room air, nitrogen, oxygen, etc., may be used. Forced media (*e.g.,* forced cool air) can be circulated above the occlusion device 1180 illustrated as a balloon. A wide range of different types of sources 1181 with one or more pumps (*e.g.,* piston pumps, positive displacement pumps, roller pumps, etc.) or blowers can pass media through a conduit 1183. The illustrated conduit 1183 is positioned in the lumen of the esophagus 30 to circulate the media in the lumen of the esophagus 30. The media can flow at a relatively high flow rate to protect the trachea and/or esophagus. The occlusion device 1180 prevents media from distending the stomach and/or the gastrointestinal tract.

[0136] As shown in the exemplary embodiment of Figure 44, the occlusion device 1180 is a balloon, but other devices which provide substantial blockage to the passage of gas can be used. Additionally, Figure 44 shows the protectant being introduced via the nose or the mouth directly. Custom nose plugs or facemasks can be designed to effect this delivery. For example, a pump or blower can deliver chilled media to the airway or esophagus of the patient via a facemask. Alternatively (not shown), side holes in the shaft of the occlusion device can be used for introduction of protectant. In this case, liquefied gas that is allowed to warm in the catheter shaft and exit the catheter as a gas can be used. The degree of protection, as with all of the protective devices, can be varied through temperature of the protective media, or through the flow rate of the protective media.

[0137] Figures 45 and 46 show further alternative embodiments of a distal occlusion protective device wherein a conductive element is incorporated into the system. This enables bipolar trachea-to-esophagus treatment. The conductive element may be attached to the same shaft as the occlusion device, such that the entire system is introduced at once. Alternatively, the conductive elements could be a separate device which is placed alongside of or over top of the occlusion device, and which is insertable and operable separately from the occlusion device. The conductive element may be constructed similarly to any of the esophageal devices described herein, such as a basket electrode array 1190 having a plurality of electrode bands.

[0138] Figure 46 shows the embodiment of Figure 45 with protectant circulating around and through the elements of the conductive system. As with prior embodiments, the protectant can be introduced through the nose or mouth, through

the central shafts of the devices, or through the conductive elements themselves. Introduction through the conductive elements themselves provides the added bonus of cooling those elements and preventing tissue charring during thermal ablation. Charring on the electrodes greatly increases the impedance of the system and decreases or eliminates the effectiveness of the ablation.

[0139] Microwave energy has found increasing uses over the past few years and may be used in embodiments of the present invention as an alternative energy system. Principally, microwave energy is delivered through an antenna. There are a number of different types of microwave antennae. With suitable modifications based on the teachings of the instant disclosure, some the basic microwave antenna forms may be incorporated into devices designed for modulating or modifying pulmonary nerves as described herein. Of particular use for the application of catheter based microwave energy within the trachea-to-esophagus region is the family of antenna based upon coaxial wire leads. There are a number of different designs using the coaxial leads. These types of antennae come in many different configurations-monopole, dipole, slot, capped, choked, cap-choke, sleeved, etc. Each antenna variation is intended to either shift the field orientation, to improve the efficiency of energy delivery, or both. Wave guide antennae are another known antennae for microwave applications. Wave guide antennae are typically a metal jacketed dielectric, which is fed with a coaxial cable inserted into a side hole in the device.

[0140] Examples of basic configurations for microwave antennae that may be modified and configured for use with embodiments of the present invention by persons of ordinary skill in the art may be found in the following publications: Microwave Catheter Design; Robert D. Nevels, G. Dickey Arndt, George W. Raffoul, James R. Carl, and Antonio Pacifico. IEEE TRANSACTIONS ON BIOMEDICAL ENGINEERING, VOL. 45, NO. 7, JULY 1998, and A Review of Coaxial-Based Interstitial Antennas for Hepatic Microwave Ablation, John M. Bertram, Deshan Yang, Mark C. Converse, John G. Webster, & David M. Mahvi; Critical Reviews™ in Biomedical Engineering, 34(3):187-213 (2006). Both of these publications are incorporated by reference in their entirety. Among the reasons that such antennae designs cannot be directly incorporated into embodiments of the present invention is their unsuitability for pulmonary devices without modification. Among the parameters that must be reconfigured for deployment in the pulmonary tree according to embodiments of the present invention are the size, stiffness and general deliverability.

[0141] In pulmonary applications, the devices need to be introduced through or in conjunction with bronchoscopes, and manipulated down tortuous paths into the area of the lung to be treated. This necessitates the translation of conventional microwave antenna designs into application specific embodiments, such as the exemplary embodiments shown in Figures 51A-54C. One generally common aspect for these pulmonary devices is flexibility, although in some cases a flexible body member is coupled to more rigid segments in the area of the slots, caps, and chokes. Other aspects that must be specially considered for pulmonary applications are features to provide tissue coupling, maintain positioning relative to the target tissue, cool non-target tissue, etc.

[0142] In one exemplary embodiment, an antenna that may be particularly effective in pulmonary applications for microwave energy delivery is a multi-slot coaxial design such as shown Figure 47. In this embodiment, in addition to a slot near the tip, a plurality of additional slots are positioned at appropriate distances down the shaft of the device, with the distances being determined by wavelengths of operation, desired specific absorption rate (SAR) pattern, etc. Specific absorption rate, or SAR, is a proxy for energy delivery to the tissue, or heating profiles of the tissue, and are the standard way in which antenna designs are evaluated and optimized.

[0143] In many microwave antenna applications in medicine, the desire is to provide the largest effective area of energy delivery to tissue, with the area of treatment extending from the edge of the antenna or applicator to the periphery of the largest area possible. However, in the case of pulmonary nerve modulation, protection of the structures immediately adjacent the applicator is preferred. Ideally, the energy would pass through a cooling or protective layer, heat tissue within a few millimeters of a zone, and then drop off in intensity in order not to harm critical non-target tissues such as the esophagus and alveoli. This is not possible in any of the antenna designs shown from the prior art. Embodiments to achieve these ends are shown and described in detail below in Figures 58A-53.

[0144] In microwave terms, the more "lossy" a material is, the higher the propensity of that material to heat up. Lossy materials in the body are typically those with higher water content. This is due to the fact that microwaves heat dipole molecules by causing rotation of the dipole molecule under the oscillations of the wave. Water is a strong dipole molecule, and heats extremely well under microwaves.

[0145] The tables below show various electrical properties of different tissues at two different commonly used medical microwave frequencies, 915 MHz and 2.45 GHz. One aspect that is apparent from these data is that as microwave frequency increases, depth of penetration decreases-so lesions are made more shallowly. For this reason, it is likely that the preferred frequency for pulmonary nerve modulation will be 2.45 GHz or higher. At least one microwave system designed by Micrōsulis Inc. operates at frequencies in the 9 GHz region. The frequency can be selected so that the microwave energy penetrates the tissue to a depth of the target tissue with an intensity sufficient to alter the target tissue while having insufficient intensity in non-target tissue, such as non-target tissue beyond the nerve tissue.

[0146] Frequency alone does not determine depth and character of penetration and tissue modification. It is known that standing waves can develop in microwave fields, and specific systems must be modeled with FEA systems to

determine the most likely resultant SAR patterns within a given tissue system.

[0147] For example, the permittivities of most of the tissue types listed below are roughly in a similar range, indicating that they will heat similarly. However, there are a couple of exceptions-the esophagus may heat more easily than other tissues, and so may require the protection that has been discussed throughout this disclosure. Also, it is of particular interest that the permittivity of the lung differs significantly as between the inflated and deflated states.

Tissue name	Frequency [Hz]	Conductivity [S/m]	Relative permittivity	Loss tangent	Wavelength [m]	Penetration depth [m]
Cartilage	915000000	0.7892	42.6	0.36394	0.049412	0.044603
Cartilage	2450000000	1.7559	38.77	0.33228	0.019393	0.019077
Tissue name	**Frequency [Hz]**	**Conductivity [S/m]**	**Relative permittivity**	**Loss tangent**	**Wavelength [m]**	**Penetration depth [m]**
LungInflated	915000000	0.45926	21.972	0.41063	0.068523	0.05527
LungInflated	2450000000	0.80416	20.477	0.28813	0.02677	0.030175
Tissue name	**Frequency [Hz]**	**Conductivity [S/m]**	**Relative permittivity**	**Loss tangent**	**Wavelength [m]**	**Penetration depth [m]**
Mucous Membrane	915000000	0.85015	46.021	0.36291	0.047545	0.043032
Mucous Membrane	2450000000	1.5919	42.853	0.27255	0.018524	0.022029
Tissue name	**Frequency [Hz]**	**Conductivity [S/m]**	**Relative permittivity**	**Loss tangent**	**Wavelength [m]**	**Penetration depth [m]**
Nerve	915000000	0.57759	32.486	0.34929	0.056652	0.053157
Nerve	2450000000	1.0886	30.145	0.26494	0.022097	0.027006
Tissue name	**Frequency [Hz]**	**Conductivity [S/m]**	**Relative permittivity**	**Loss tangent**	**Wavelength [m]**	**Penetration depth [m]**
Oesophagus	915000000	1.1932	65.02	0.36053	0.040007	0.036435
Oesophagus	2450000000	2.2105	62.158	0.26092	0.015392	0.019092
Tissue name	**Frequency [Hz]**	**Conductivity [S/m]**	**Relative permittivity**	**Loss tangent**	**Wavelength [m]**	**Penetration depth [m]**
Trachea	915000000	0.7757	41.971	0.36308	0.049785	0.04504
Trachea	2450000000	1.4488	39.733	0.26753	0.019244	0.023299

[0148] The significance of the change in permittivity of the lung upon inspiration may be of particular interest in a case where the nerve modulation is to be conducted at or below the area of the carina. Once into the right and left bronchi, tissue surrounding the bronchi is increasingly alveolar tissues-highly compliant, and highly air-filled. It is this air that is likely responsible for the decrease in permittivity of filled lungs. The permittivity of air is 1-it does not heat in any significant way in the presence of microwaves.

[0149] One significance of this fact for the subject applications is that it may be beneficial to tie the application of microwave energy to the inspiration cycle of respiration, when the lung is filled with air. Alternatively, the method of treatment could include a breath-hold or a ventilatory hold induced by a ventilator machine in order to ensure air-filled tissue surrounding the bronchi supporting the nerves to be treated.

[0150] Microwaves encountering materials of different permittivities can also act in unusual ways. Reflections can be created at tissue interfaces or air/tissue interfaces which can be exploited to focus ablative or modulatory energy more specifically on the tissues to be treated.

[0151] Figures 48A and 48B show embodiments of microwave systems. The pulmonary treatment apparatus 1201 includes an elongate member 1203 and a microwave antenna 1210 coupled the elongate member 1203. The microwave antenna 1210 is positioned at treatment location proximate a target site in or proximate to the airway. The microwave antenna 1210 delivers microwave energy so as to alter nerve tissue in a manner which disrupts transmission of nerve signals while non-target tissue disposed between the microwave antenna 1210 and the nerve tissue is not permanently injured.

[0152] Expandable or deployable supporting elements 1200 are provided which ensure solid coupling of the antenna 1210 to the tissue. The supporting elements 1200 are movable from a contracted position (shown in dashed line in Figure 48A) to the illustrated expanded position. These elements can be wires, balloons, fingers, or the like. The supporting elements 1200 of Figures 48A and 48B are illustrated as a pair of elongate members 1210 configured to bow outwardly to engage the anterior wall of the airway. Optionally, shielding 1220 can be provided on one or more sides of the device to further focus the microwave energy into the tissue and/or to protect non-target tissues. Shielding 1220 can be metallic foil, metal loaded polymer, metallic mesh with mesh opening of an appropriate fraction of the wavelength in use so as to block transmission of the waves therethrough, or any known microwave shielding material. Not shown in Figures 48A and 48B is an optional esophageal protection system. This system can take any of the forms previously disclosed.

[0153] Also noted in Figure 48B is a tissue plane discontinuity between the esophagus and the trachea. If therapy is to be delivered at this level rather than down in the bronchi below the carina, it is possible that the differences in tissue properties will cause reflection, or that the air in the esophagus, or the protectant system in the esophagus, will cause reflection of the microwaves. Reflection of waves can result in cancellation, summation, or additive power of the waves, or it can result in standing waves. Cancellation would tend to negate clinical effectiveness and must be avoided in the system design. Summation or standing waves can be beneficial, and may be designed into the system to provide higher effective energy levels at the target tissue than the level of energy delivered by the system alone. Figure 49 shows emitted waves.

[0154] Figures 50A and 50B illustrate a further alternative embodiment of the present invention including a dual antenna system 1300 built on the same basic principles as described in connection with the embodiments disclosed above. A shield of dielectric material 1311 can be mechanically coupled to antennae 1302a, 1302b. Support structures 1310a, 1310b can help hold the antennae 1302a, 1302b proximate or against the posterior tissue of the trachea 18. The support structures 1310a, 1310b can be elongate arms, ribs, inflatable members, or the like. The antennae 1302a, 1302b can cooperate to form standing waves in a desired configuration. Optionally, a protective device can be used to protect tissue of the esophagus 30 or any other bridging tissue proximate or adjacent to the trachea 18 and/or the esophagus 30. Note that while two antennae 1302a, 1302b are shown in this embodiment, any number of antennae can be included without departing from the teachings of the present invention. The antennae may be bound edge-to-edge down the longitudinal axis of the catheters, or they may be separated by an appropriate dielectric material. The antennae 1302a, 1302b can be fired simultaneously, in sequence, alternating or in various other patterns to modify or optimize the SAR distribution to the desired tissue.

[0155] Figures 51A and 51B illustrates yet another embodiment of the microwave therapy system wherein an esophageal device 1340 is included to modify or optimize the microwave SAR pattern in the target tissues. The esophageal device 1340 shown here is a reflector 1342. The reflector 1342 includes a balloon filled with inflation media chosen for specific dielectric properties that alter the SAR pattern in the tissue therebetween. This alteration of the SAR pattern acts to reflect microwave energy back toward the delivering device in order to sum the wave energies or to create a standing wave within the tissue. It could alternatively be used to provide negation of oncoming waves, or it could be used to absorb microwave energy in order to draw the energy deeper into the tissue and then negate it at the device. The balloon 1342 can be connected to the media source. The media source can be the media delivery system 246 discussed in connection with Figure 10.

[0156] While a balloon is shown in the embodiment of Figures 51A and 51B, persons of ordinary skill in the art will recognize based on the teachings herein that other devices may be used whose materials, design, use or any combination of these factors provide an alteration to the SAR pattern created by the matched microwave antenna when used in concert with that antenna. Other types of reflectors may include, without limitation, one or more balloons, plates, or the like. Also note that although the microwave embodiment in Figure 51B is a dual antenna design, any contemplated antenna design could be substituted in this system. Although the use of the dielectric SAR altering device is described with that device in the esophagus and the microwave antenna in the trachea or bronchi, the devices could be placed in the reverse arrangement as desired.

[0157] In another alternative embodiment, as shown in Figures 52A and 52B, microwave systems such as those shown in Figures 48A-50B can be outfitted with a cooling device in the form of an outer jacket 1356 through which media can be introduced or circulated. A plurality of channels can extend through a main body 1357. This media can serve as a

cooling agent via temperature control or flow control of the media, or a combination of the two. The media may be chosen for dielectric properties which provide better coupling between the antenna and the tissue. The outer jacket 1356 may also include shielding 1360.

[0158] Figure 53 illustrates another alternative embodiment including cooling or coupling media in a chamber 1370 to surround an antenna 1372. In this embodiment, a cooling device includes an outer member 1374 (illustrated as a balloon wall) of the device that surrounds the antenna 1372 and couples with substantially the entire circumference of the trachea or bronchi. The outer member 1374 cools at least a portion of the non-target tissue while the microwave antenna 1372 delivers the microwave energy. Thus, the wall of the outer member 1374 is positioned between the microwave antenna 1372 and the wall of the airway. The microwave energy can pass through the outer member 1374 and penetrates the airway wall to a depth of the target tissue with an intensity sufficient to alter the tissue. Optionally, shielding 1384 may be built into the device to block transmission on a portion of the circumference to protect that portion from treatment as explained below. In other embodiments, the shielding 1384 can absorb the microwave energy. This shielding could be used to protect the esophagus, for example.

[0159] Alternatively, the embodiment of Figure 53 could be used in a method of treatment for which multiple embodiments throughout this disclosure may be used. To use the device in Figure 53 with shielding, as an example of a method of treatment according to one embodiment of the present invention, the device would be introduced to a point along the desired treatment zone of the airway. Energy is delivered to a portion of the circumference of the airway which is less than 360 degrees. The device is then advanced or withdrawn so that the next treatment zone either barely overlaps, or allows a small gap between it and the last treatment zone. Additionally, the device is rotated such that there is either a slight overlap or a slight gap circumferentially as compared to the prior treatment site. By repositioning the device both longitudinally and circumferentially, in two or more treatments the entire circumference of the airway could be treated, but not contiguously. In effect, there is a spiral treatment area created, with the proximal and distal ends of the spiral approximately matched or overlapped when compared circumferentially, but which are separated longitudinally.

[0160] This spiral or displaced treatment pattern would allow modulation or ablation of the nerves surrounding an airway, without risking the creation of a circumferential zone of treatment which could cause unwanted wall effects such as hyperproliferation of cells during healing, scarring, stenosis or the like.

[0161] Another embodiment that would provide the spiral treatment pattern desired would be a multi-slotted antennae 800 as was described in connection with Figure 47. In addition to the extra slots 811 a, 811b, 811c, and hence extra treatment zones spaced longitudinally down a catheter shaft 820, the spiral design may have partial-circumferential shielding (device not shown). Figure 47 also shows a SAR pattern. The position of the shielding would vary by position along the length of the catheter. For example, a multi-slot design providing four treatment areas longitudinally could be shielded from 12-3 o'clock in longitudinal segment 1, 3-6 o'clock in longitudinal segment 2, 6-9 o'clock in longitudinal segment 3, and 9-12 o'clock in the final longitudinal segment. Thus, it is possible with a single energy application that the entire spiral-shaped energy deposition is made.

[0162] Figure 54A shows a further alternative embodiment for a microwave antenna intended to create as large an area of ablation as possible for a given insertion into the body. While the bifurcated shape of the antenna in Figures 54A and 54B are interesting for lung applications, several issues make it infeasible to use for this application as shown. Given the rigidity of coaxial cable used in antennae such as that shown in Figures 54A and 54B, it may require specific device designs to achieve delivery of such a split tip design to the lung. Pull wires 1402, 1404 attached to the tips 1412, 1414 could be added to deflect the tips 1412, 1414 actively as desired. Memory materials could be built into the shafts of the split segments to bias them outward, and an outer sheath provided to hold them together for delivery. Given the stiffness of some coaxial wire, a wedge-shaped element 1415 (illustrated in dashed line) can be added between legs 1416, 1417 of the split tip 1419, which when retracted via pull wires 1402, 1404 or the like, the legs 1416, 1417 are forced outward and apart.

[0163] Additionally, the actual SAR pattern of the antenna shown is not applicable in the pulmonary indication. Note the "tail" of the SAR pattern which extends downward between the legs 1416, 1417 of the device shown in Figure 54B. This energy deposition would occur in non-target tissues if used in the lung as designed-most probably, the heart.

[0164] Significant redesign of the system shown can be performed for pulmonary applications. One embodiment which would provide both the deployment of the legs 1416, 1417 of the split antenna device as well as creating a more desirable SAR pattern would be to provide a sliding wedge element 1415to separate the legs 1416, 1417, but the material of which is a dielectric material selected to modify the SAR pattern to more closely follow the legs 1416, 1417 of the antennae, without the unwanted "tail" energy directed towards the heart.

[0165] High intensity ultrasound (HIFU) is another energy modality that can be employed to provide pulmonary nerve modulation. In HIFU, ultrasound transducers are shaped, or in some cases multiple transducers are electronically beam-formed to a focal point. At the focal point, relatively low intensity ultrasound departs the ultrasound transducer(s) and converges at the focal point designed into the transducer to create a zone of heating and tissue ablation.

[0166] A jacketed esophageal HIFU device appears in "US2007/0027445 Method and Apparatus for Noninvasively Treating Patent Foramen Ovale Using High Intensity Focused Ultrasound" by the present inventors, which disclosure

is incorporated herein by reference in its entirety. This device is a transesophageal HIFU device coupled to the target tissue with a cooling jacket or balloon surrounding the HIFU elements. This device was initially designed to treat atrial fibrillation by targeting the posterior wall of the heart from the esophagus. However, the same or similar device could be adapted for use in the currently disclosed methods for pulmonary treatment.

[0167] HIFU devices are to be used to fire energy into structures which are either tissue or fluid. While reflections of ultrasound may occur at transitions between different tissue types, all of the structures are essentially acoustic conductors. Air, however, will not conduct ultrasound. So in the unique case of pulmonary neuromodulation, HIFU fired from either the airway or esophagus will encounter an air barrier just beyond the target tissue, and become attenuated, or reflect to form a standing wave within the target tissues.

[0168] In order to maximize the desired effects, a device similar to the one shown in Figures 54A and 54B may be employed wherein the microwave device would be replaced with a HIFU transducer. For HIFU, the dielectric properties of the fluid in the balloon 1342 would be replaced by specific acoustic properties, to either enhance the absorption or reflection of the applied acoustic power.

[0169] Different types of modifications can be made to treat tissue with different types of energy. Energy can be used to damage target regions. As used herein, the term "energy" is broadly construed to include, without limitation, thermal energy, cryogenic energy (*e.g.,* cooling energy), electrical energy, acoustic energy (*e.g.,* ultrasonic energy), HIFU energy, RF energy, pulsed high voltage energy, mechanical energy, ionizing radiation, optical energy (*e.g.,* light energy), microwave energy, and combinations thereof, as well as other types of energy suitable for treating tissue. In some embodiments, the catheter system, devices, or apparatus disclosed herein delivers energy and one or more substances (*e.g.,* radioactive seeds, radioactive materials, etc.), treatment agents, and the like. For example, the assembly 208 of Figures 5 and 6 can include one or more ports through which a treatment agent is delivered. Exemplary non-limiting treatment agents include, without limitation, one or more antibiotics, antiinflammatory agents, pharmaceutically active substances, bronchoconstrictors, bronchodilators (*e.g.,* beta-adrenergic agonists, anticholinergics, etc.), nerve blocking drugs, photoreactive agents, or combinations thereof. For example, long acting or short acting nerve blocking drugs (*e.g.,* anticholinergics) can be delivered to the nerve tissue to temporarily or permanently attenuate signal transmission. Substances can also be delivered to chemically damage the nerve tissue. The electrodes, antenna, or other energy emitting components can be replaced with other types of components based on the desired type of energy to be used for treatment.

[0170] The various embodiments described above can be combined to provide further embodiments. These and other changes can be made to the embodiments in light of the above-detailed description. The embodiments, features, systems, devices, materials, methods and techniques described herein may, in some embodiments, be similar to any one or more of the embodiments, features, systems, devices, materials, methods and techniques described in U.S. Provisional Patent Application No. 61/321,346 filed April 6, 2010; U.S. Application No. 12/463,304 filed on May 8, 2009; U.S. Application No. 12/913,702 filed on October 27, 2010; PCT Application No. PCT/US2010/056424 filed November 11, 2010; U.S. Application No. 12/944,666 filed November 11, 2010; and PCT Patent Application No. PCT/US2010/56425 filed November 11, 2010. Each of these applications is incorporated herein by reference in its entirety. In addition, the embodiments, features, systems, devices, materials, methods and techniques described herein may, in certain embodiments, be applied to or used in connection with any one or more of the embodiments, features, systems, devices, materials, methods and techniques disclosed in the above-mentioned U.S. Application No. 12/463,304 filed on May 8, 2009; U.S. Application No. 12/913,702 filed on October 27, 2010; PCT Application No. PCT/US2010/056424 filed November 11, 2010; U.S. Application No. 12/944,666 filed November 11, 2010; and PCT Patent Application No. PCT/US2010/56425 filed November 11, 2010. For example, the apparatuses of disclosed in U.S. Application No. 12/463,304 may incorporate the electrodes or other features, such as the protection devices, disclosed herein. All of the U.S. patents, U.S. patent application publications, U.S. patent application, foreign patents, foreign patent application and non-patent publications referred to in this specification and/or listed in the Application Data Sheetare incorporated herein by reference, in their entirety. Aspects of the embodiments can be modified, if necessary to employ concepts of the various patents, application and publications to provide yet further embodiments.

[0171] These and other changes can be made to the embodiments in light of the above-detailed description. In general, in the following claims, the terms used should not be construed to limit the claims to the specific embodiments disclosed in the specification and the claims, but should be construed to include all possible embodiments along with the full scope of equivalents to which such claims are entitled. Accordingly, the claims are not limited by the disclosure.

[0172] Further preferred embodiments of the invention are as follows:

1. A system for pulmonary treatment, comprising: a pulmonary treatment device having an energy delivery element positionable through at least a portion of a trachea into an airway and configured to deliver energy to a wall of the airway to alter nerve tissue located in or proximate to the wall of the airway; and
a protection device having a protection member positionable in an esophagus while the pulmonary treatment device is positioned in the airway, the protection member being configured to absorb heat from a wall of the esophagus to inhibit damage to esophageal tissue.

2. The system of embodiment 1 wherein the pulmonary treatment device is configured to deliver a sufficient amount of energy to the wall of the airway to heat and damage the nerve tissue, wherein the protection device is configured to absorb a sufficient amount of heat from the wall of the esophagus to inhibit damage to esophageal tissue while the nerve tissue is damaged.

3. The system of embodiment 1, further comprising a media delivery system fluidically coupled to the pulmonary treatment device and the protection device, the media delivery system being configured to deliver cooling media through the pulmonary treatment device to cool the energy delivery element and configured to deliver cooling media through the protection device to cool the protection member.

4. The system of embodiment 1 wherein the airway treatment device comprises a first elongate member configured for insertion through the airway, and the at least one energy delivery element is disposed on the first elongate member in a position corresponding to the anatomical location of at least one nerve in or proximate to the airway wall when said first elongate member is positioned therein.

5. The system of embodiment 4 wherein the protection device comprises a second elongate member configured for insertion in the esophagus, the protection member being disposed on the second elongate member in a position generally aligned with the position of the at least one energy delivery element when the airway treatment device is positioned in the airway and the second elongate member is positioned in the esophagus.

6. The system of embodiment 1, further comprising cooling means associated with said at least one energy delivery element to limit tissue damage adjacent select denervation sites.

7. The system of embodiment 1 wherein said protection member comprises an expandable member configured for insertion into the esophagus.

8. The system of embodiment 7 wherein said expandable member comprises an inflatable balloon configured to circulate a cooling medium therein.

9. The system of embodiment 7 wherein said expandable member comprises a balloon configured to occlude the esophagus and said cooling means further comprises means for circulating a cooling fluid within the occluded esophagus.

10. The system of embodiment 1 wherein said airway treatment device comprises an inflatable balloon.

11. The system of embodiment 10 wherein said inflatable balloon is configured for circulation of cooling fluid therein.

12. The system of embodiment 1 wherein the active electrode is balloonlessly expandable from a contracted configuration to an expanded configuration.

13. The apparatus of embodiment 12 wherein the active electrode is configured to fit between adjacent cartilage rings of the airway in the expanded configuration.

14. The system of embodiment 1 wherein said airway treatment device comprises a helical or ring-shaped member that includes the energy delivery element.

15. The system of embodiment 1 wherein said pulmonary treatment device comprises an energy delivery device configured to be positioned in the airway to locate the energy delivery element into an intercartilaginous region.

16. The system of embodiment 1 wherein said at least one energy delivery element comprises an RF electrode.

17. The system of embodiment 16 wherein said energy delivery element further comprises a return electrode, said electrodes being configured for bipolar energy delivery.

18. The system of embodiment 1 wherein said at least one energy delivery element comprises a microwave antenna.

19. The system of embodiment 1 wherein said protection device comprises at least one electrode configured to be operatively coupled with the energy delivery element of the airway treatment device.

20. A method for pulmonary treatment, comprising: positioning at least one energy delivery element through at least a portion of the trachea into an airway adjacent a treatment site to be treated;
delivering energy from said at least one element to a portion of the circumference of the airway at said treatment site; and
cooling tissues of an esophagus to prevent damage of the tissues of the esophagus while the energy is delivered.

21. The method of embodiment 20 wherein said cooling comprises delivering a cooling medium into the esophagus.

22. The method of embodiment 20 wherein said portion of the circumference of the trachea of the subject is less than 360 degrees around the trachea.

23. The method of embodiment 20, further comprising:

repositioning the at least one energy delivery element in close proximity to the previous position;
and
delivering energy in an adjacent treatment site wherein said adjacent site barely overlaps or allows a small gap with the previous treatment site.

24. The method of embodiment 20, further comprising rotating the at least one energy delivery element to provide a slight overlap or a slight gap circumferentially with respect to the previous treatment site.

25. The method of embodiment 20 wherein said delivering comprises delivering RF energy.

26. The method of embodiment 20 wherein said delivering further comprises bipolar delivery of RF energy.

27. The method of embodiment 20 wherein said delivering comprises delivering microwave energy.

28. The method of embodiment 20, further comprising positioning at least one esophageal energy delivery element in the esophagus and delivering or receiving energy to or from said esophageally positioned element.

29. The method of embodiment 20 wherein the energy delivery element comprises a first electrode, the first electrode being positioned within a first space between a first pair of adjacent cartilage rings of the airway.

30. The method of embodiment 29, further comprising placing a second electrode in a second space between a second pair of adjacent cartilage rings of the airway.

31. The method of embodiment 30, further comprising delivering energy between the first and second electrodes to alter target tissue in a wall of the airway longitudinally displaced from the first and second spaces.

32. A pulmonary treatment apparatus comprising:

an elongate member insertable through at least a portion of a trachea into an airway; and

a microwave antenna coupled to the elongate member and positionable in the airway at a treatment location proximate nerve tissue in a wall thereof, the microwave antenna being configured to deliver microwave energy so as to alter the nerve tissue in a manner which disrupts transmission of nerve signals therein while non-target tissue disposed between the microwave antenna and the nerve tissue is not permanently injured.

33. The pulmonary treatment apparatus of embodiment 32, further comprising a cooling device coupled to the elongate member configured to cool at least a portion of the non-target tissue while the microwave antenna delivers the microwave energy.

34. The pulmonary treatment apparatus of embodiment 32 wherein the cooling device comprises a jacket surrounding the microwave antenna.

35. The pulmonary treatment apparatus of embodiment 32 wherein the cooling device comprises an inflatable balloon having a chamber, the microwave antenna being disposed in the chamber.

36. The pulmonary treatment apparatus of embodiment 32 wherein at least a portion of the cooling device is disposed between the antenna and the wall of the airway when the antenna is positioned at the treatment location.

37. The pulmonary treatment apparatus of embodiment 32 wherein the microwave antenna is configured to heat the nerve tissue to a lethal nerve temperature while the non-target tissue is maintained at a temperature below a lethal tissue temperature.

38. The pulmonary treatment apparatus of embodiment 32 wherein the microwave antenna is configured to alter the nerve tissue while non-target tissue disposed beyond the nerve tissue is not permanently injured.

39. The pulmonary treatment apparatus of embodiment 32 wherein the microwave antenna operates at a frequency selected so that the microwave energy penetrates the airway wall to a depth of the nerve tissue with an intensity sufficient to alter the nerve tissue while having insufficient intensity in non-target tissue beyond the nerve tissue to cause permanent injury.

40. The pulmonary treatment apparatus of embodiment 32, further comprising at least one supporting element movable from a contracted position to an expanded position and configured to engage the wall of the airway to position the microwave antenna.

41. The pulmonary treatment apparatus of embodiment 32 wherein the antenna comprises a plurality of longitudinally spaced slots.

42. The pulmonary treatment apparatus of embodiment 32 wherein the microwave antenna comprises a dual antenna system configured to produce a standing wave at a location corresponding to the nerve tissue when the microwave antenna is at the treatment location.

43. The pulmonary treatment apparatus of embodiment 32, further comprising a shield positioned and configured to block or attenuate the microwave energy emitted in a selected direction from the microwave antenna.

44. The pulmonary treatment apparatus of embodiment 32, further comprising a reflector positionable at a location spaced apart from the microwave antenna and configured to reflect the microwave energy delivered therefrom.

45. The pulmonary treatment apparatus of embodiment 44 wherein the reflector is positionable in an esophagus.

46. The pulmonary treatment apparatus of embodiment 45 wherein the reflector comprises an inflatable member connected to a source of inflation fluid.

47. The pulmonary treatment apparatus of embodiment 32, further comprising a protection member positionable in an esophagus.

48. The pulmonary treatment apparatus of embodiment 47 wherein the protection member comprises an expandable member configured to engage esophageal tissue and absorb heat therefrom.

49. The pulmonary treatment apparatus of embodiment 47 wherein the protection member is configured to absorb microwave energy delivered from the microwave antenna.

50. The pulmonary treatment apparatus of embodiment 32 wherein the microwave antenna is positionable through a bronchoscope to the treatment location.

51. A method of pulmonary treatment comprising:

positioning an elongate member through at least a portion of the trachea into an airway, the elongate member having a treatment element and an sensor coupled thereto;

sensing a first tissue characteristic using the sensor with the treatment element at a first airway location;

comparing the first tissue characteristic to a reference value to evaluate the location of the treatment element in the airway; and

activating the treatment element to treat the airway.

52. The method of embodiment 51 wherein the sensor comprises at least one impedance sensor configured to sense tissue impedance.

53. The method of embodiment 51 wherein the treatment element is activated at a second airway location between two adjacent cartilage rings of the airway.

54. The method of embodiment 53 wherein the first airway location is at least partially surrounded by one of the cartilage rings, further comprising re-positioning the treatment element to the second airway location before activating the treatment element.

55. The method of embodiment 51 , further comprising estimating the location of a non-target structure relative to the treatment element based on the first impedance.

56. The method of embodiment 55, further comprising, after estimating the location of the non-target structure, repositioning the treatment element before actuation thereof so as to avoid injury to the non-target structures.

57. The method of embodiment 51 wherein the non-target structure comprises the esophagus.

58. The method of embodiment 51 , further comprising detecting previously treated tissue based on the first impedance.

59. The method of embodiment 58, further comprising, after detecting the previously treated tissue, repositioning the treatment element before actuation thereof to avoid re-treatment of the previously treated tissue.

60. The method of embodiment 51 wherein activating the treatment element comprises delivering energy therefrom to tissue in a wall of the airway.

61. The method of embodiment 60 wherein the energy alters nerve tissue in the wall of the airway to disrupt transmission of nerve signals therein.

62. The method of embodiment 61, further comprising protecting non-target tissue between the treatment element and the nerve tissue from permanent injury.

63. An apparatus for pulmonary treatment comprising: an elongate member insertable through a trachea into an airway;
an active electrode coupled to the elongate member and configured to deliver energy to target tissue in a wall of the airway.
a return electrode positionable in the airway or the esophagus and configured to receive the energy from the target tissue; and
a protection member configured to cool non-target tissue proximate to the target tissue.

64. The apparatus of embodiment 63 wherein the return electrode is coupled to the elongate member so as to be positionable in the airway adjacent to the active electrode.

65. The apparatus of embodiment 63 wherein the active electrode is configured to engage a posterior aspect of the airway and the return electrode is configured to engage an anterior aspect of the airway.

66. The apparatus of embodiment 63 wherein the active electrode comprises a plurality of conductive bands movable from a contracted configuration to an expanded configuration.

67. The apparatus of embodiment 66 wherein the return electrode comprises at least one additional conductive band coupled to the conductive bands of the active electrode and electrically isolated therefrom, the return electrode being movable with the active electrode from a contracted configuration to an expanded configuration.

68. The apparatus of embodiment 63 wherein the active electrode is disposed on the exterior of an expandable balloon coupled to the elongate member.

69. The apparatus of embodiment 68 wherein the balloon is connected to source of coolant, the protection member comprising a cooled portion of the balloon.

70. The apparatus of embodiment 63 wherein the active electrode is expandable from a contracted configuration to an expanded configuration without the use of a balloon.

71. The apparatus of embodiment 70 wherein the active electrode is configured to fit between a first pair of adjacent cartilage rings of the airway in the expanded configuration.

72. The apparatus of embodiment 70 wherein the return electrode is configured to fit between a second pair of adjacent cartilage rings of the airway while the active electrode is positioned between the first pair of adjacent cartilage rings.

73. The apparatus of embodiment 63 wherein the active electrode is carried by an actuable device movable between a delivery configuration and a deployed configuration, the actuable device is coupled to the elongate member.

74. The apparatus of embodiment 73 wherein the actuable device defines a plurality of spaced apart rings configured to preferentially seat in one or more intercartilaginous spaces.

75. The apparatus of embodiment 74 wherein the actuable device has a helical or ring-shape in the deployed configuration.

76. The apparatus of embodiment 63 wherein the active electrode comprises a cooling channel fluidly coupled to a source of coolant.

77. The apparatus of embodiment 63 wherein the return electrode is coupled to an elongate shaft positionable in the esophagus.

78. The apparatus of embodiment 63 wherein the protection member is positionable in the esophagus while the elongate member and active electrode are positioned in the airway.

79. The apparatus of embodiment 78 wherein the protection member comprises an expandable member configured to engage esophageal tissue.

80. The apparatus of embodiment 79 wherein the return electrode is coupled to the expandable member.

81. A method of pulmonary treatment comprising:

inserting an elongate member through at least a portion of a trachea such that an energy delivery element coupled to the elongate member is positioned at a treatment site in an airway;

delivering energy at a first power level from an active portion of the energy delivery element to create a first lesion covering a first portion of a

circumference of the airway;

moving the energy delivery element; and

delivering energy at a second power level from the active portion of the energy delivery element to create a second lesion covering a second portion of the circumference of the airway displaced from the first portion;

wherein the first power level is substantially greater than the second power level.

82. The method of embodiment 81 wherein the second portion is circumferentially or axially displaced from the first portion relative to lumen of the airway.

83. The method of embodiment 81 wherein the first portion of the circumference is on an anterior aspect of the airway.

84. The method of embodiment 81 wherein the second portion is on a posterior aspect of the airway.

85. The method of embodiment 81 wherein the second power level is about 50% to about 80% of the first power level.

86. The method of embodiment 81 wherein the second power level is selected to avoid permanent injury to non-target tissue proximate to the treatment site.

87. The method of embodiment 86 wherein the first power level would permanently injure the non-target tissues if delivered to the second portion of the circumference.

88. The method of embodiment 87 wherein the non-target tissue comprises tissue of the esophagus.

89. The method of embodiment 81 wherein the airway comprises the left main bronchus.

90. The method of embodiment 81 wherein the first and second lesions are created at a depth in the airway wall without permanently injuring non-target tissue of the airway wall between the energy delivery element and the first and second lesions.

91. The method of embodiment 90, further comprising cooling tissue of the airway wall during the creation of the first and second lesions.

92. The method of embodiment 81 wherein at least one of the first and second lesions are created so as to alter nerve tissue in or proximate to the airway wall to disrupt signal transmission along the airway.

93. The method of embodiment 81 wherein moving the energy delivery element includes rotating the energy delivery element about a longitudinal axis of the airway.

94. A method of pulmonary treatment comprising:

delivering a first amount of energy from an energy delivery device to a first portion of a wall of an airway; and

delivering a second amount of energy from the energy delivery device to a second portion of the wall of the airway, the first portion of the wall and the second portion of the wall are spaced apart from one another or partially overlap one another, and the second amount of energy is different from the first amount of energy.

95. The method of embodiment 94, further comprising moving an elongate body and the energy delivery device coupled to the elongated body relative to the wall of the airway after delivering the first amount of energy and prior to delivering the second amount of energy.

96. The method of embodiment 94 wherein the first portion of the airway is located at an anterior region of the airway, and the first amount of energy is greater than the second amount of energy.

97. The method of embodiment 94 wherein delivering the first amount of energy comprises delivering energy at a first power level from an active portion of the energy delivery device, and delivering the second amount of energy comprises delivering energy at a second power level from the active portion of the energy delivery device.

98. The method of embodiment 94, further comprising ablating substantially all of the nerve trunks travelling along the wall of the airway using energy delivered from the energy delivery device.

99. A method of pulmonary treatment comprising:

positioning an energy delivery element in an airway of a subject;

non-inflatably moving the energy delivery element into engagement with a wall of the airway;

delivering energy from the energy delivery element to the wall of the airway to alter target nerve tissue therein or proximate thereto; and

introducing a cooling medium into the airway into direct contact with the wall to absorb heat from the wall while delivering the energy.

100. The method of embodiment 99 wherein the energy delivery element comprises a first electrode, the first electrode being positioned within a first space between a first pair of adjacent cartilage rings of the airway.

101. The method of embodiment 100, further comprising placing a second electrode in a second space between a second pair of adjacent cartilage rings of the airway.

102. The method of embodiment 100, further comprising delivering energy between the first and second electrodes to alter target tissue in a wall of the airway longitudinally displaced from the first and second spaces.

103. The method of embodiment 99, further comprising positioning a protection device in the esophagus to absorb heat from esophageal tissue while delivering the energy.

104. The method of embodiment 103, further comprising receiving energy with or delivering energy from a second electrode coupled to the protection device.

105. The method of embodiment 99 wherein a surface layer of tissue of the wall is protected from permanent injury while a lesion of permanently injured tissue is created at a depth below the surface layer.

106. The method of embodiment 105 wherein the surface layer is at least about 2 mm in thickness.

107. The method of embodiment 105 wherein the lesion contains the nerve tissue.

108. The method of embodiment 105 wherein the nerve tissue is altered sufficiently to reduce airway constriction in the subject.

109. The method of embodiment 99 wherein the cooling medium is a gas.

110. The method of embodiment 99 wherein the energy delivery element is coupled to an elongate member, and the cooling medium is introduced into the airway through a channel in the elongate member.

111. The method of embodiment 110 wherein the cooling medium flows through a channel in the energy delivery element to absorb heat therefrom.

Claims

1. A pulmonary treatment apparatus comprising:

   an elongate member insertable through at least a portion of a trachea into a first airway;
   a microwave antenna coupled to the elongate member and positionable in the first airway at a treatment location proximate nerve tissue of a nerve trunk in or around an airway wall thereof; and
   a cooling device having an outer member surrounding the microwave antenna and configured to contact the airway wall, the cooling device including a cooling chamber configured to contain coolant so as to cool the outer member,
   wherein the microwave antenna is configured to deliver microwave energy through the outer member and the airway wall to a depth of the nerve tissue so as to alter the nerve tissue in a manner which reduces airway resistance in a second airway of higher generation than the first airway, and
   wherein the cooling device is configured to absorb sufficient heat from non-target tissue disposed between the outer member and the nerve tissue during delivery of the microwave energy such that the non-target tissue is not permanently injured.

2. The pulmonary treatment apparatus of claim 1, wherein the cooling device comprises a jacket surrounding the microwave antenna.

3. The pulmonary treatment apparatus of claim 1 or 2, wherein the cooling device comprises an inflatable balloon

having a chamber, the microwave antenna being disposed in the chamber.

4. The pulmonary treatment apparatus of any of the preceding claims, wherein at least a portion of the cooling device is disposed between the antenna and the wall of the airway when the antenna is positioned at the treatment location.

5. The pulmonary treatment apparatus of any of the preceding claims, wherein the microwave antenna operates at a frequency selected so that the microwave energy penetrates the airway wall to a depth of the nerve tissue with an intensity sufficient to alter the nerve tissue while having insufficient intensity in non-target tissue beyond the nerve tissue to cause permanent injury.

6. The pulmonary treatment apparatus of any of the preceding claims, further comprising at least one supporting element movable from a contracted position to an expanded position and configured to engage the wall of the airway to position the microwave antenna.

7. The pulmonary treatment apparatus of any of the preceding claims, wherein the antenna comprises a plurality of longitudinally spaced slots.

8. The pulmonary treatment apparatus of any of the preceding claims, wherein the microwave antenna comprises a dual antenna system configured to produce a standing wave at a location corresponding to the nerve tissue when the microwave antenna is at the treatment location.

9. The pulmonary treatment apparatus of any of the preceding claims, further comprising a shield positioned and configured to block or attenuate the microwave energy emitted in a selected direction from the microwave antenna.

10. The pulmonary treatment apparatus of any of the preceding claims, further comprising a reflector positionable at a location spaced apart from the microwave antenna and configured to reflect the microwave energy delivered therefrom.

11. The pulmonary treatment apparatus of claim 10, wherein the reflector is positionable in an esophagus and preferably comprises an inflatable member connected to a source of inflation fluid.

12. The pulmonary treatment apparatus of any of the preceding claims, further comprising a protection member positionable in an esophagus.

13. The pulmonary treatment apparatus of claim 12, wherein the protection member comprises an expandable member configured to engage esophageal tissue and absorb heat therefrom.

14. The pulmonary treatment apparatus of claim 12, wherein the protection member is configured to absorb microwave energy delivered from the microwave antenna.

15. The pulmonary treatment apparatus of any of the preceding claims, wherein the microwave antenna is positionable through a bronchoscope to the treatment location.

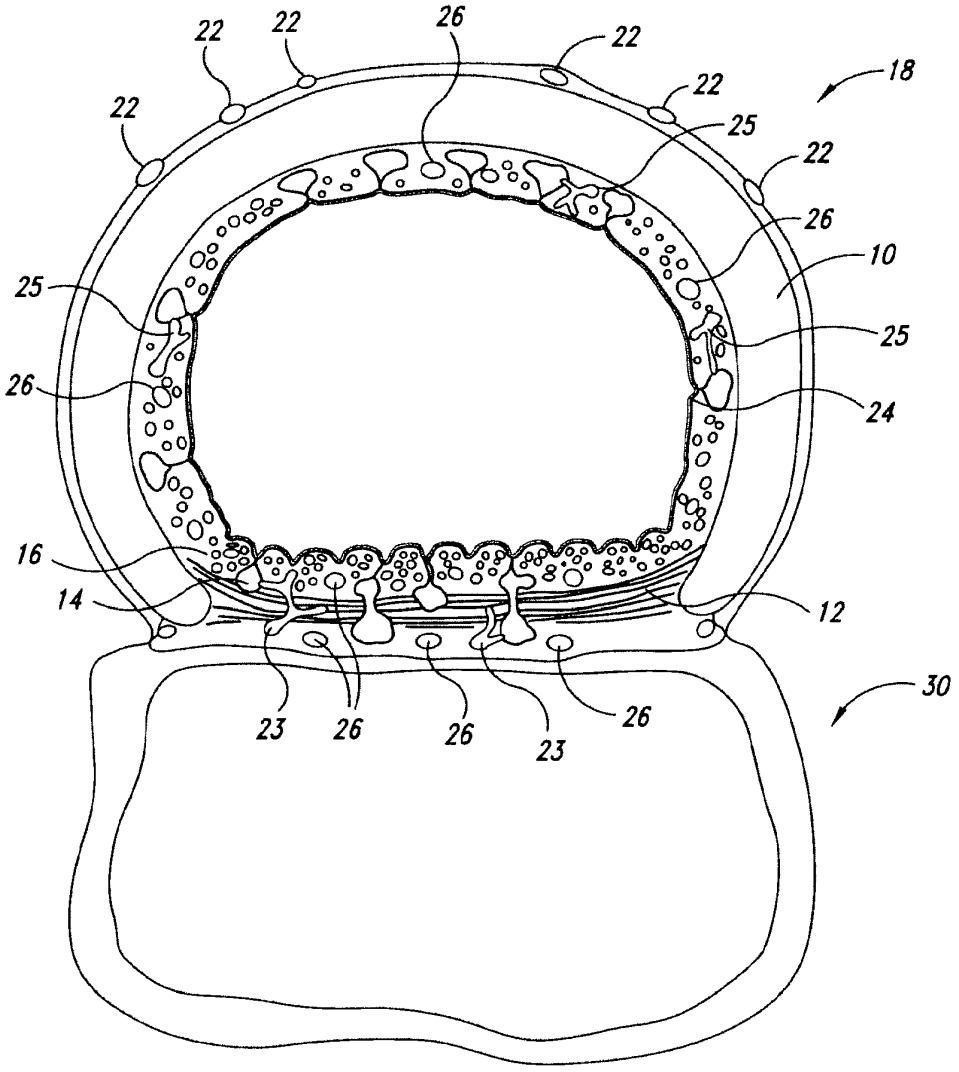

FIG. 1

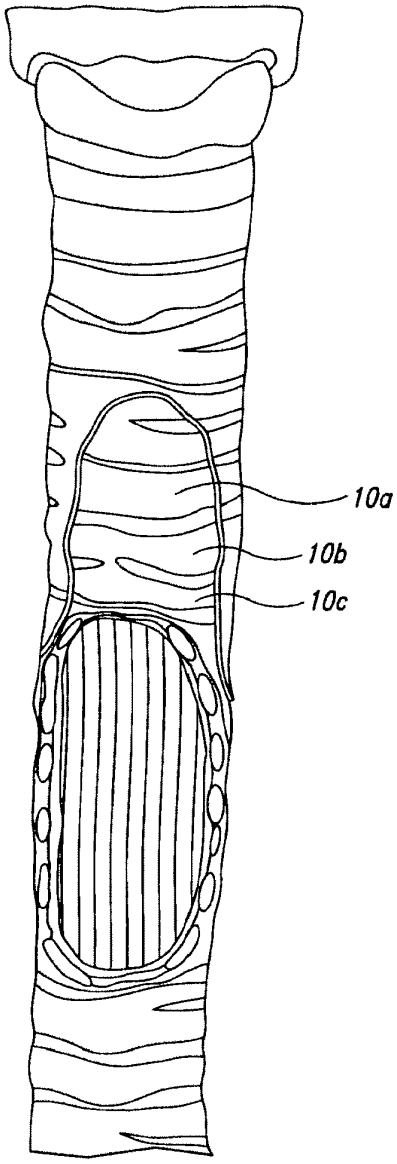

FIG. 2

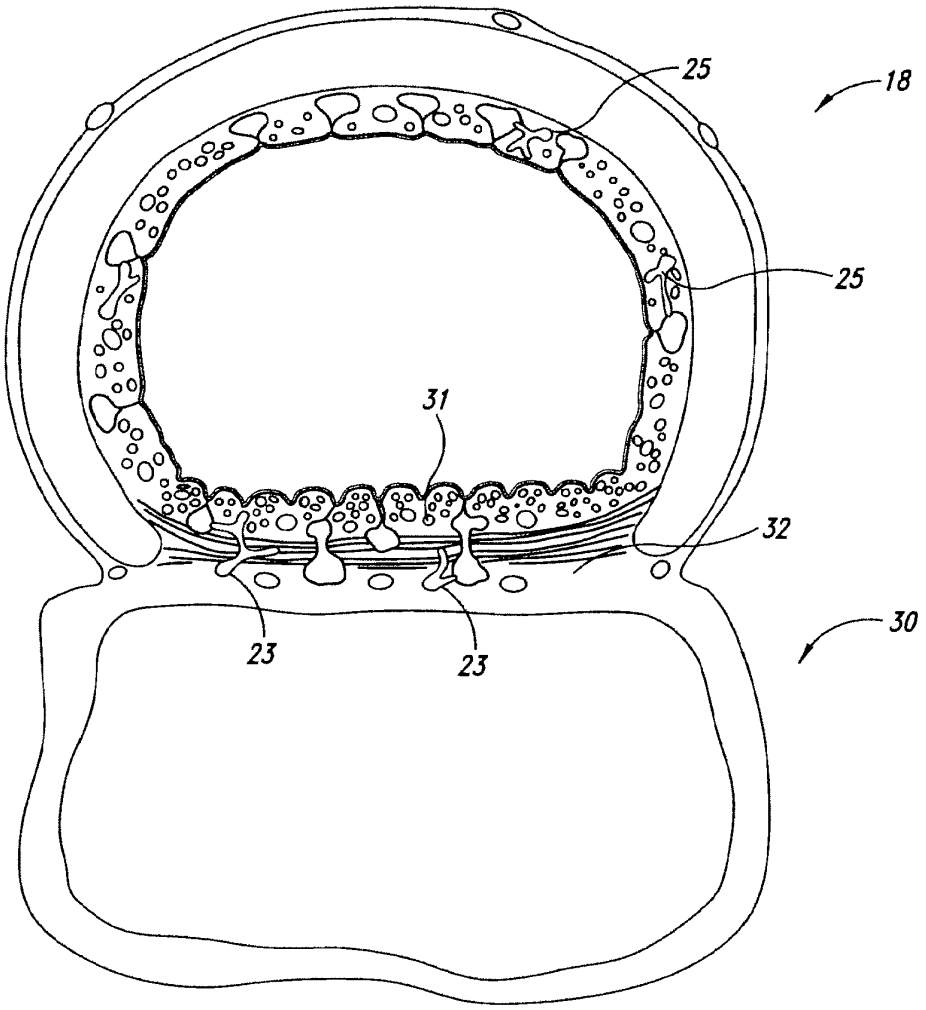

FIG. 3

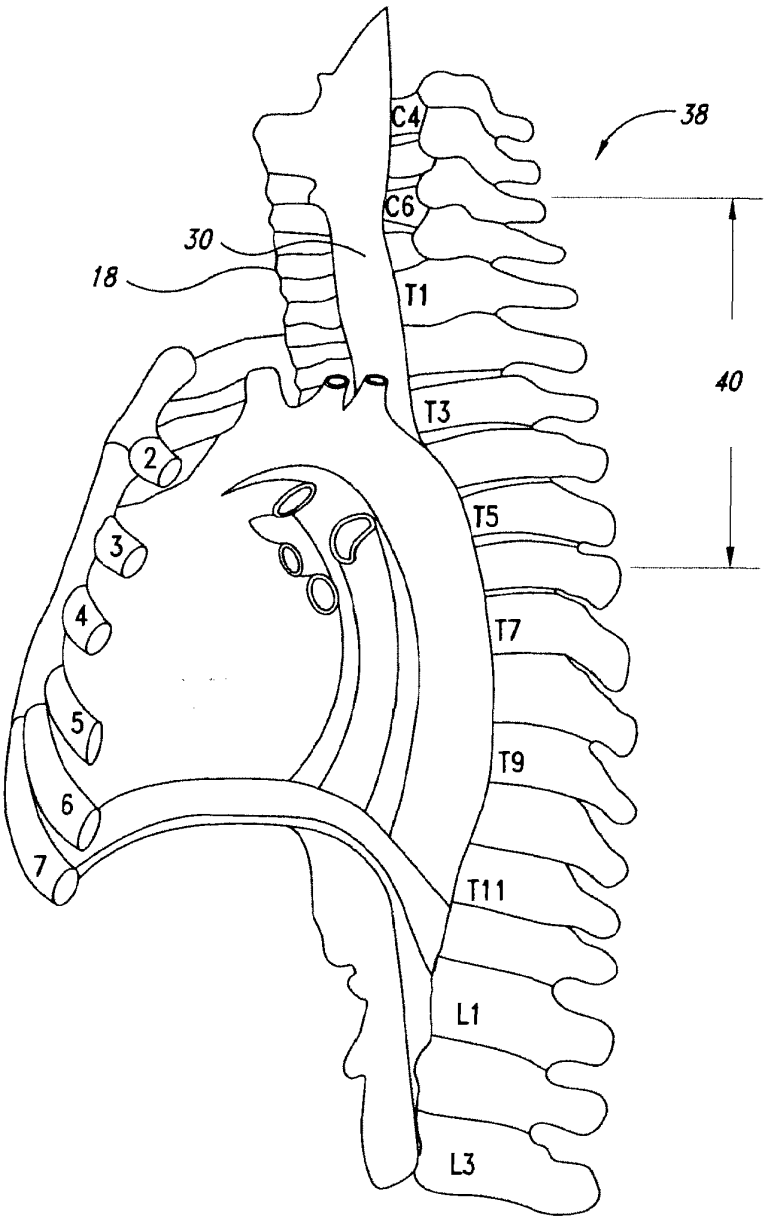

FIG. 4

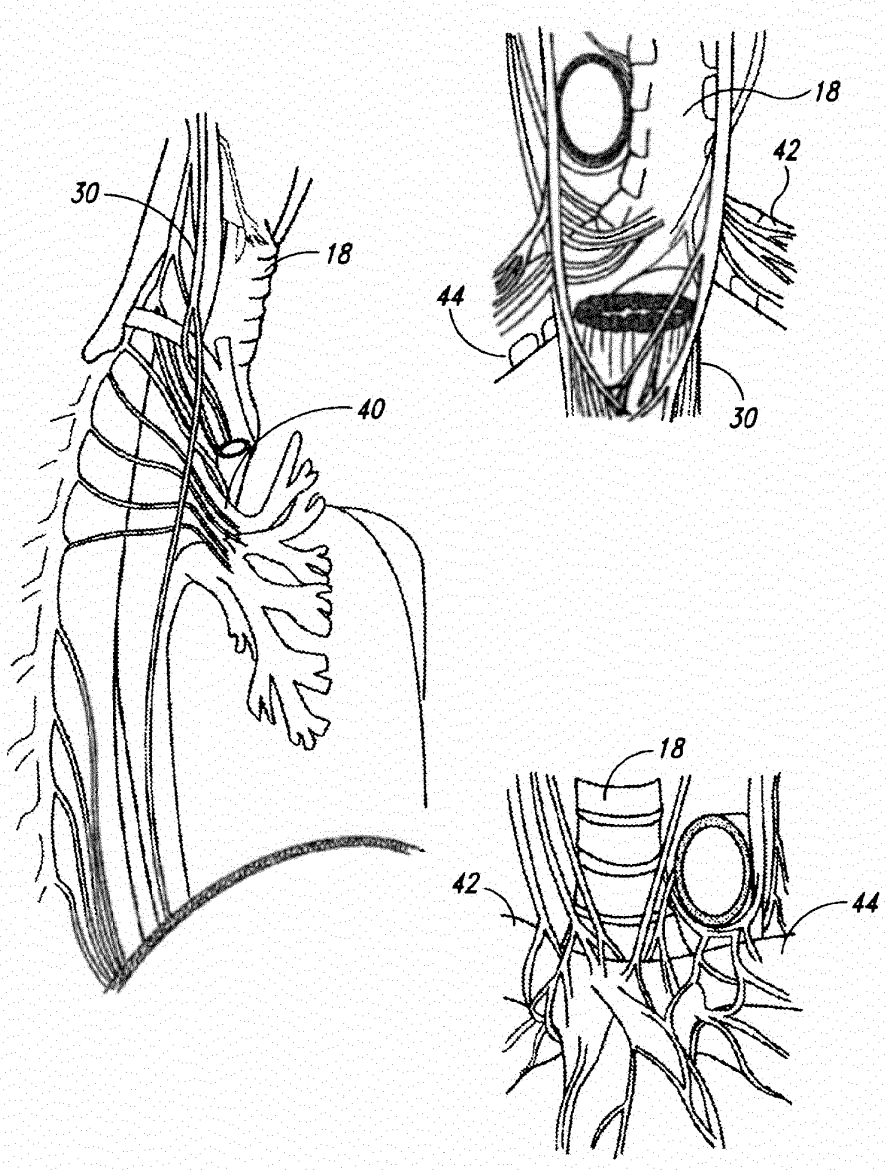

FIG. 4A

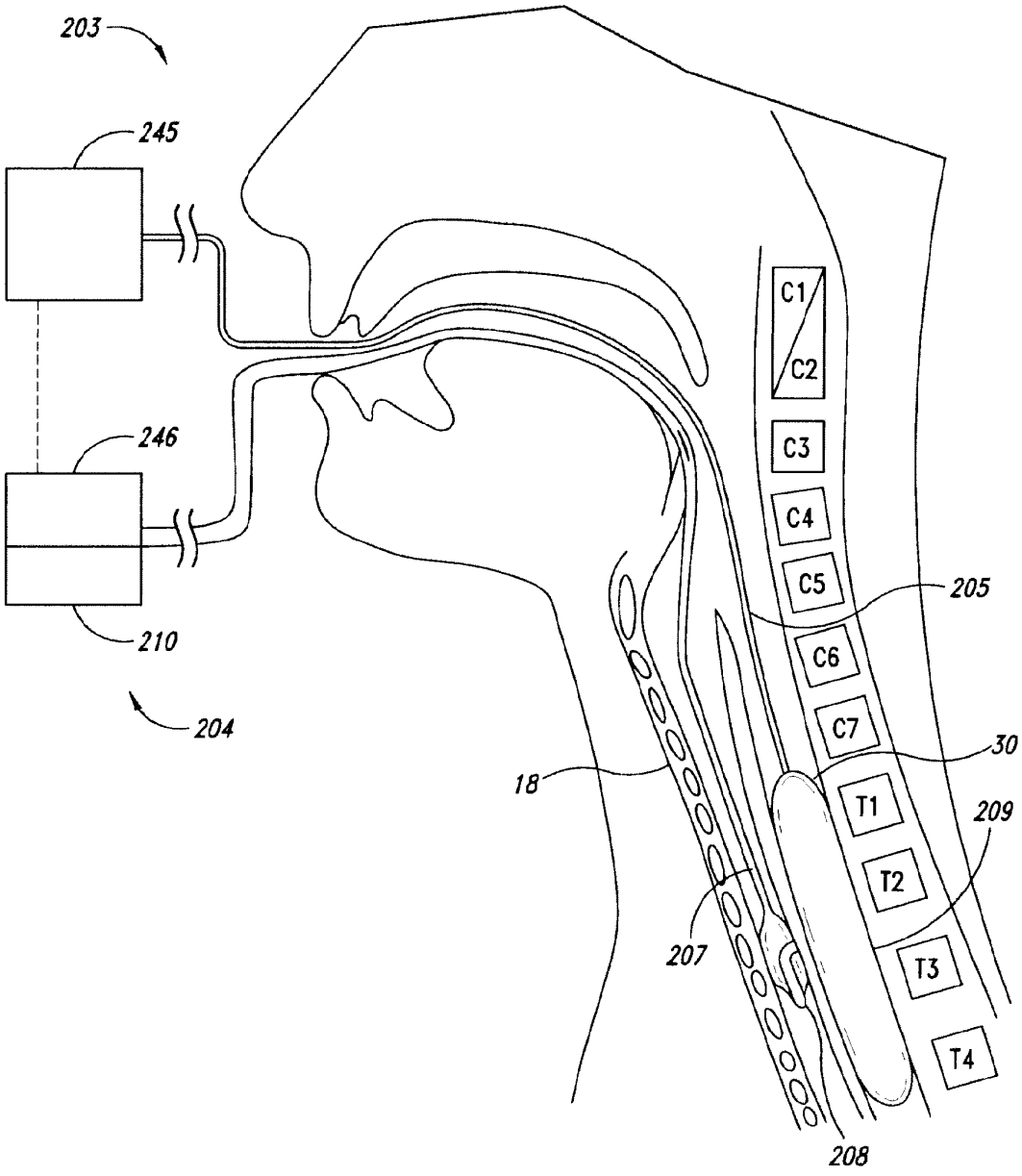

FIG. 5

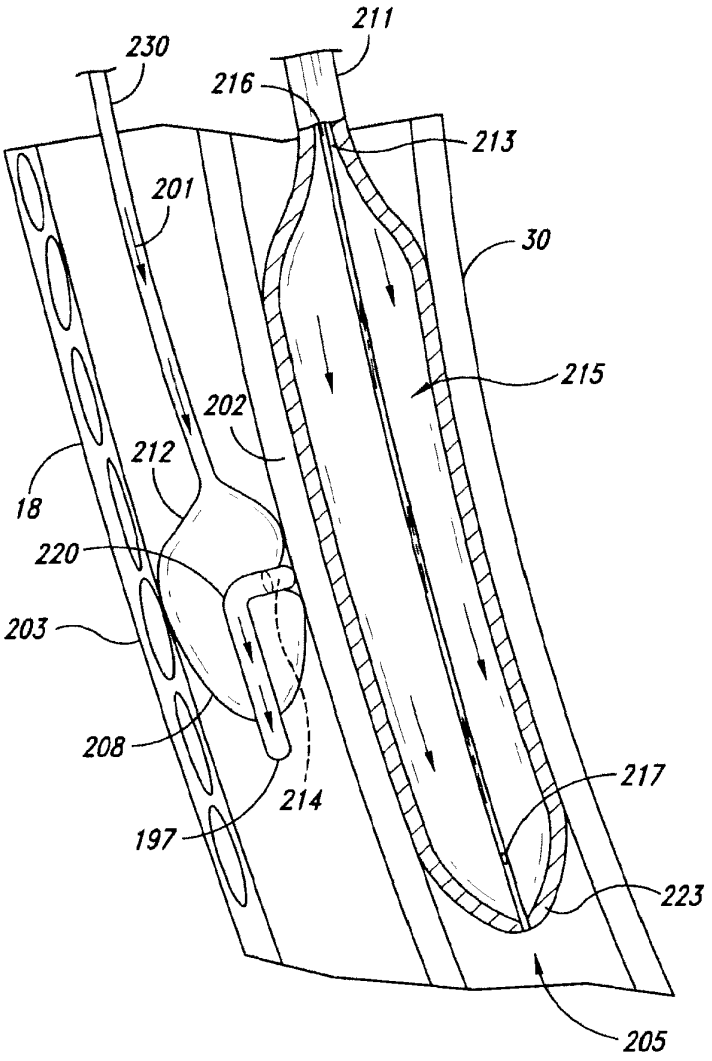

FIG. 6

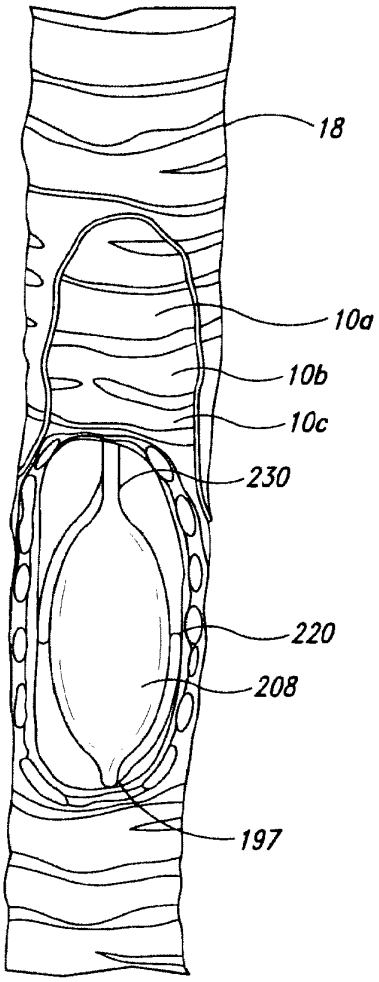

FIG. 7

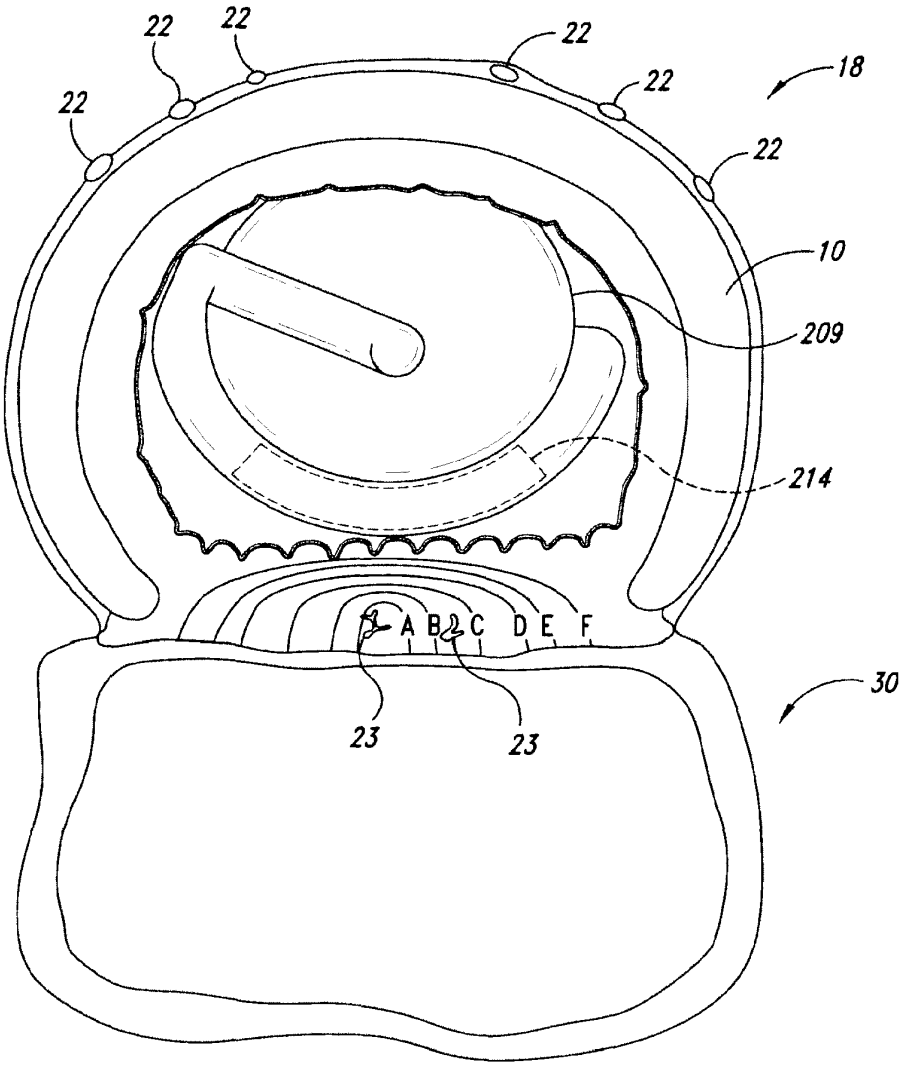

FIG. 8A

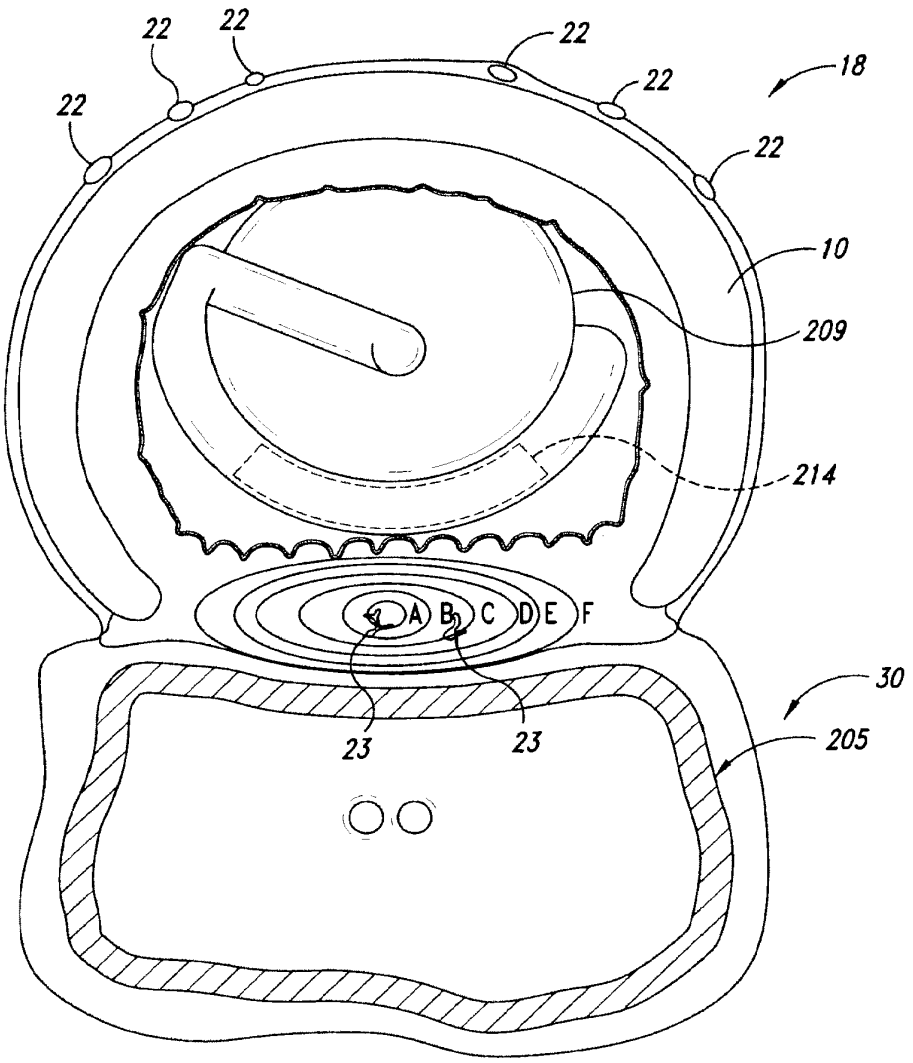

FIG. 8B

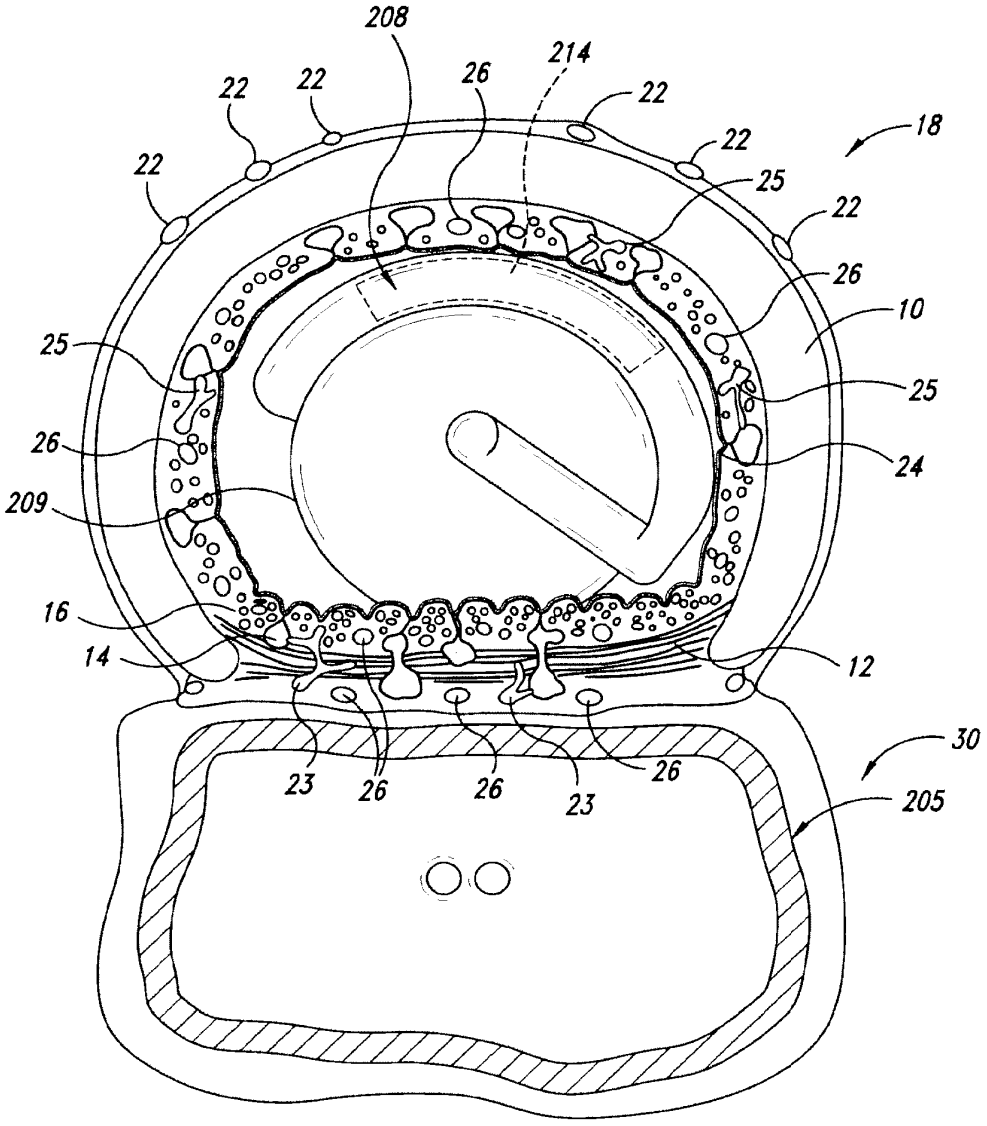

FIG. 9

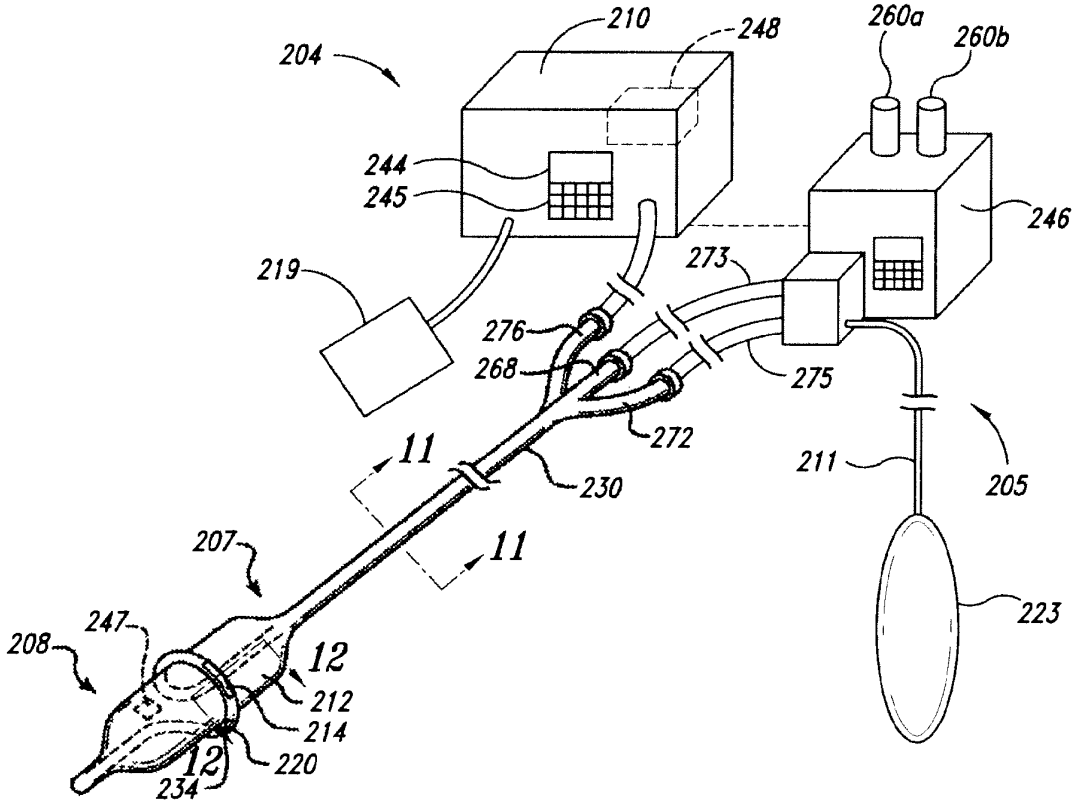

FIG. 10

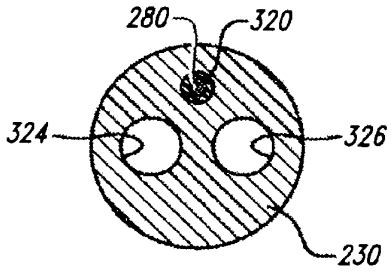

FIG. 11

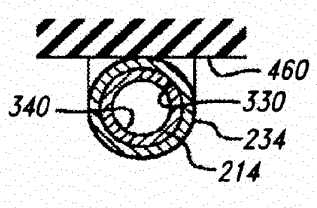

FIG. 12

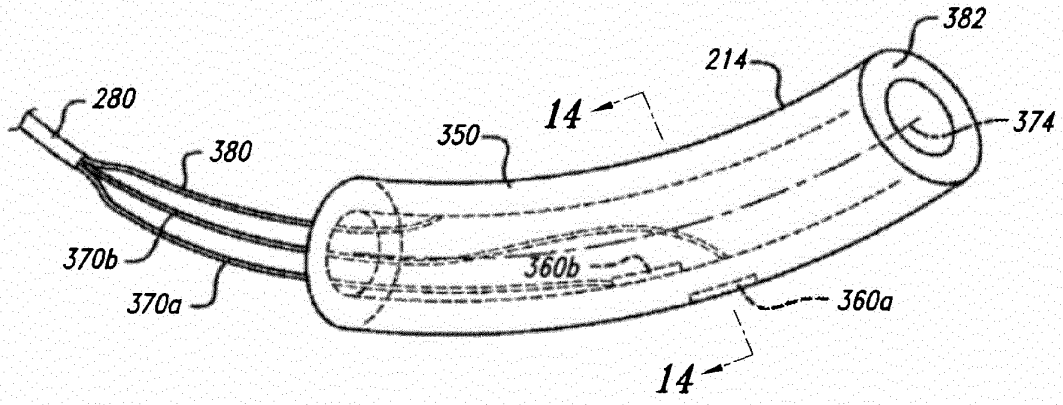

FIG. 13

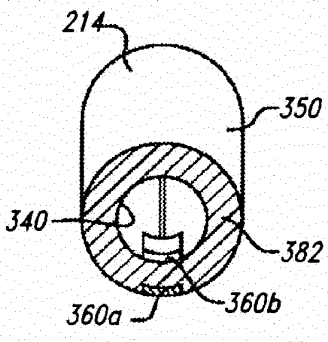

FIG. 14

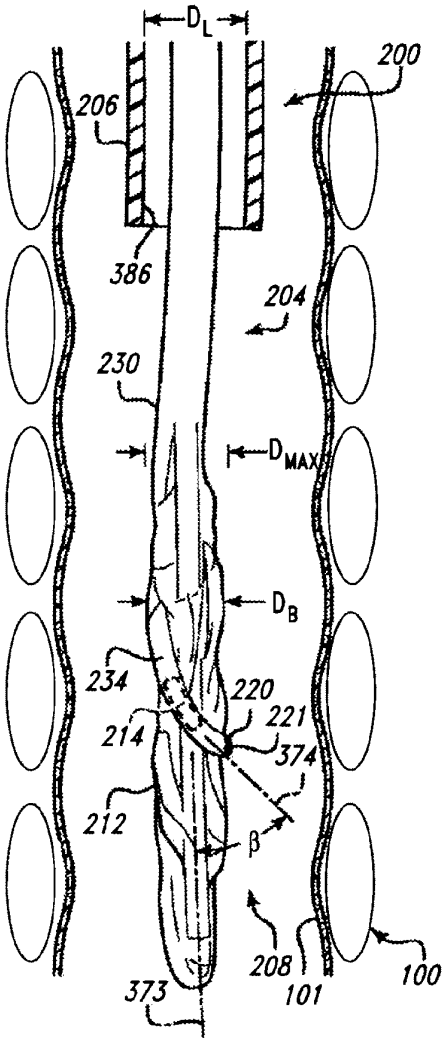

FIG. 15

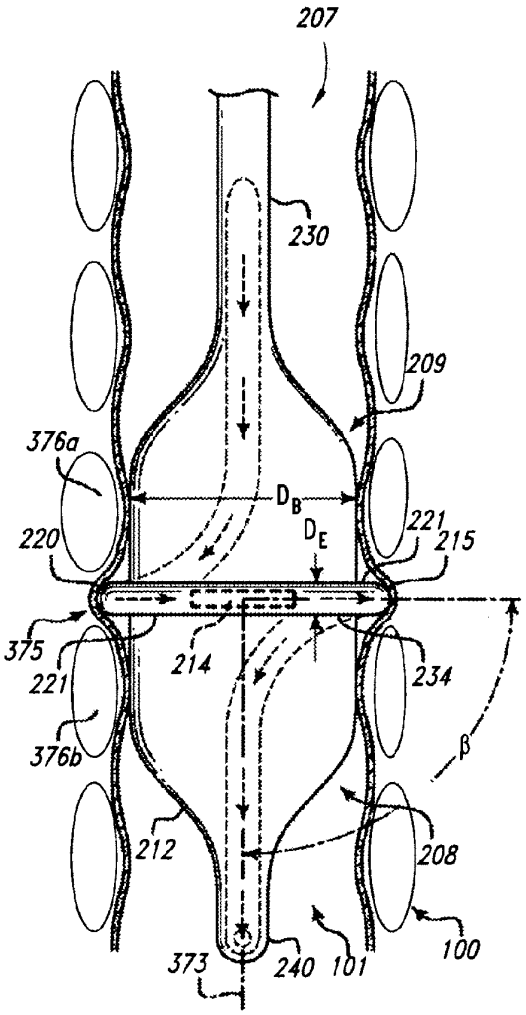

FIG. 16

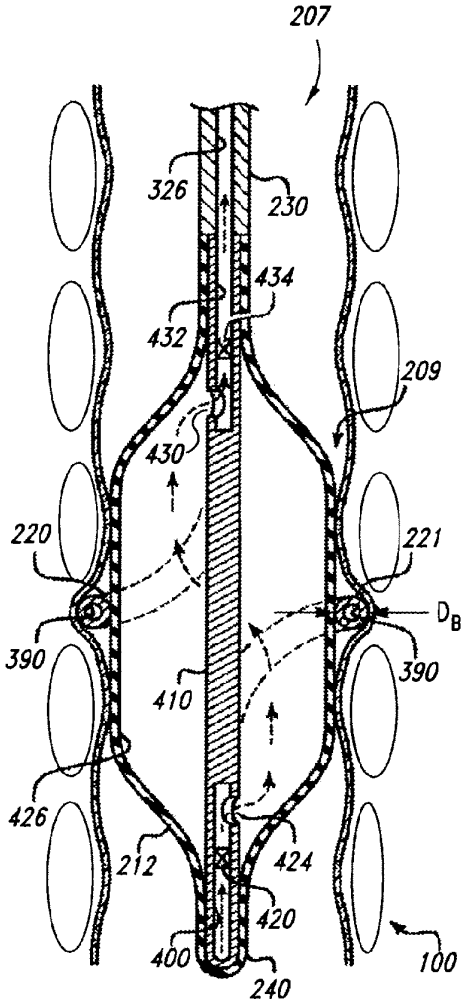

FIG. 17

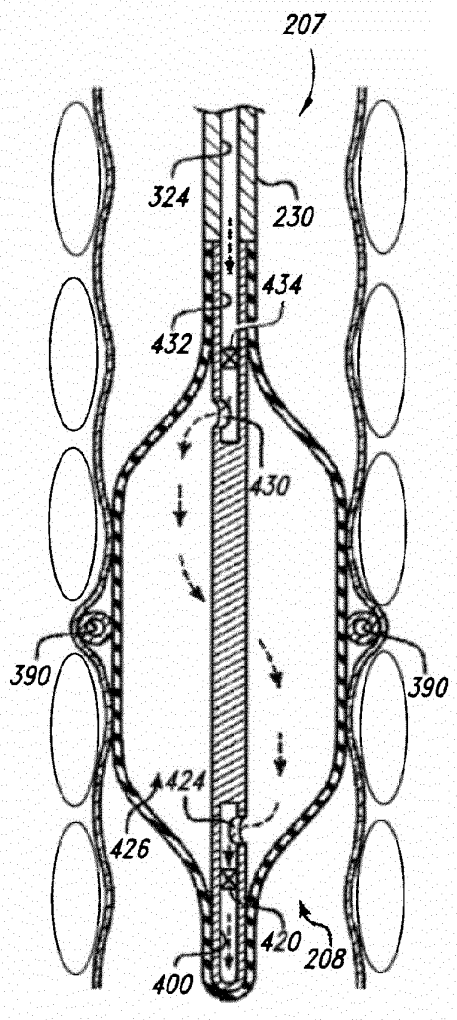

FIG. 18

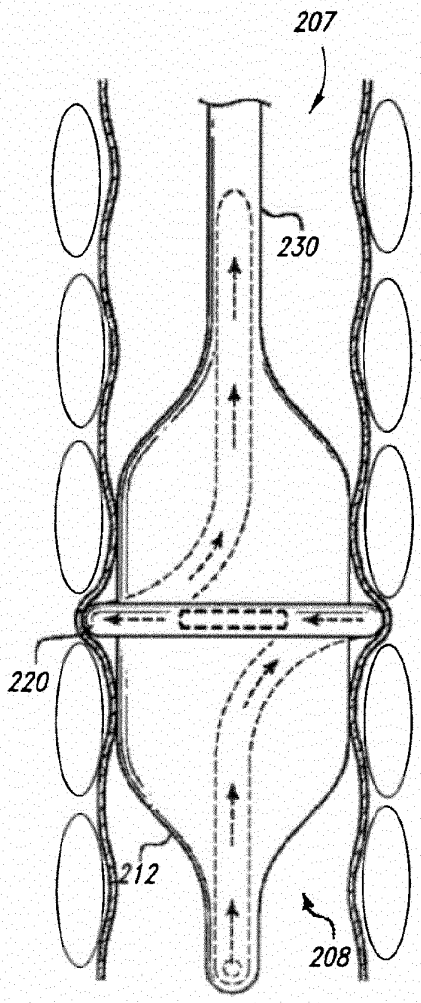

FIG. 19

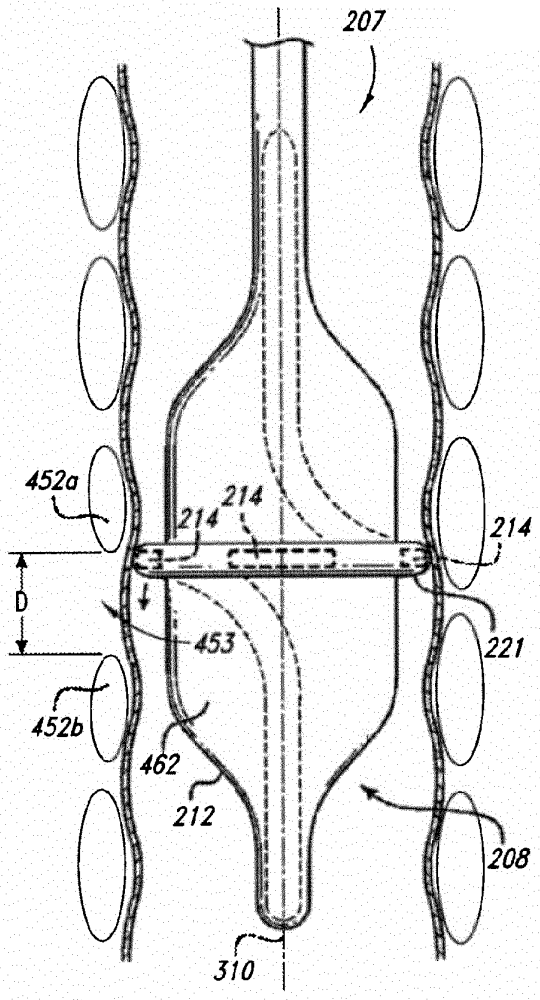

FIG. 20

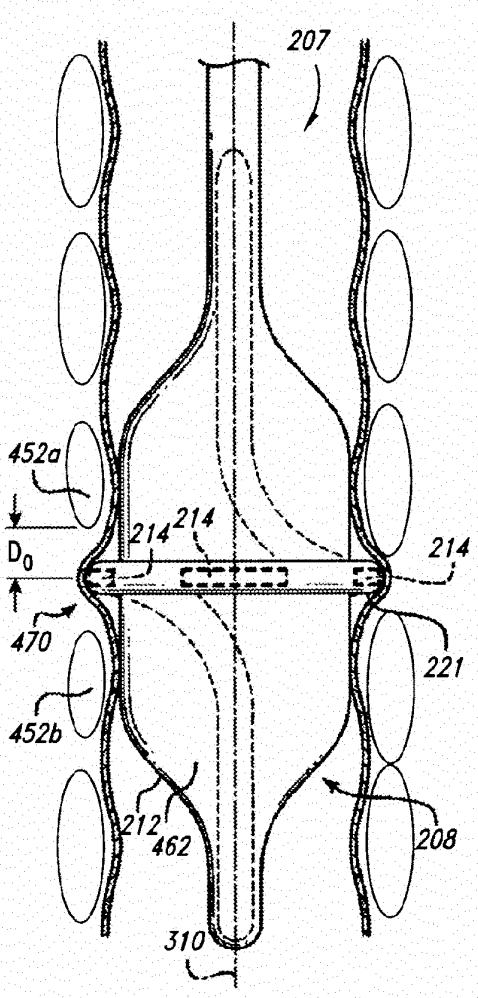

FIG. 21

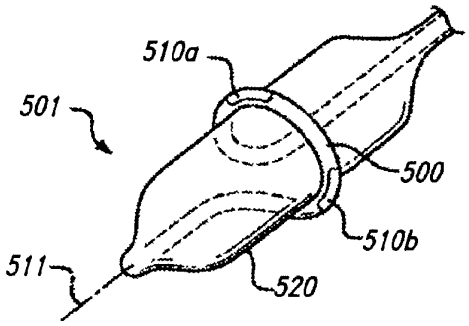

FIG. 22

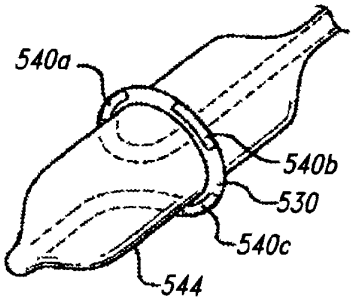

FIG. 23

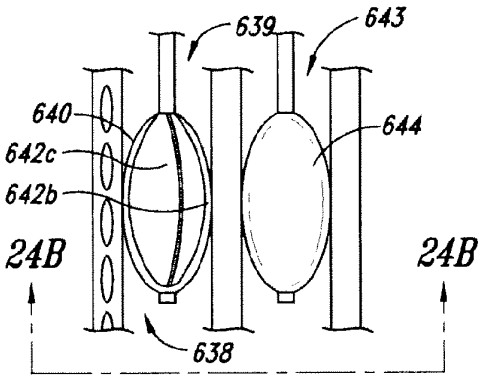

FIG. 24A

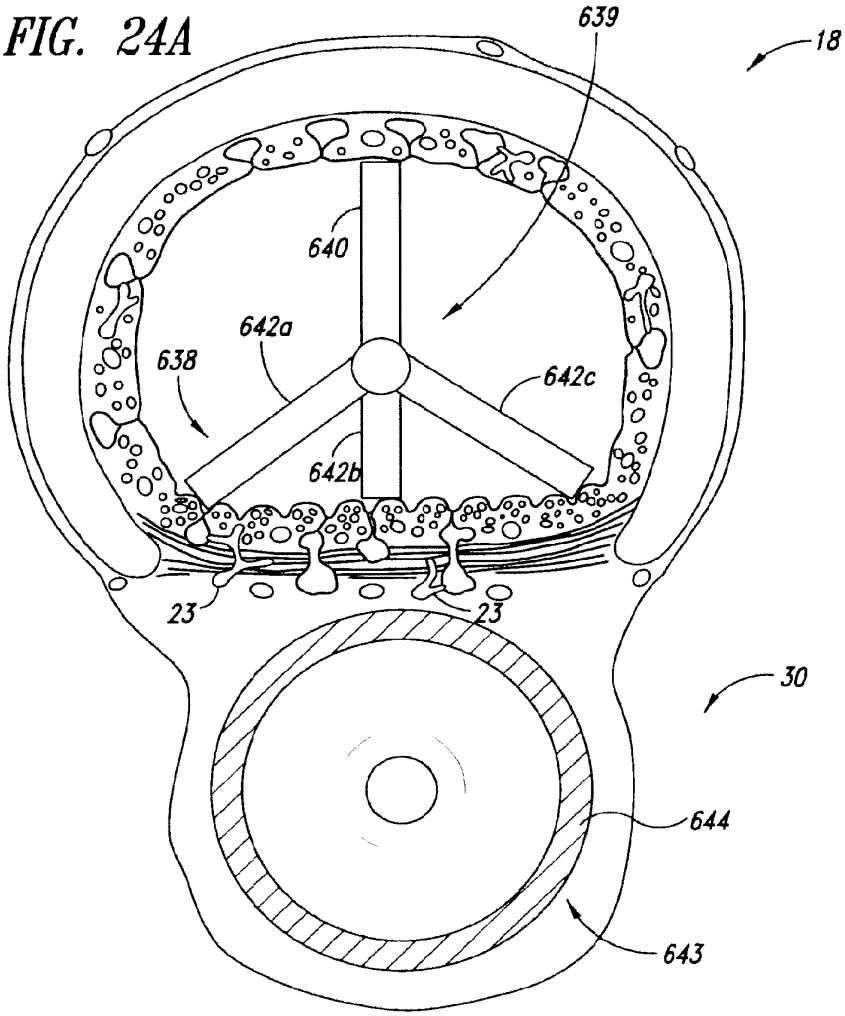

FIG. 24B

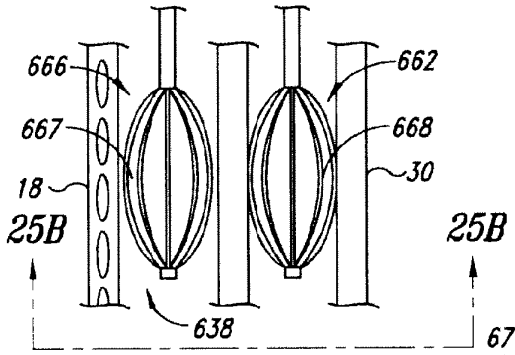

FIG. 25A

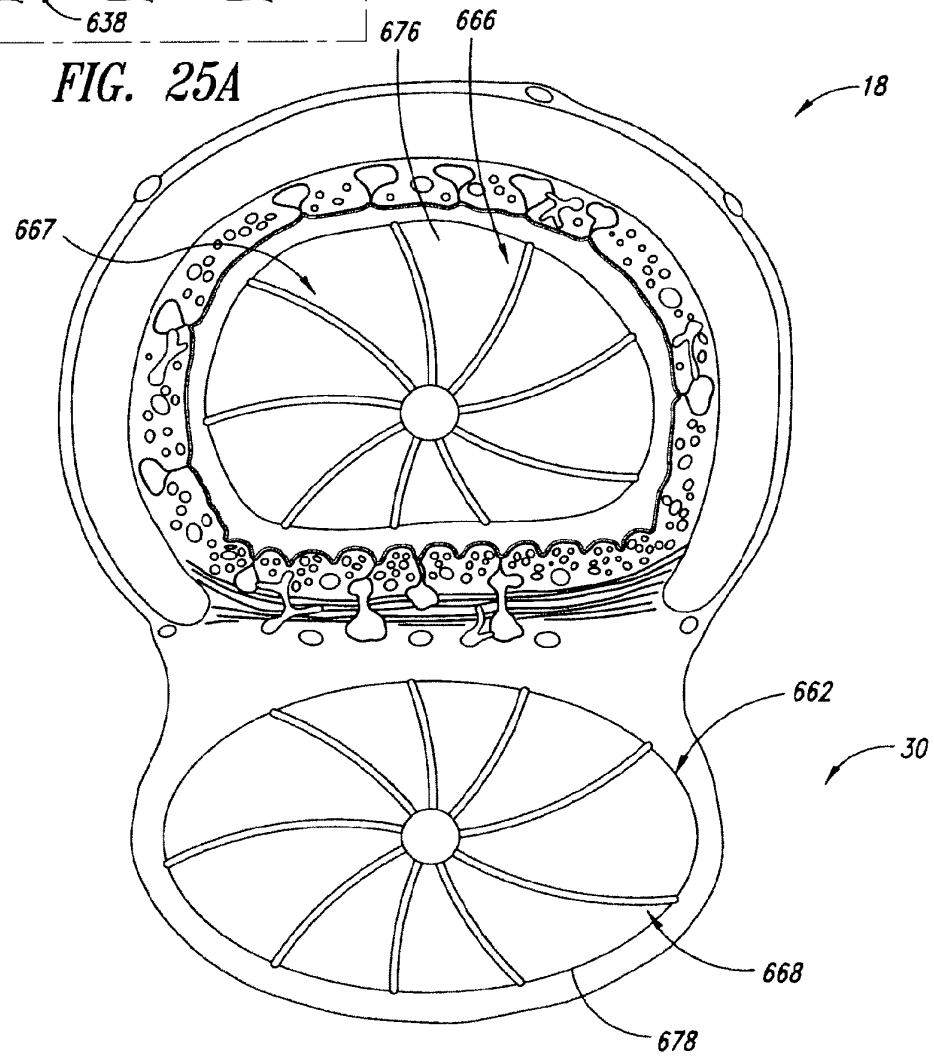

FIG. 25B

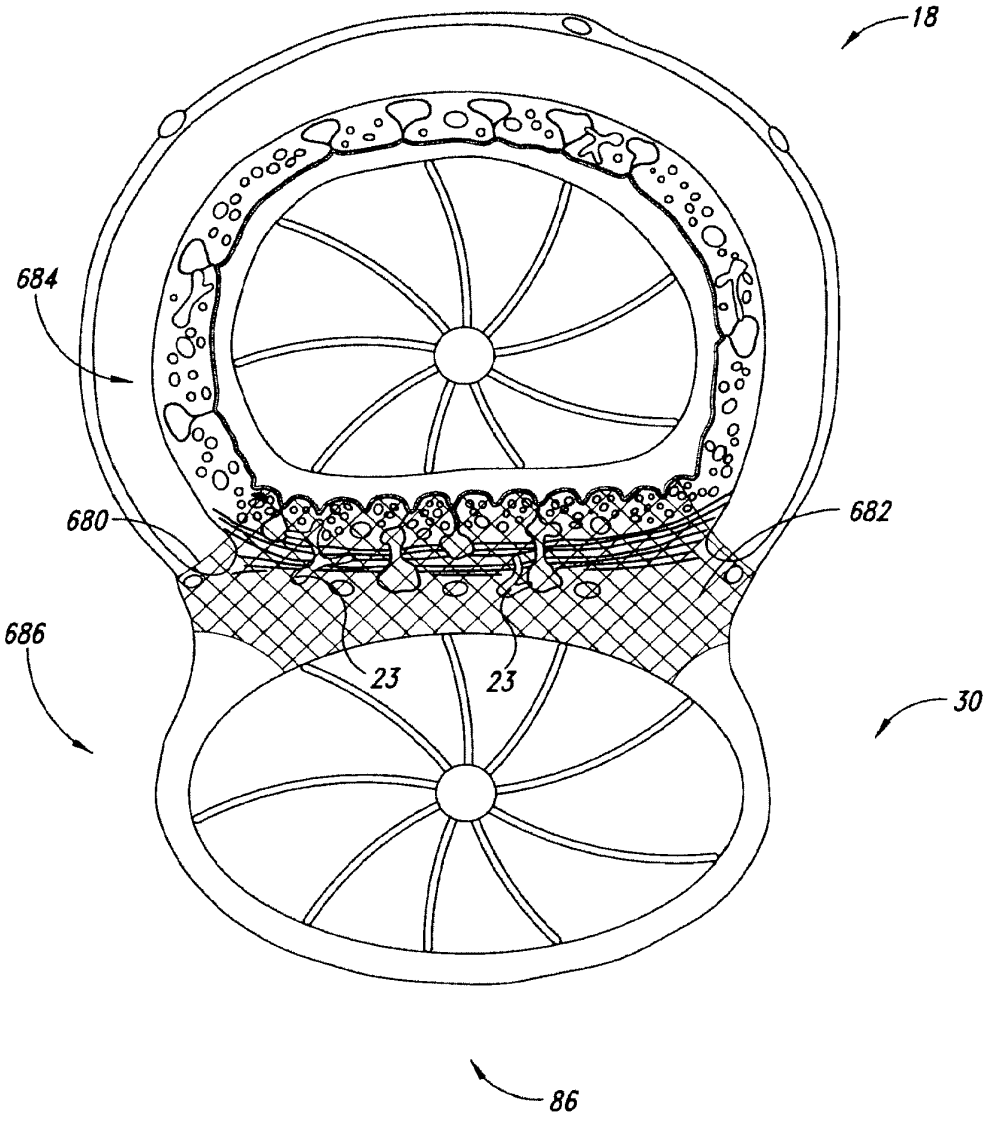

FIG. 26

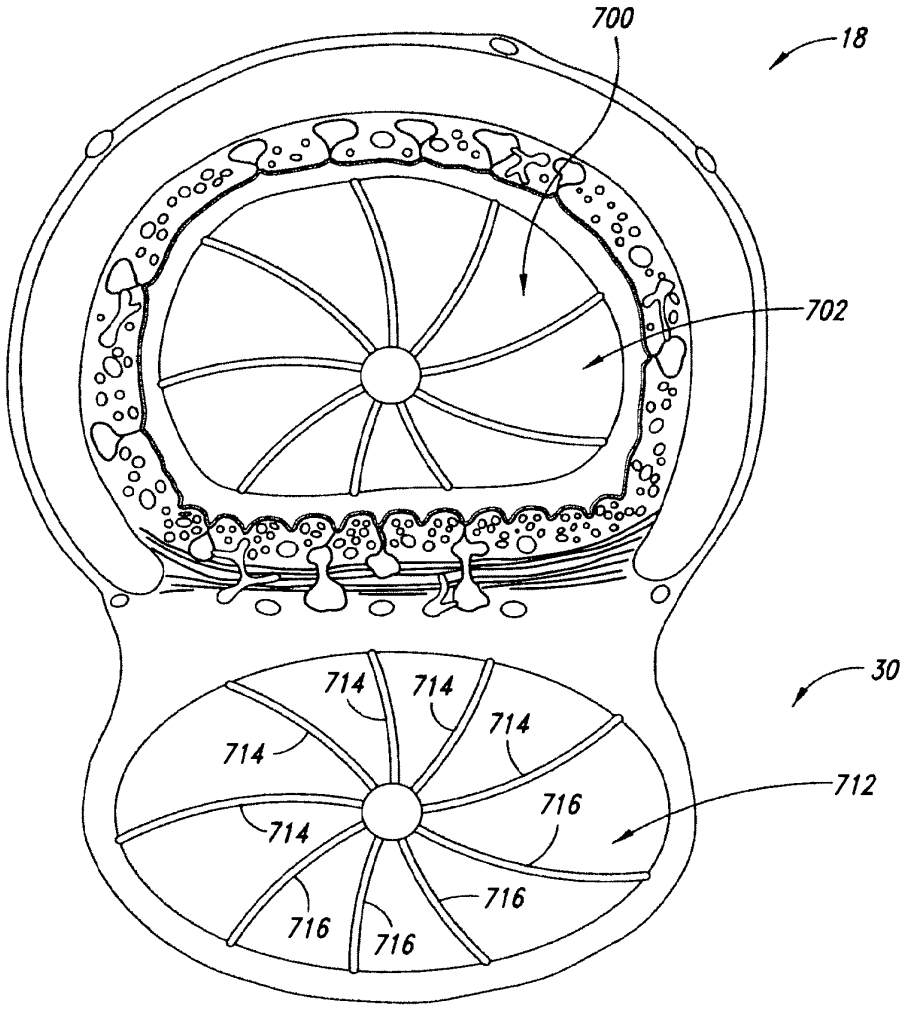

FIG. 27

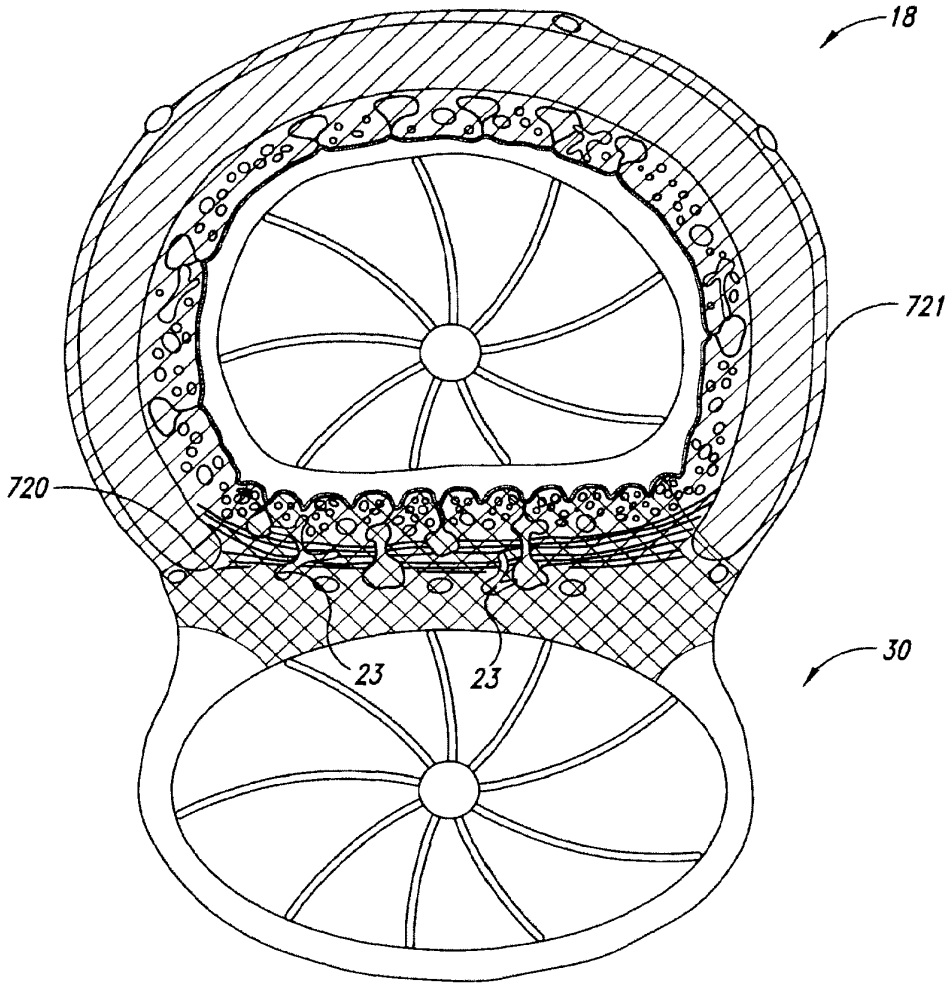

FIG. 28

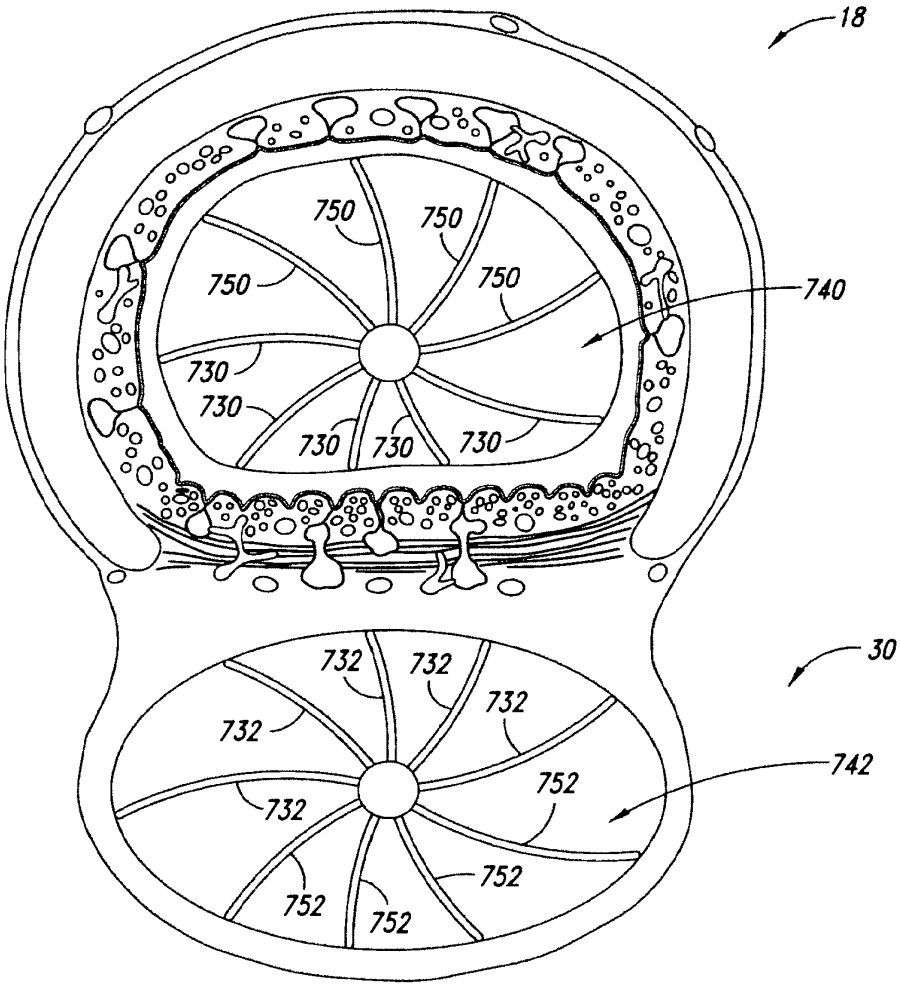

FIG. 29

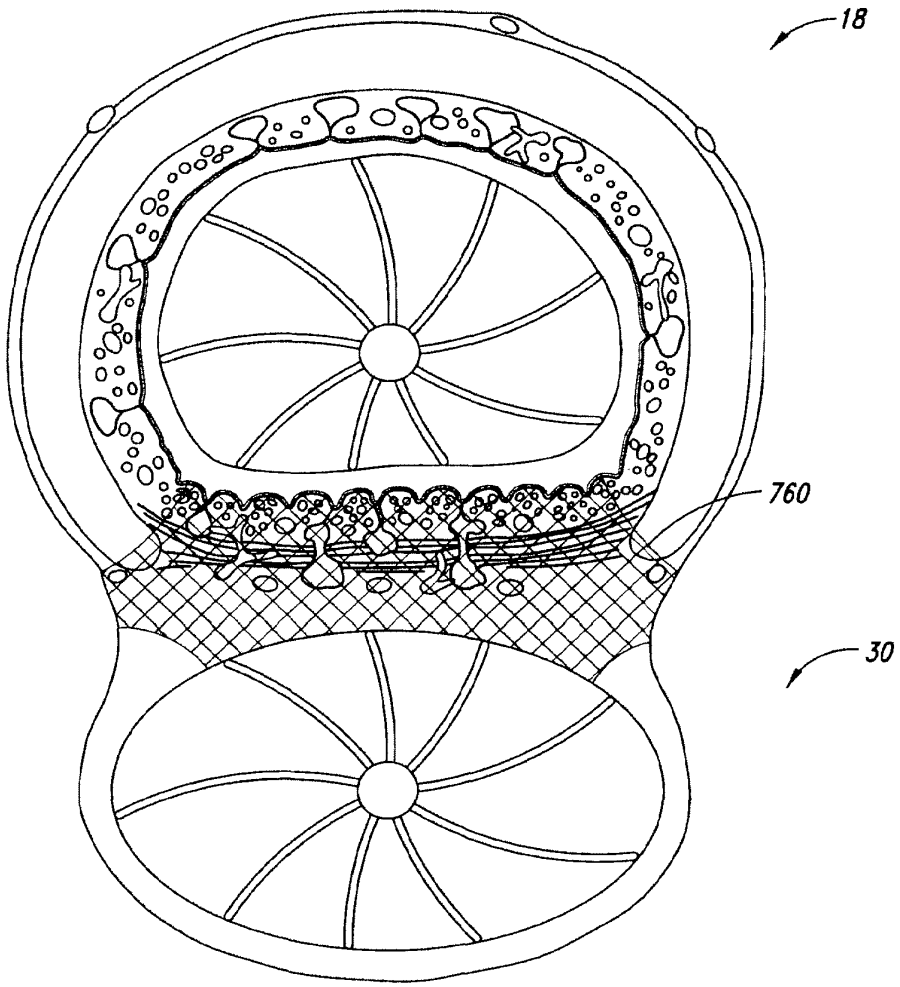

FIG. 30

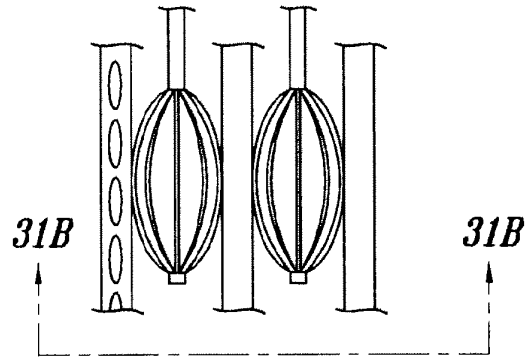

FIG. 31A

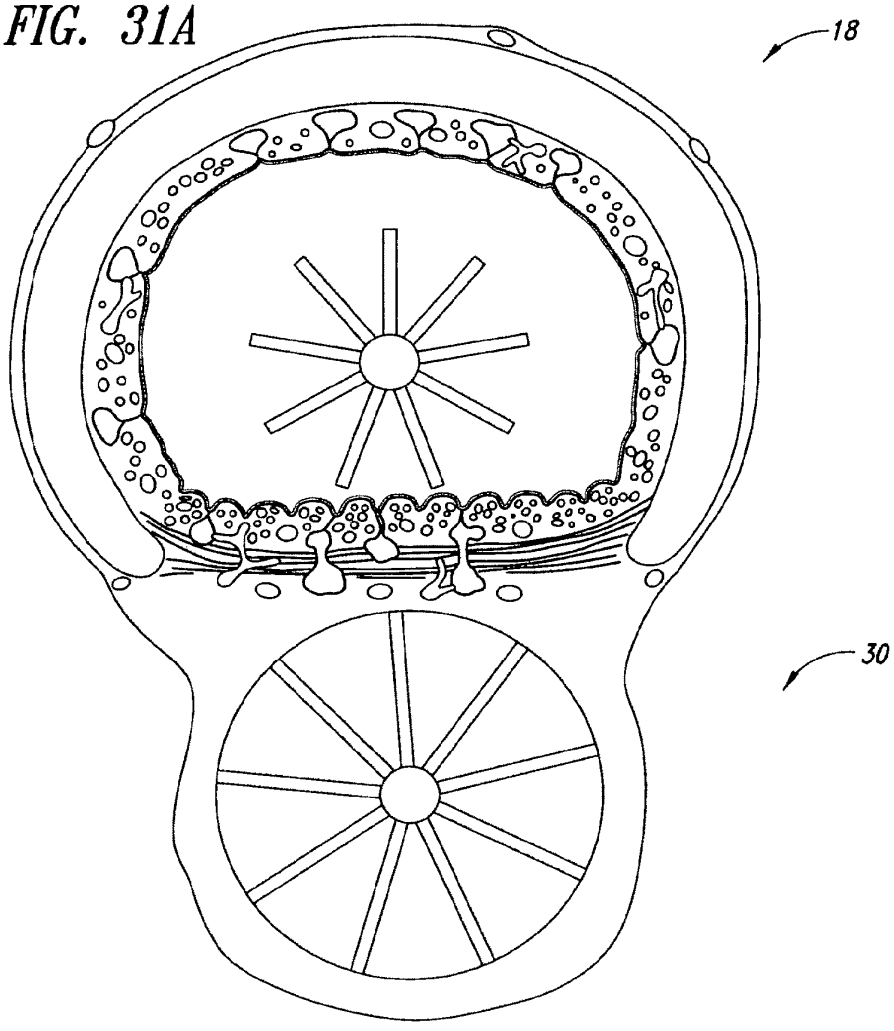

FIG. 31B

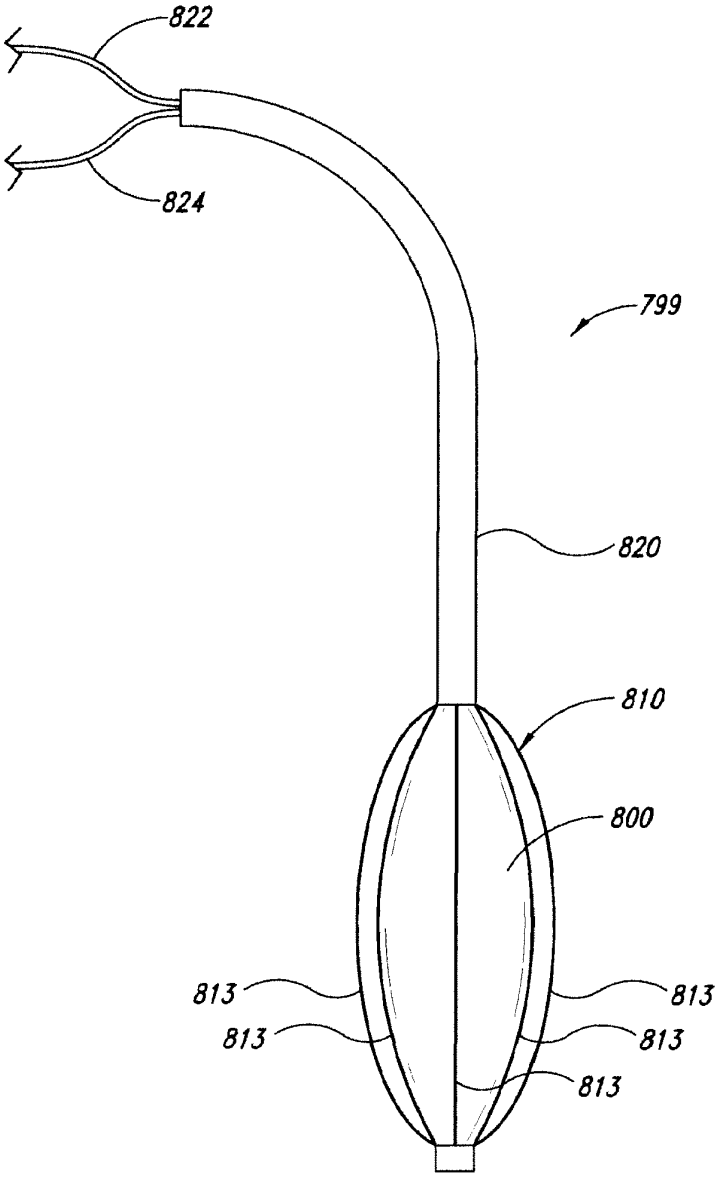

FIG. 32

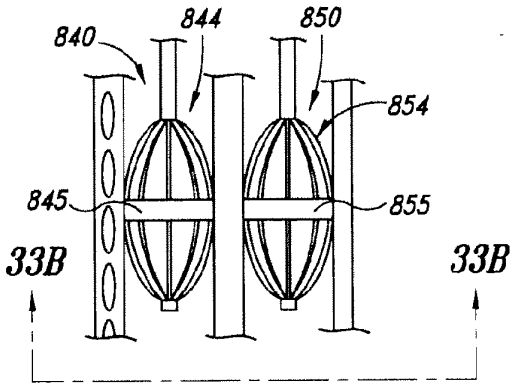

FIG. 33A

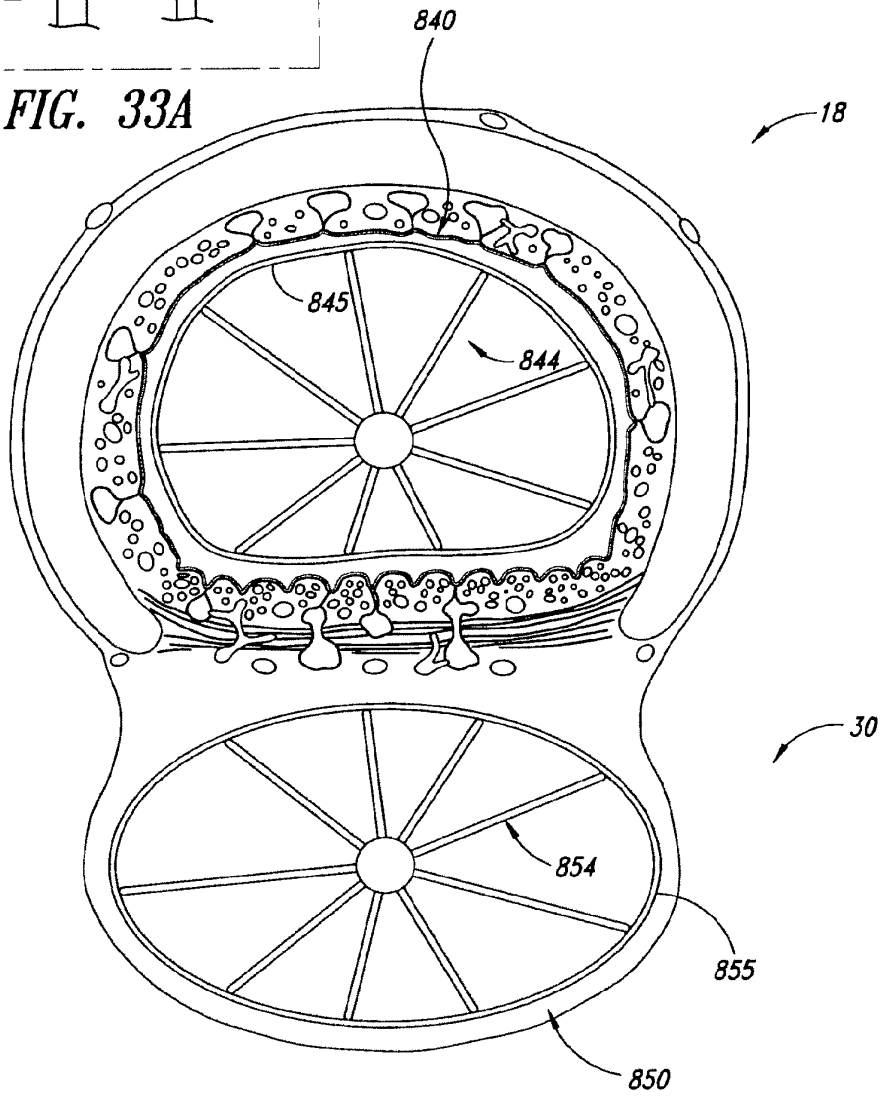

FIG. 33B

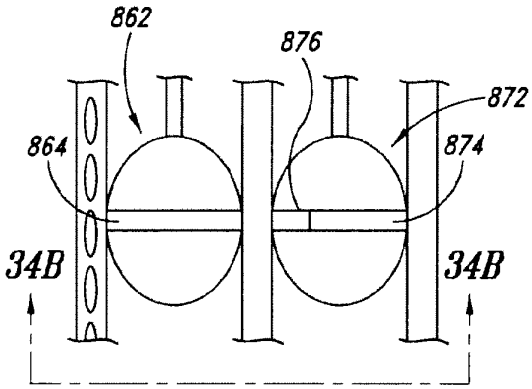

FIG. 34A

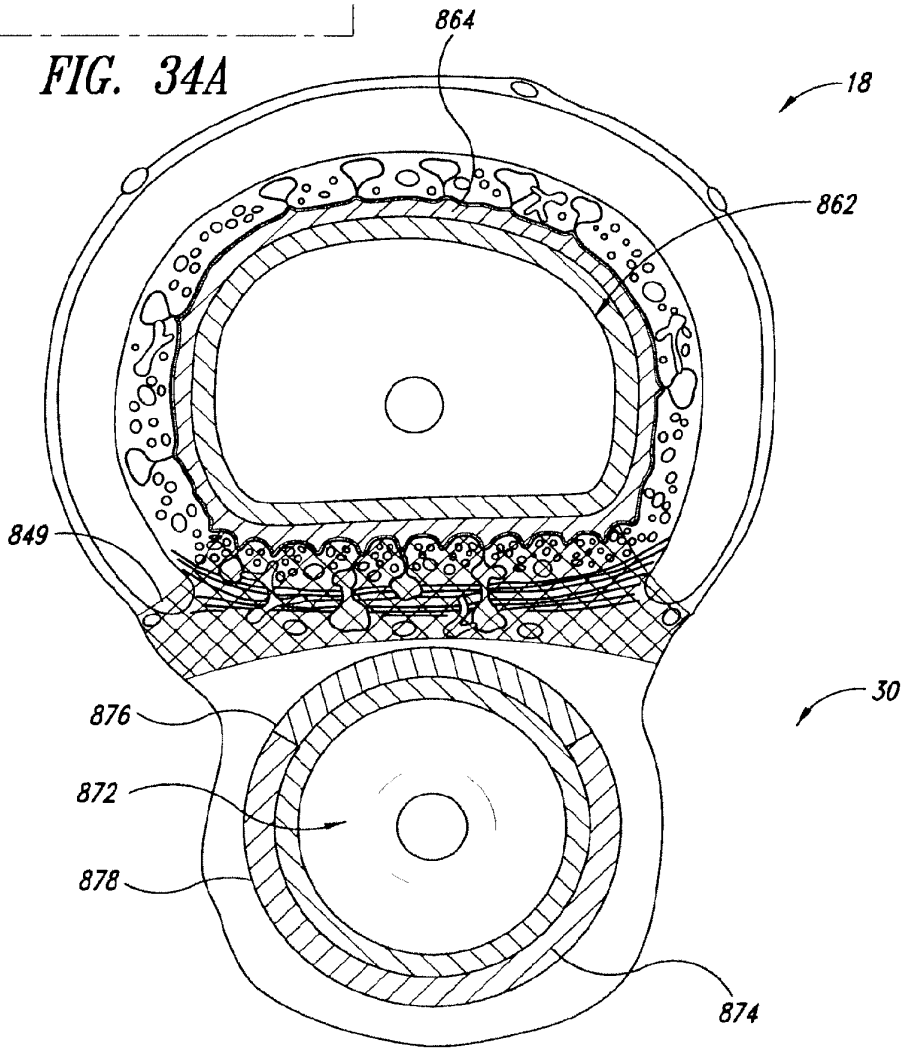

FIG. 34B

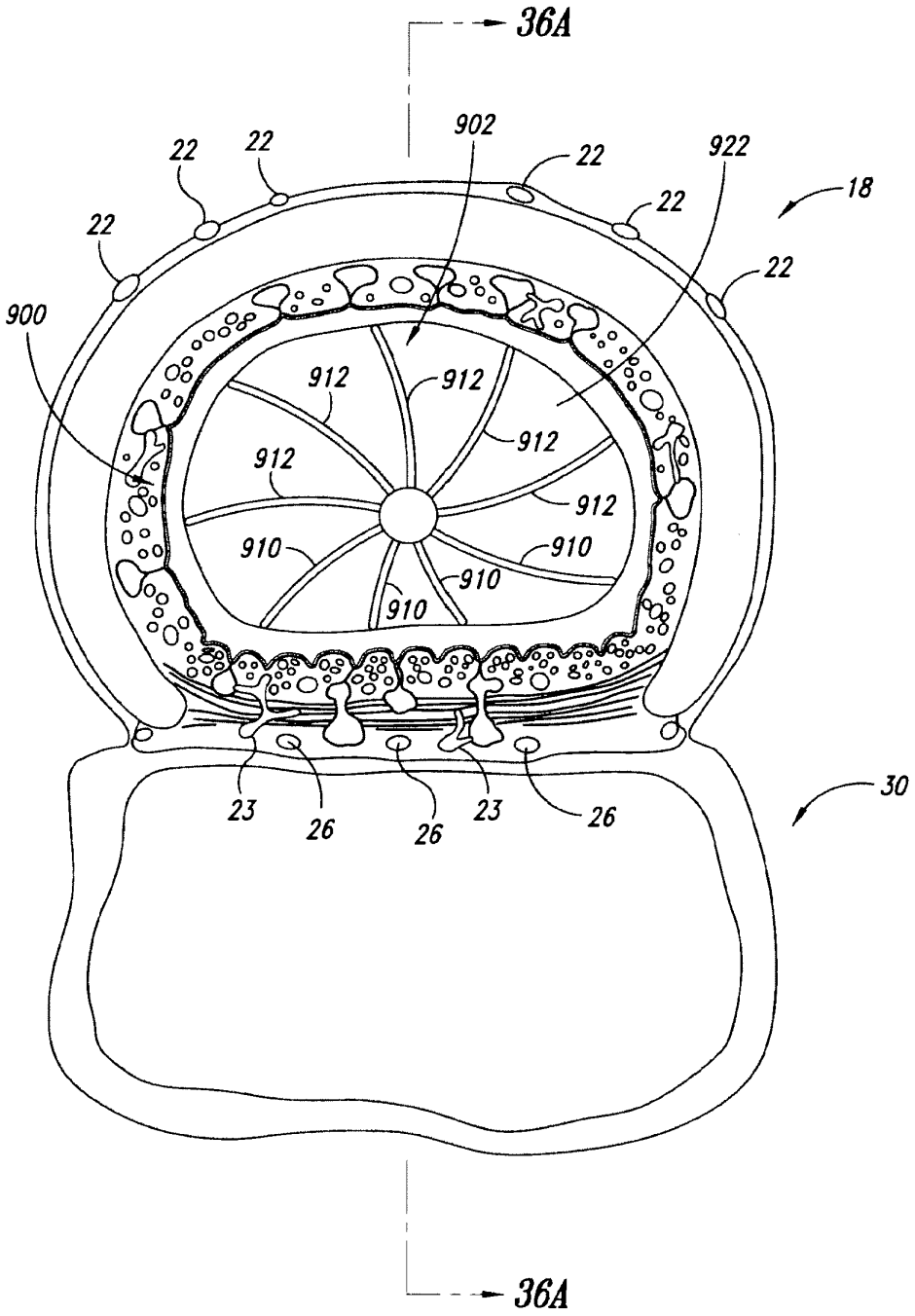

FIG. 35

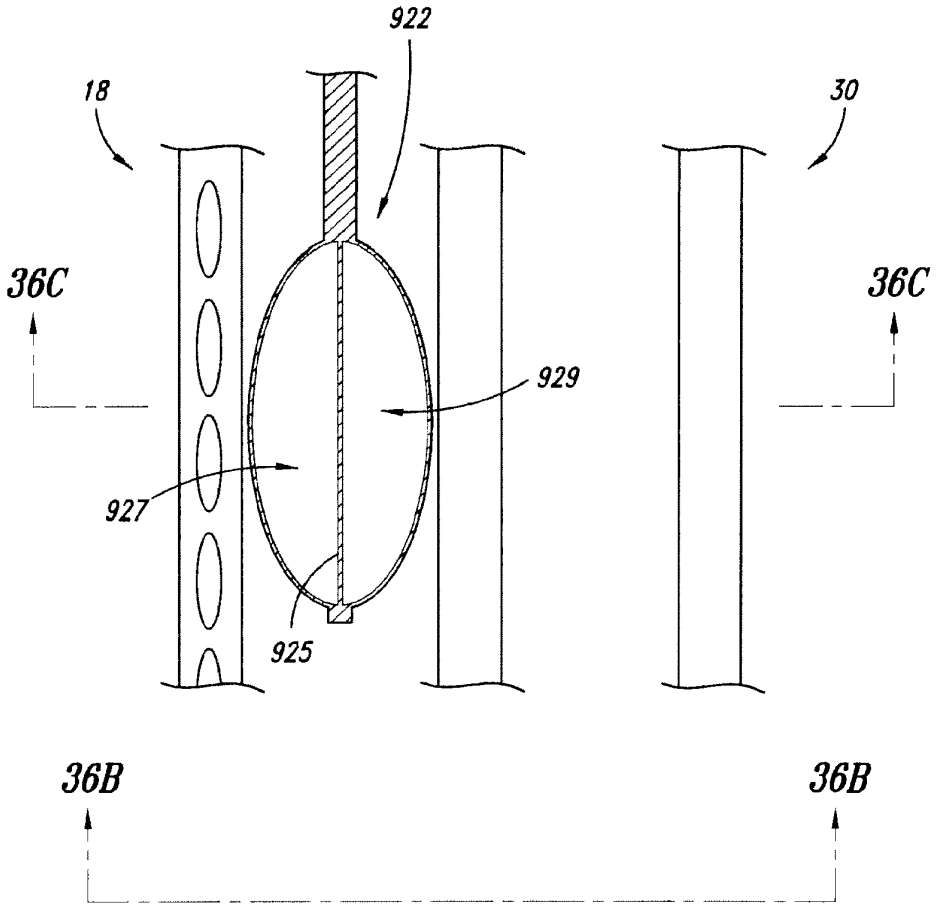

FIG. 36A

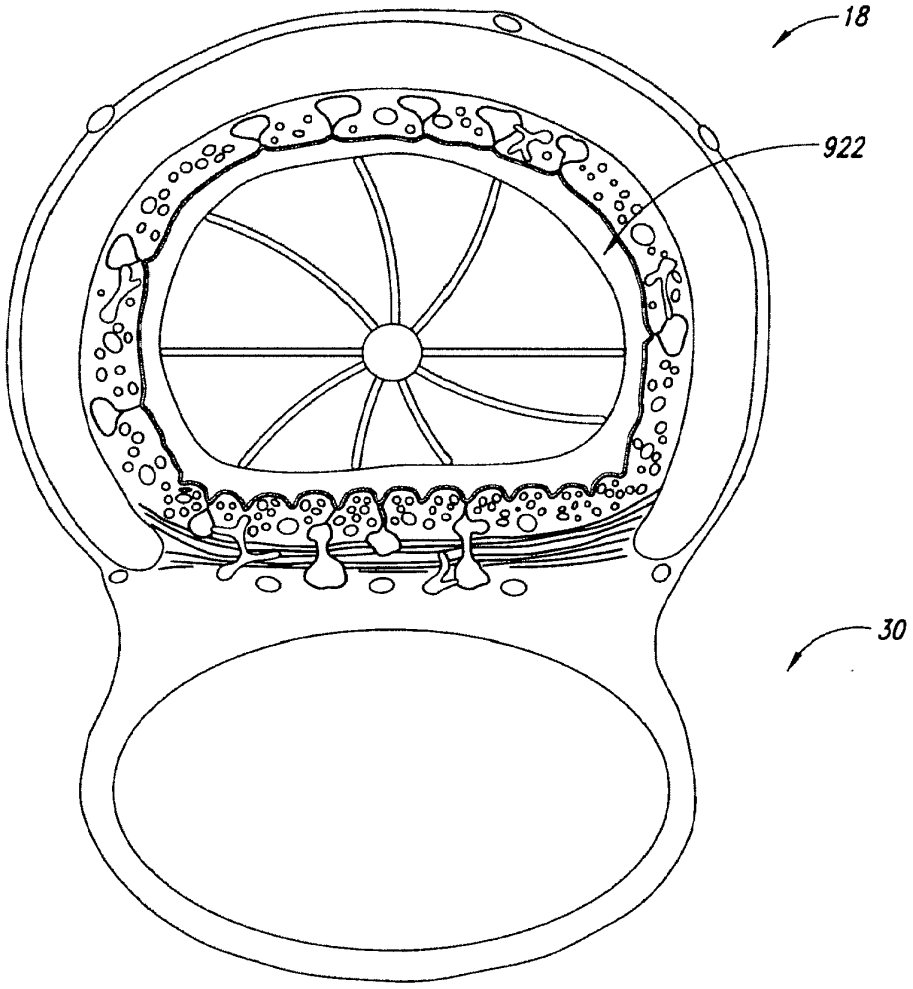

FIG. 36B

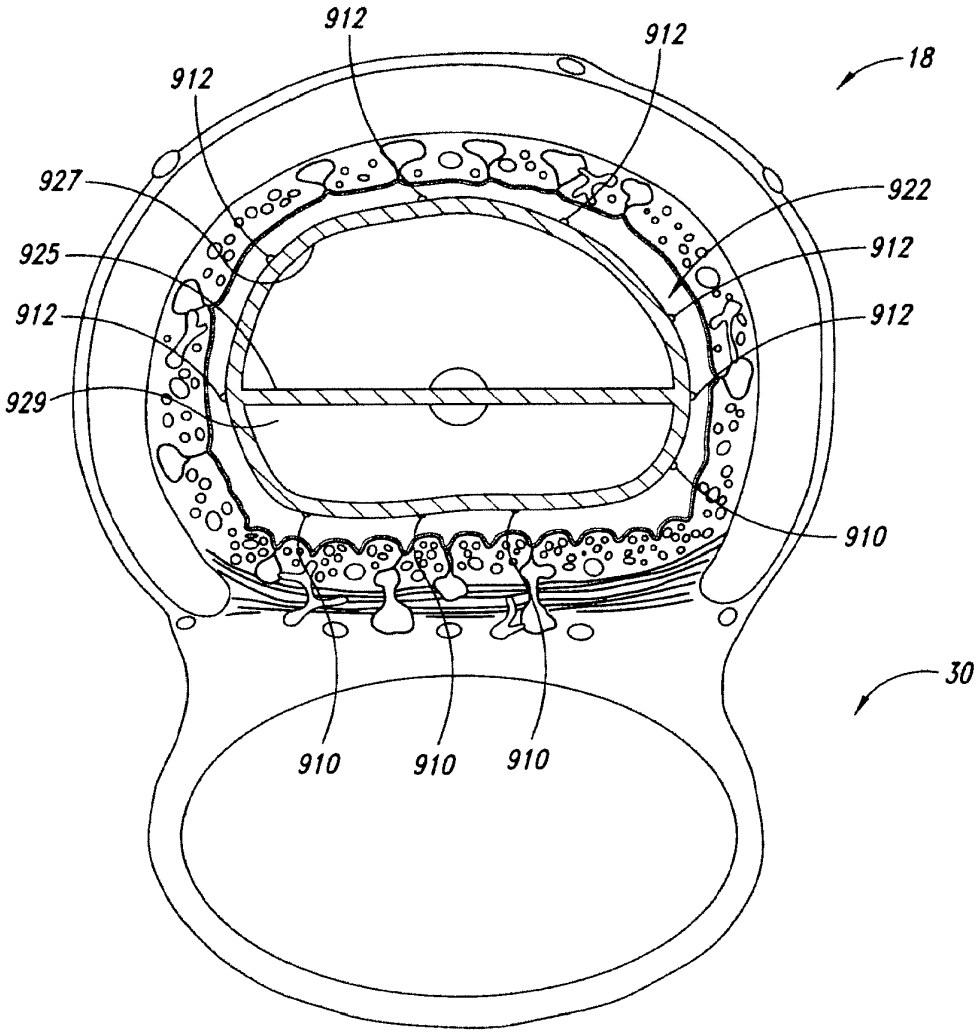

FIG. 36C

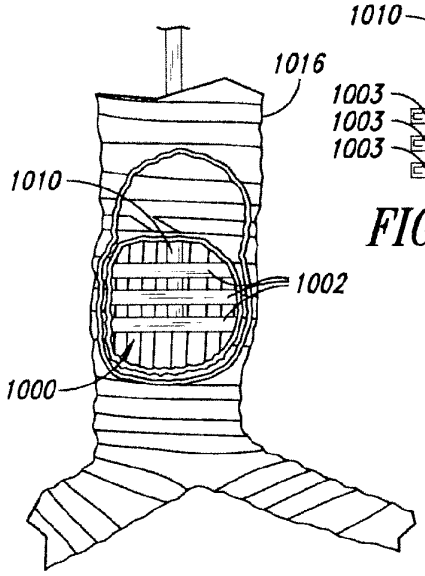

FIG. 37A

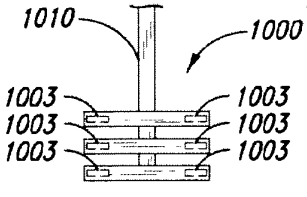

FIG. 37B

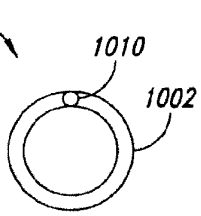

FIG. 37C

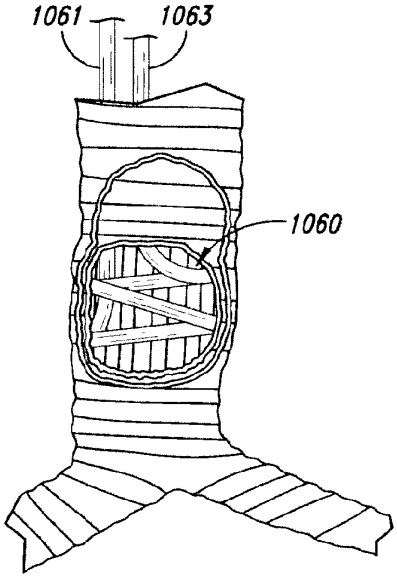

FIG. 39A

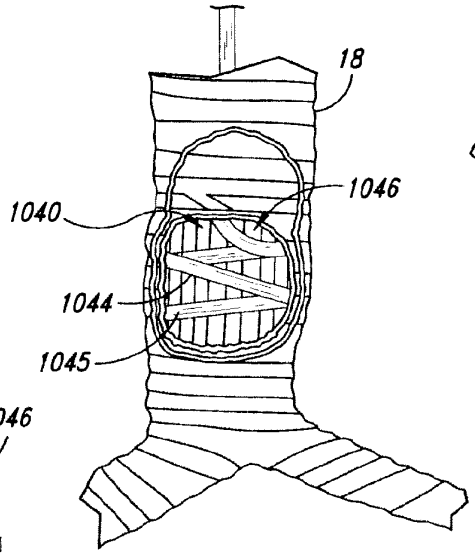

FIG. 38A

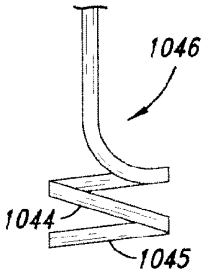

FIG. 38B

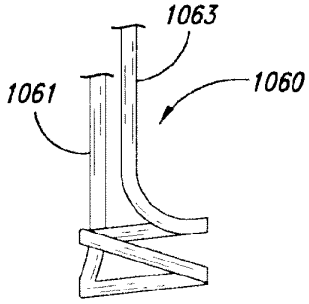

FIG. 39B

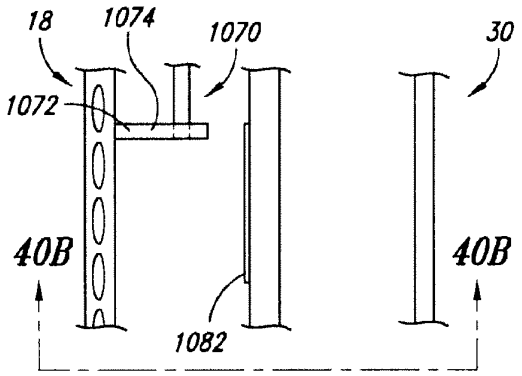

FIG. 40A

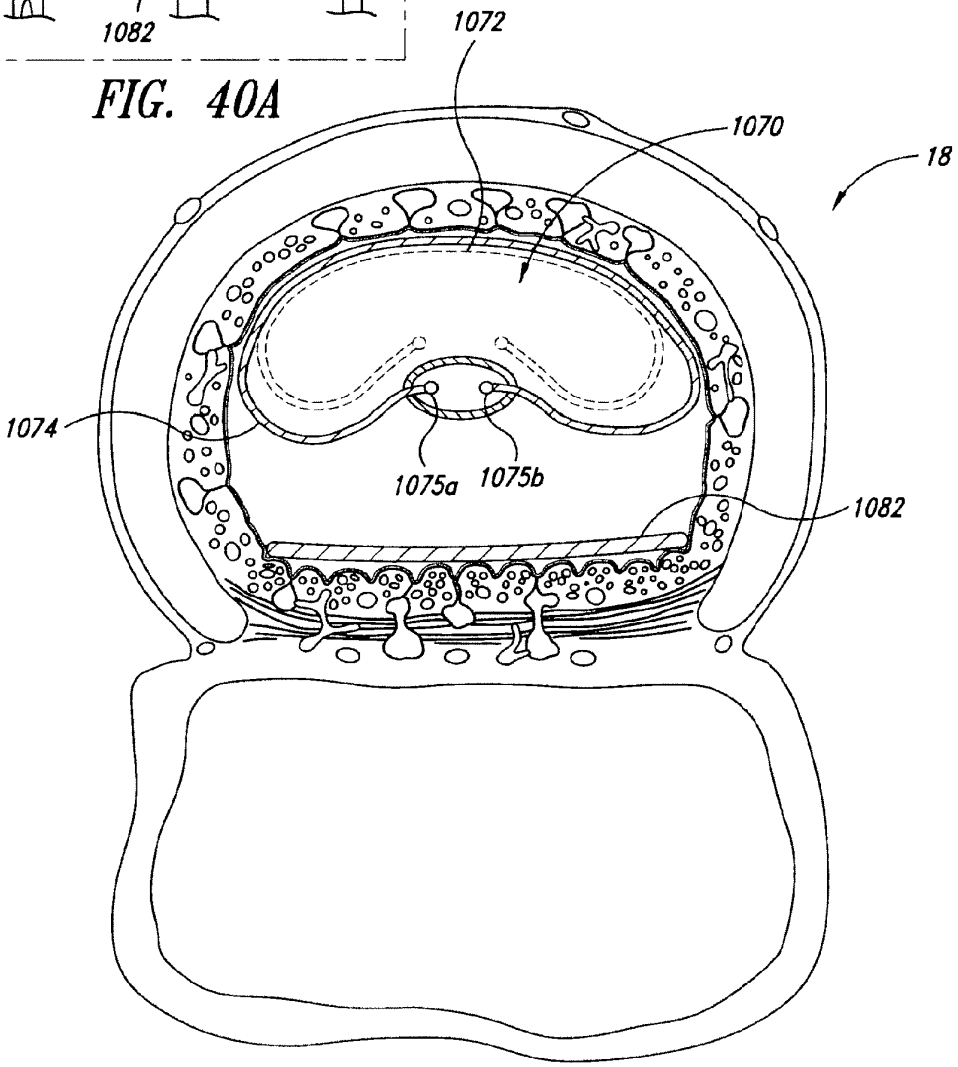

FIG. 40B

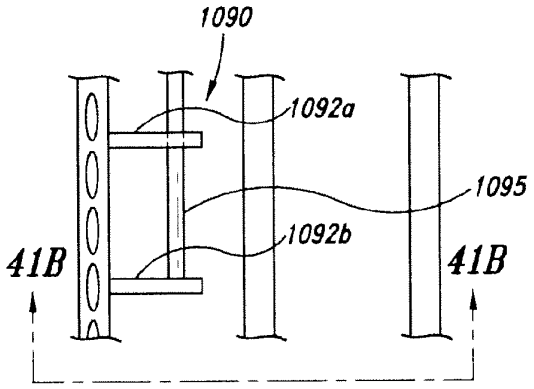

FIG. 41A

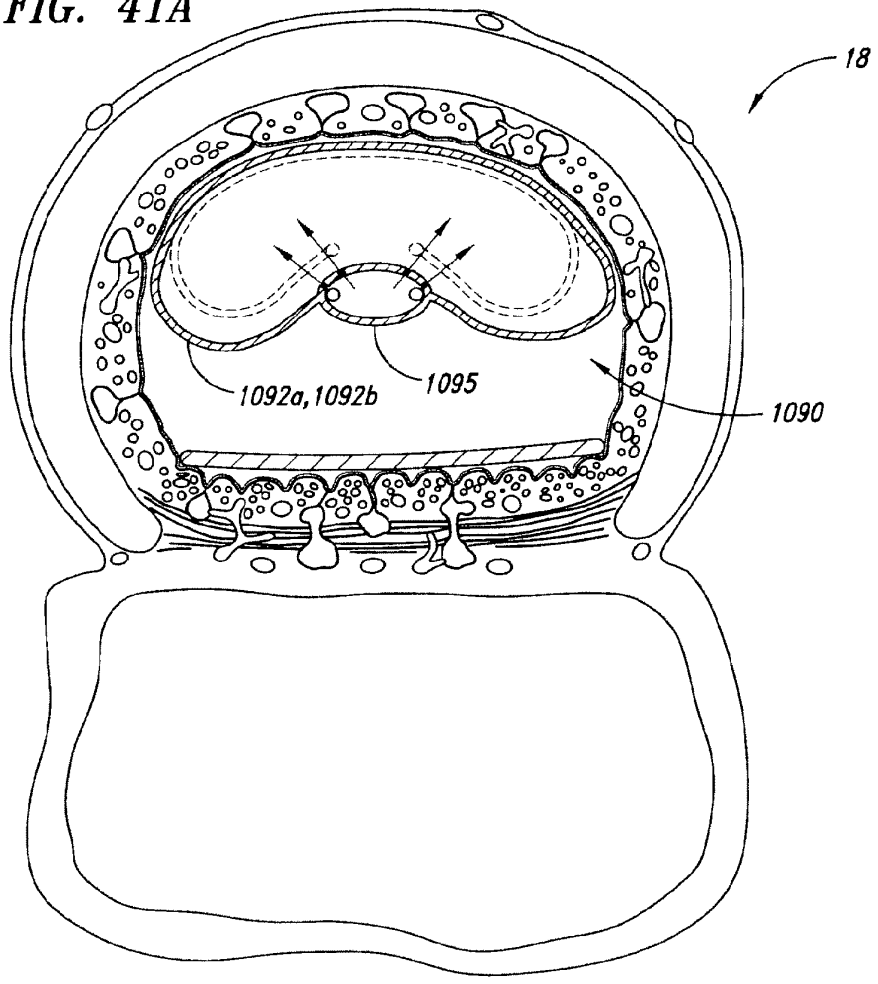

FIG. 41B

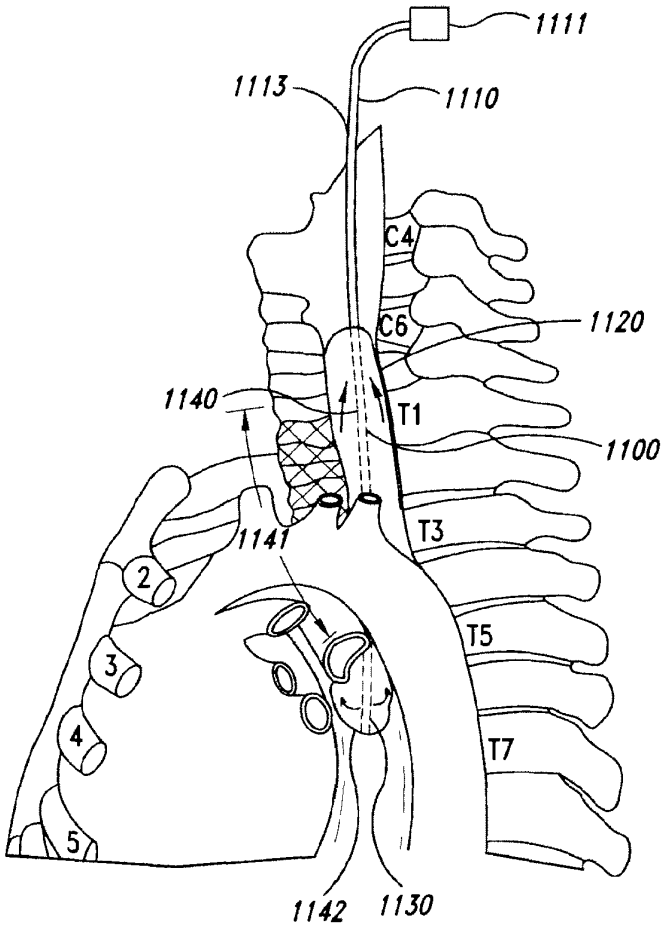

FIG. 42

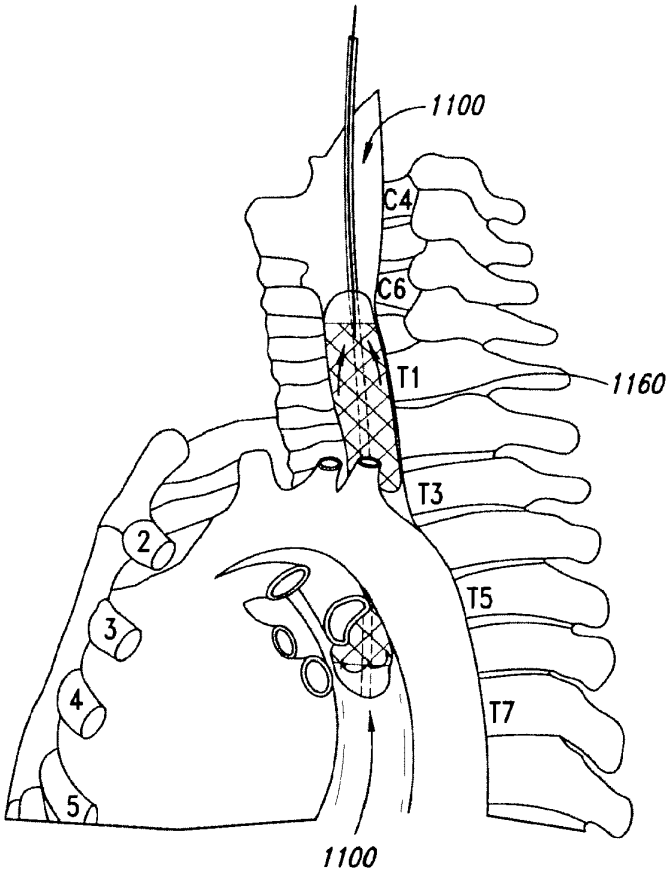

FIG. 43

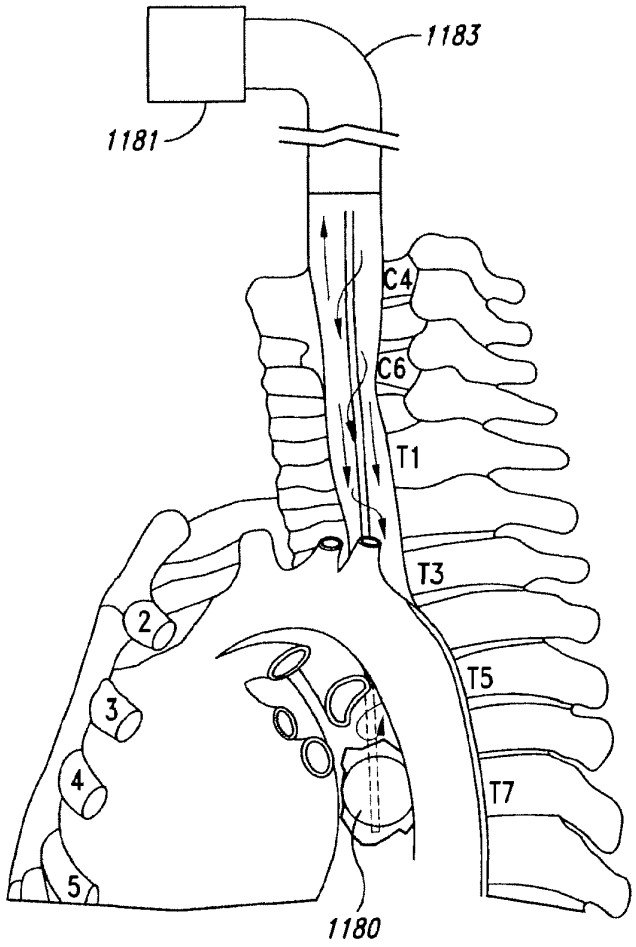

FIG. 44

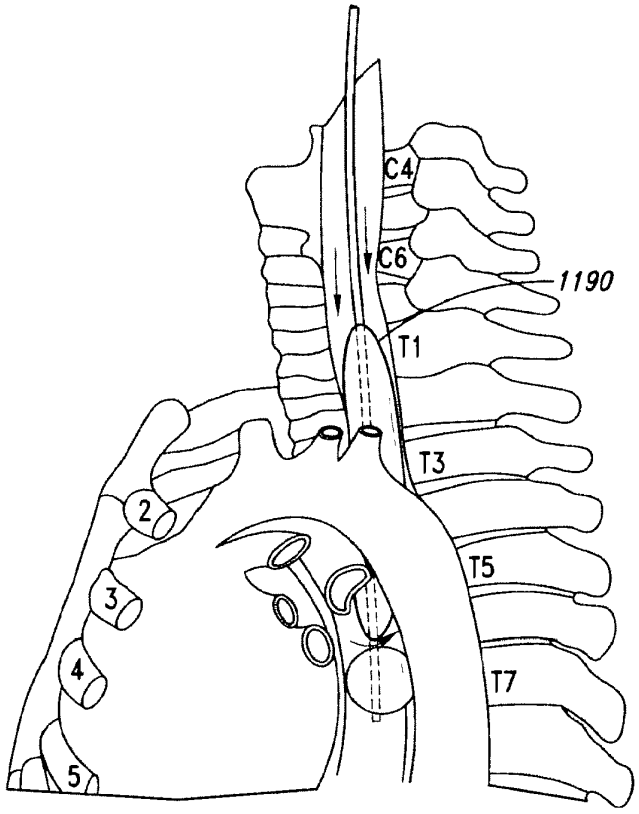

FIG. 45

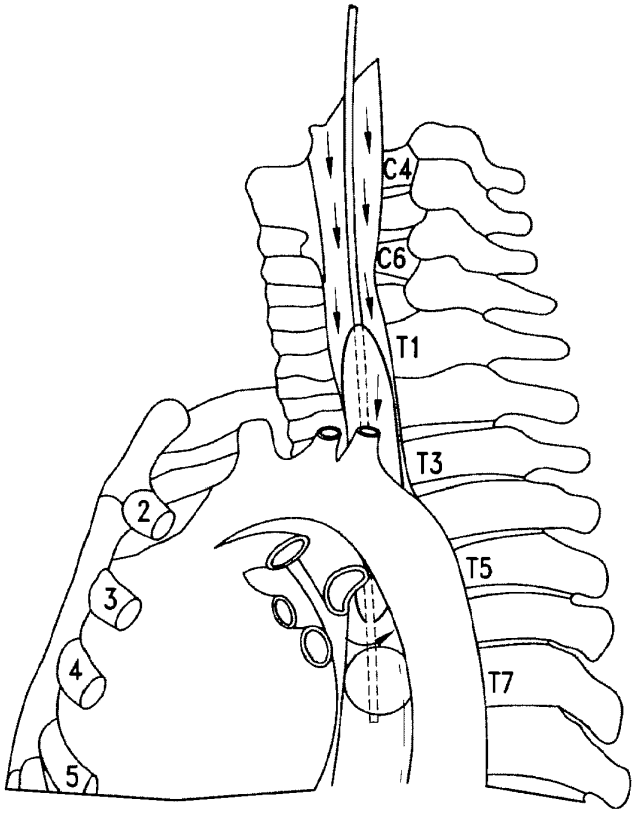

FIG. 46

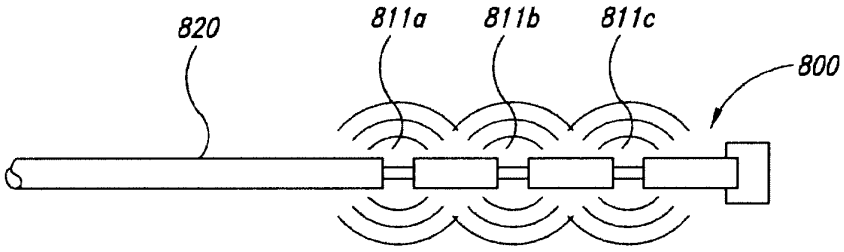

FIG. 47

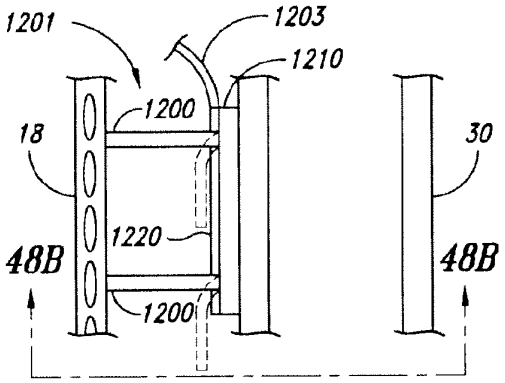

FIG. 48A

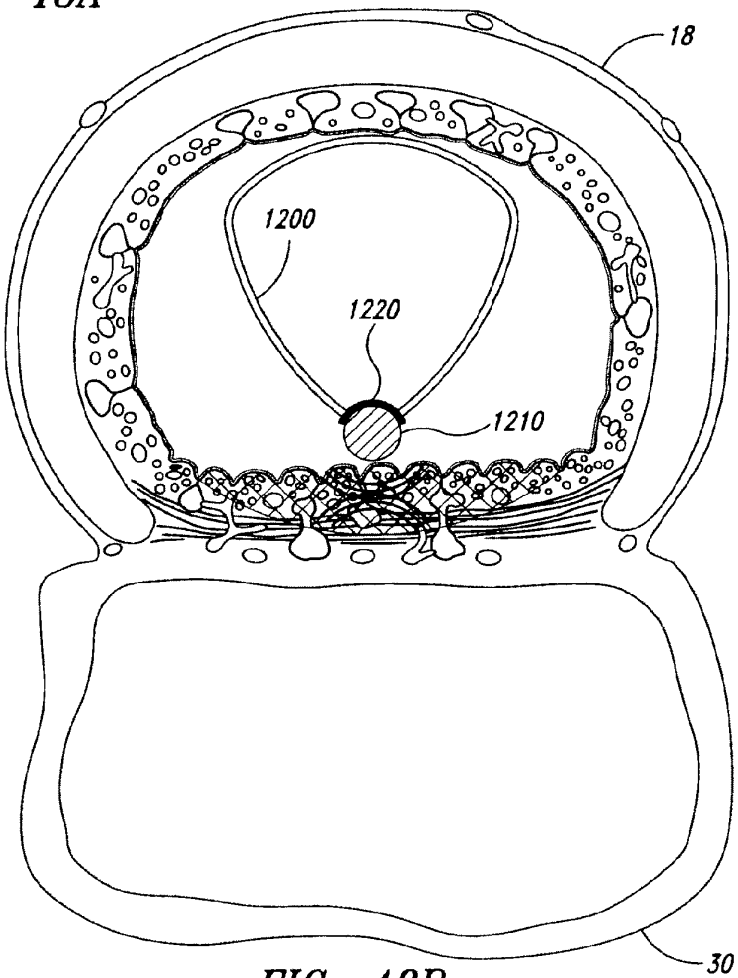

FIG. 48B

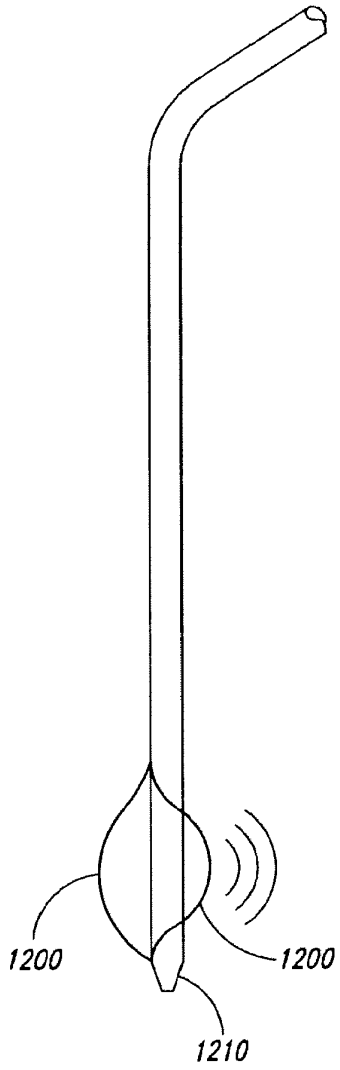

FIG. 49

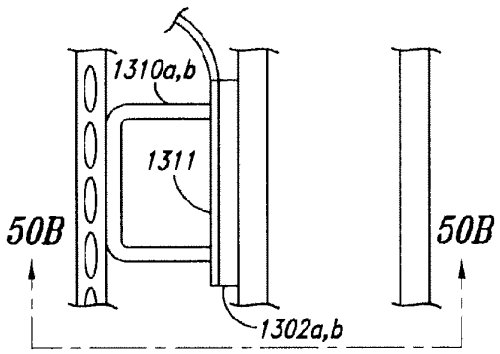

FIG. 50A

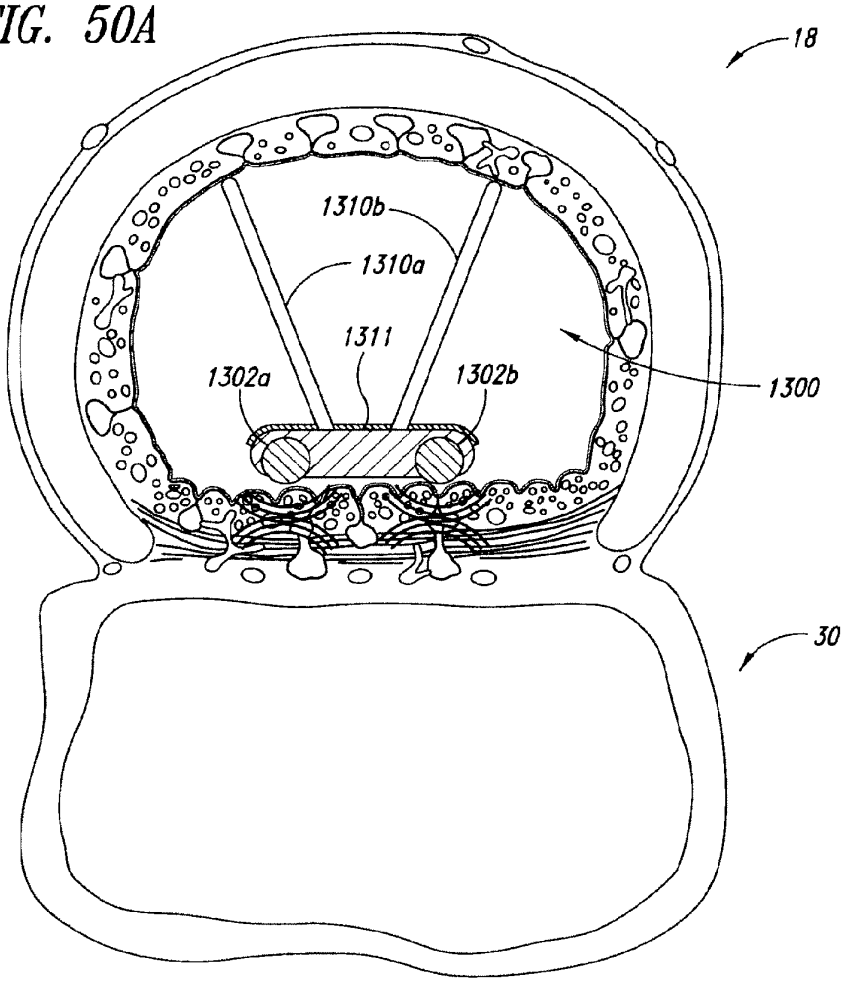

FIG. 50B

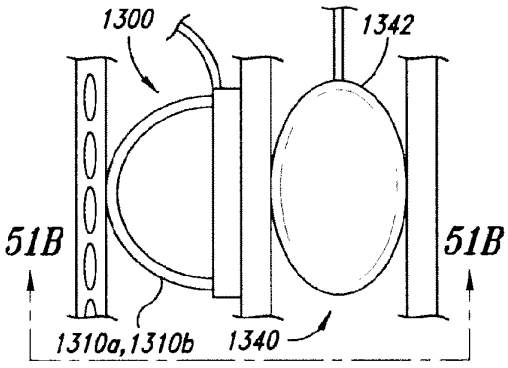

FIG. 51A

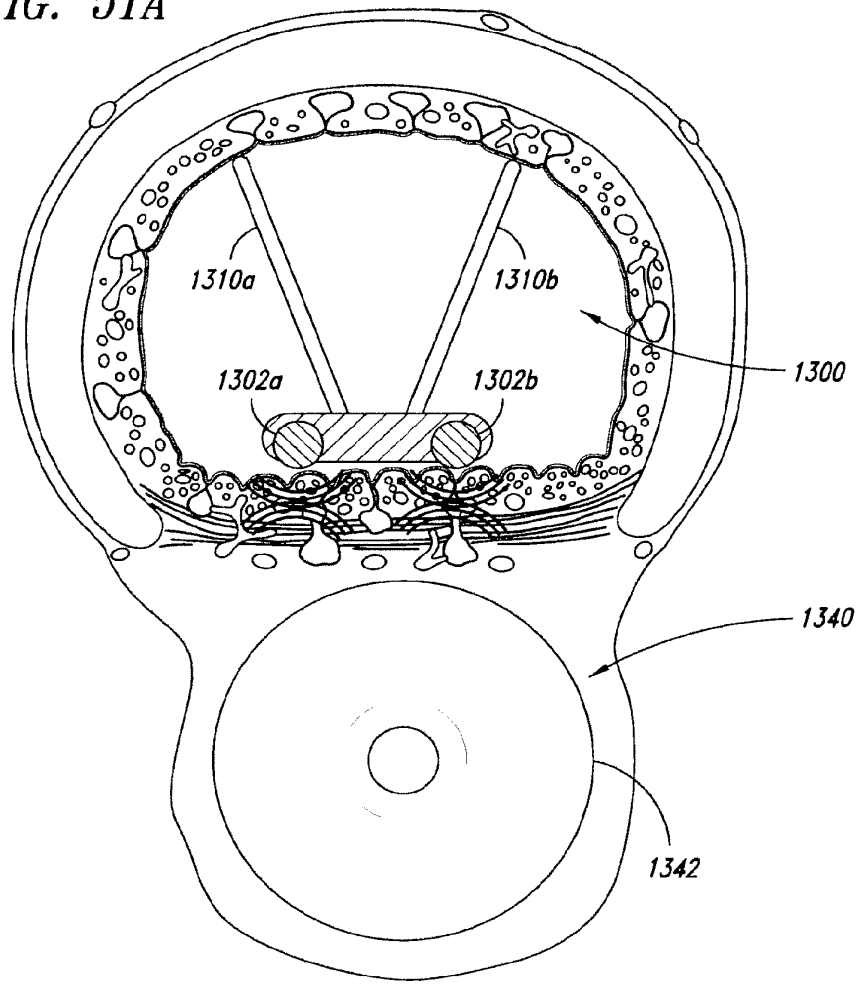

FIG. 51B

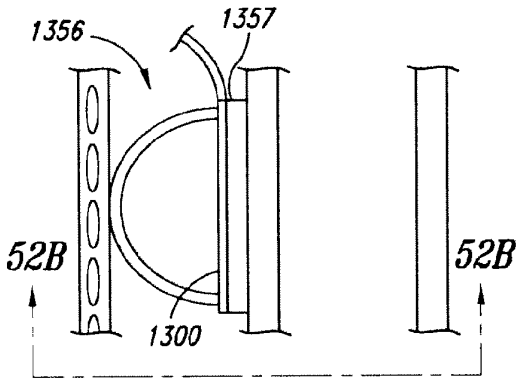

FIG. 52A

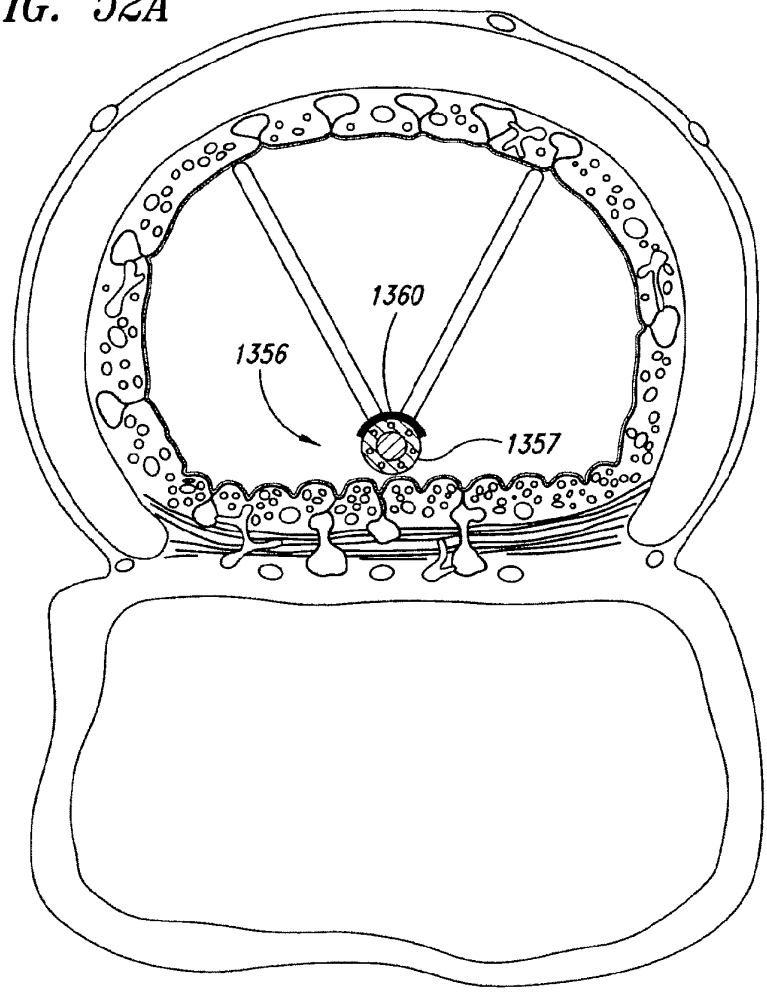

FIG. 52B

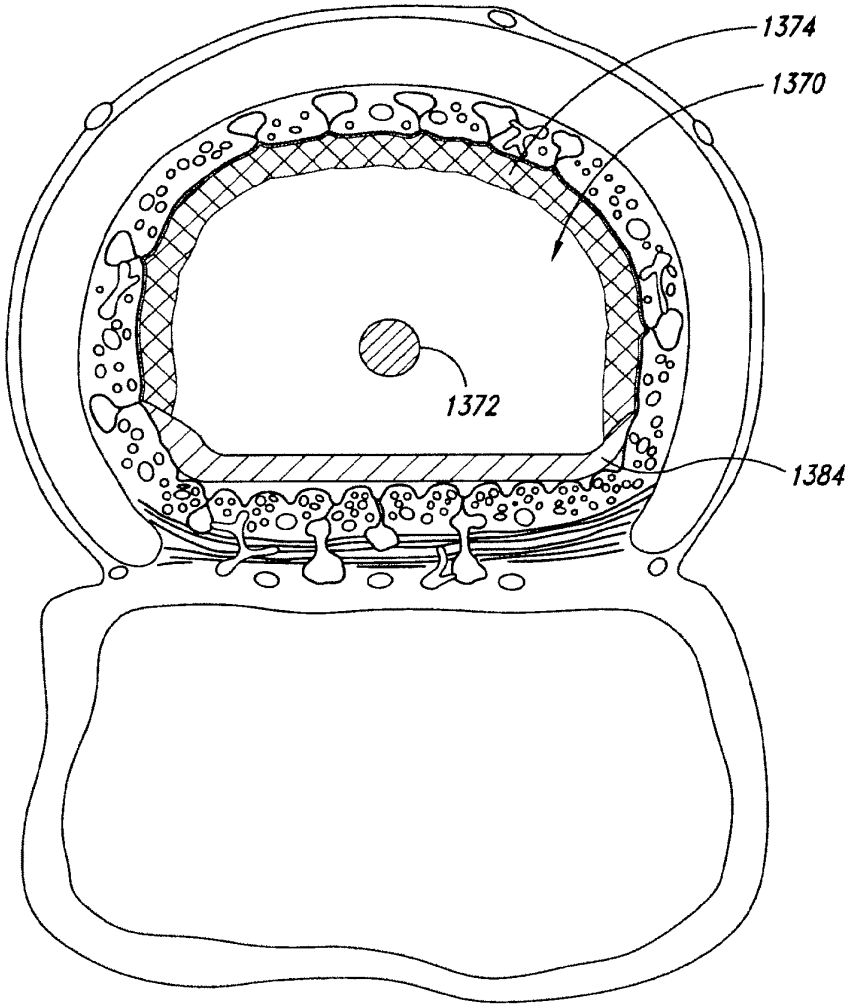

FIG. 53

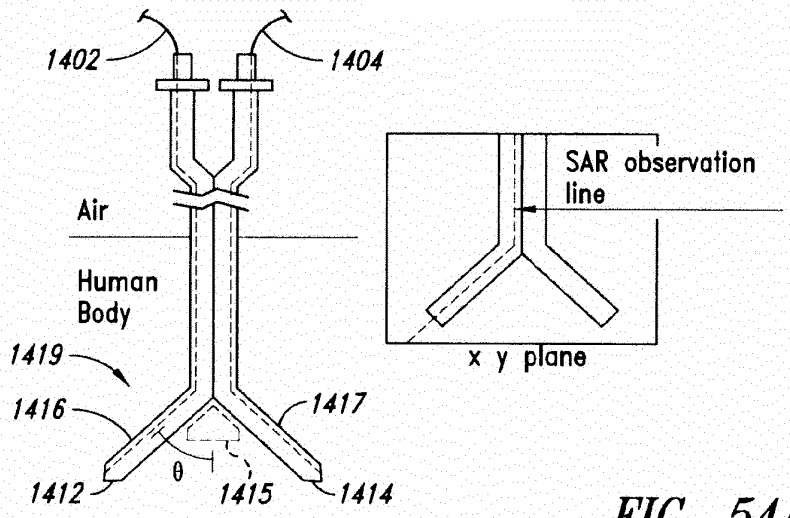

FIG. 54A

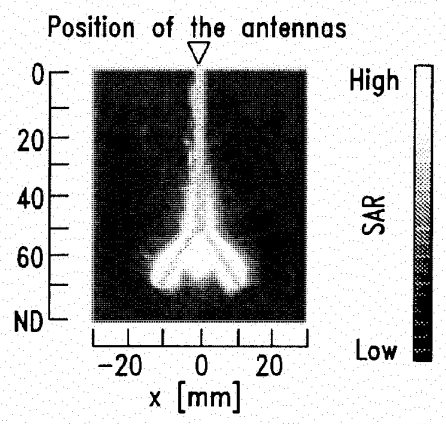

FIG. 54B

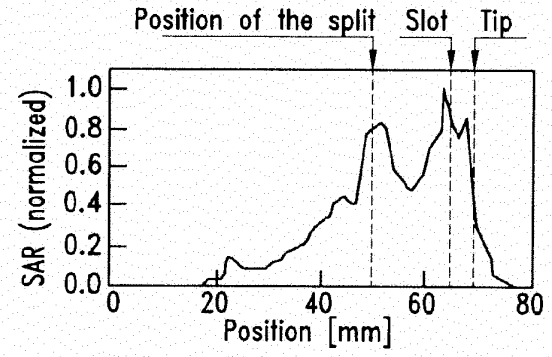

FIG. 54C

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EUROPEAN SEARCH REPORT

Application Number
EP 15 16 4212

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
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The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
Munich	20 July 2015	Rodríguez Cosío, J

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X : particularly relevant if taken alone
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EPO FORM 1503 03.82 (P04C01)

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EUROPEAN SEARCH REPORT

Application Number
EP 15 16 4212

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Place of search	Date of completion of the search	Examiner
Munich	20 July 2015	Rodríguez Cosío, J

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20-07-2015

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

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(71) Applicant *(for all designated States except US)*: **ABLATION FRONTIERS** [US/US]; 5835-118 Avenida Encinas, Carlsbad, CA 92008 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **WERNETH, Randell, L.** [US/US]; 3868 Arverne Street, San Diego, CA 92111 (US).

(74) Agents: **WIECZOREK, Mark, D.** et al.; MAYER & WILLIAMS PC, 251 North Avenue West, 2nd Floor, Westfield, NJ 07090 (US).

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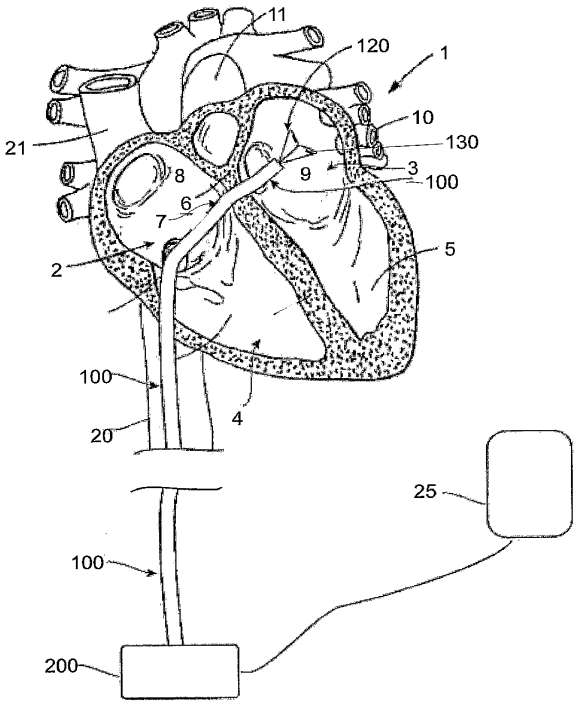
(54) Title: LOW POWER TISSUE ABLATION SYSTEM



(57) Abstract: Devices, systems and methods are disclosed for the ablation of tissue. Embodiments include an ablation catheter that has an array of ablation elements attached to a deployable carrier assembly. The carrier assembly can be constrained within the lumen of a catheter, and deployed to take on an expanded condition. The carrier assembly includes multiple electrodes that are configured to ablate tissue at low power. Additional embodiments include a system that includes an interface unit for delivering one or more forms of energy to the ablation catheter.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

LOW POWER TISSUE ABLATION SYSTEM

DESCRIPTION OF THE INVENTION

Statement of Related Application

[0001] This application claims the benefit of U.S. Provisional Patent Application Serial No. 60/698,355, filed July 11, 2005, entitled "Low Power Tissue Ablation System", which is incorporated by reference in its entirety herein.

Field of the Invention

[0002] The present invention relates generally to systems, catheters and methods for performing targeted tissue ablation in a subject. In particular, the present invention provides devices comprising one or more elements designed to efficiently deliver energy to tissue with precise control of the tissue to be ablated.

BACKGROUND OF THE INVENTION

[0003] Tissue ablation is used in numerous medical procedures to treat a patient. Ablation can be performed to remove undesired tissue such as cancer cells. Ablation procedures may also involve the modification of the tissue without removal, such as to stop electrical propagation through the tissue in patients with an arrhythmia. Often the ablation is performed by passing energy, such as electrical energy, through one or more electrodes causing the tissue in contact with the electrodes to heat up to an ablative temperature. Ablation procedures can be performed on patients with atrial fibrillation by ablating tissue in the heart.

[0004] Mammalian organ function typically occurs through the transmission of

electrical impulses from one tissue to another. A disturbance of such electrical transmission may lead to organ malfunction. One particular area where electrical impulse transmission is critical for proper organ function is in the heart. Normal sinus rhythm of the heart begins with the sinus node generating an electrical impulse that is propagated uniformly across the right and left atria to the atrioventricular node. Atrial contraction leads to the pumping of blood into the ventricles in a manner synchronous with the pulse.

[0005] Atrial fibrillation refers to a type of cardiac arrhythmia where there is disorganized electrical conduction in the atria causing rapid uncoordinated contractions that result in ineffective pumping of blood into the ventricle and a lack of synchrony. During atrial fibrillation, the atrioventricular node receives electrical impulses from numerous locations throughout the atria instead of only from the sinus node. This condition overwhelms the atrioventricular node into producing an irregular and rapid heartbeat. As a result, blood pools in the atria and increases the risk of blood clot formation. The major risk factors for atrial fibrillation include age, coronary artery disease, rheumatic heart disease, hypertension, diabetes, and thyrotoxicosis. Atrial fibrillation affects 7% of the population over age 65.

[0006] Atrial fibrillation treatment options are limited. Three known treatments, lifestyle change, medical therapy and electrical cardioversion all have significant limitations. Lifestyle change only assists individuals with lifestyle-related atrial fibrillation. Medication therapy assists only in the management of atrial fibrillation symptoms, may present side effects more dangerous than atrial fibrillation, and fail to cure atrial fibrillation. Electrical cardioversion attempts to restore sinus rhythm but has a high recurrence rate. In addition, if there is a blood clot in the atria, cardioversion may

cause the clot to leave the heart and travel to the brain or to some other part of the body, which may lead to stroke. What are needed are new methods for treating atrial fibrillation and other conditions involving disorganized electrical conduction.

[0007] Various ablation techniques have been proposed to treat atrial fibrillation, including the Cox-Maze procedure, linear ablation of various regions of the atrium, and circumferential ablation of pulmonary vein ostia. The Cox-Maze procedure and linear ablation procedures are unrefined, unnecessarily complex, and imprecise, with unpredictable and inconsistent results and an unacceptable level of unsuccessful procedures. These procedures are also tedious and time-consuming, taking several hours to accomplish. Pulmonary vein ostial ablation is proving to be difficult to do, and has led to rapid stenosis and potential occlusion of the pulmonary veins. There is therefore a need for improved atrial ablation products and techniques.

SUMMARY OF THE INVENTION

[0008] According to a first aspect of the invention, an ablation system used by an operator to treat a patient is disclosed. The system comprises an ablation catheter that has a flexible shaft with a proximal end and a distal end, and includes at least one ablation element for delivering energy to tissue. The system further comprises an interface unit that provides energy to the ablation catheter. The at least one ablation element is configured to rapidly transition from a first temperature to a second temperature. The first temperature approaches tissue ablation temperature, preferably 60° C, and the second temperature approaches body temperature, typically 37° C. In a preferred embodiment, the at least one ablation element has a majority of surface area in contact with circulating blood when energy is being delivered to the tissue. The majority of this blood exposed

surface area is at least 60%, preferably more than 75% and potentially greater than 85% of the total surface area of the electrode. Numerous electrode configurations are described including three segment ("triangle"), semicircular and crescent cross sections, cross sections with curvilinear, serpentine and zigzag segments; cross sections with segments with projecting fins, and cross sections that include an energy delivery portion and a non-energy delivery portion. The electrodes of the present invention are configured to rapidly cool, during energy delivery such as in bipolar energy delivery that follows monopolar energy delivery; and when no energy is being delivered. The electrodes of the present invention are configured to transition from ablation temperature to body temperature in less than 20 seconds, preferably less than 10 seconds. These electrodes are also configured to transition from body temperature to ablation temperature in less than 5 seconds.

[0009] According to a second aspect of the invention, an ablation system used by an operator to treat a patient is disclosed. The system comprises an ablation catheter that has a flexible shaft with a proximal end and a distal end, and includes at least one ablation element for delivering energy to tissue. The system further comprises an interface unit that provides energy to the ablation catheter. The at least one ablation element is configured such that a majority of its external surface area is in contact with tissue when energy is delivered to that tissue. The electrode is configured such that at least 60% of the total surface area is in tissue contact, preferably 70% or more. Numerous electrode configurations are described including three segment ("triangle"), semicircular and crescent cross sections, cross sections with curvilinear, serpentine and zigzag segments; cross sections with segments with projecting fins, and cross sections that include an

energy delivery portion and a non-energy delivery portion. The electrodes of the present invention are configured to maximize the amount of energy transferred to the tissue, thus minimizing the amount of energy delivered to the blood, such as undesired energy which may cause a blood clot.

[0010] According to a third aspect of the invention, an ablation system used by an operator to treat a patient is disclosed. The system comprises a first ablation catheter that has a flexible shaft with a proximal end and a distal end, and includes at least one ablation element for delivering energy to tissue; and a second ablation catheter that has a flexible shaft with a proximal end and a distal end, and includes at least one ablation element for delivering energy to tissue. The system further comprises an interface unit that provides energy to the ablation catheter. The energy delivered by the system is limited by a threshold that is a first value when the first ablation catheter is in use and a different value when the second ablation catheter is in use. The first and second ablation catheters preferably include one or more different functional elements, such as different ablation elements and/or patterns of ablation elements. Ablation elements can be varied in size and cross sectional geometry, cooling and heating properties, type of energy delivered, and other electrode parameters.

[0011] According to a fourth aspect of the invention, an ablation system used by an operator to treat a patient is disclosed. The system comprises an ablation catheter that has a flexible shaft with a proximal end and a distal end, and includes at least one ablation element for delivering energy to tissue. The system further comprises an interface unit that provides energy to the ablation catheter. The energy delivered by the interface unit is configured to (1) achieve a target energy level t a target tissue depth; and (2) pulse energy

such that the tissue surrounding the electrode does not exceed a threshold temperature. In a preferred embodiment, the energy delivered is RF energy, and the system is configured to automatically transition between bipolar and monopolar RF delivery. Energy delivery is adjusted based on a value selected from the group consisting of: temperature of tissue; rate of change of temperature of tissue; temperature of the at least one ablation element; rate of change of temperature of the at least one ablation element; EKG; tissue thickness; tissue location; cardiac flow rate; and combinations thereof. Automatic adjustments are made to minimize depth of the lesion, minimize the width of the lesion, or both. In a preferred embodiment, the energy delivery is adjusted to achieve a target depth of the lesion. Temperature information is preferably provided by one or more temperature sensors, such as sensors mounted in, on or near an ablation element.

[0012] According to a fifth aspect of the invention, an ablation system used by an operator to treat a patient is disclosed. The system comprises an ablation catheter that has a flexible shaft with a proximal end and a distal end, and includes at least one ablation element for delivering energy to tissue. The system further comprises an interface unit that provides energy to the ablation catheter. The interface unit monitors one or more parameters of the system, and prevents the energy delivered from exceeding a threshold. The value of the threshold is determined by the at least one ablation element. The system parameters are preferably selected from the group consisting of: temperature such as temperature from a temperature sensor; a value of measured current; a value of measured voltage; a flow measurement value; a force measurement value such as a measurement of strain; a pressure measurement value; and combinations thereof. The threshold is preferably an energy delivery threshold selected from the group consisting of: peak

energy such as peak energy below 10 Watts; average energy such as average energy below 5 Watts; and cumulative energy such as a value below 500 Watt-seconds or less than 300 Watt-seconds; and combinations thereof. In another preferred embodiment, the interface unit includes a threshold comparator for comparing a measured, calculated or otherwise determined value to the threshold. In another preferred embodiment, the threshold changes over time. In yet another preferred embodiment, the system is configured to deliver a low level energy delivery followed by a higher level energy delivery. During or immediately following the low level energy delivery, a threshold value is determined which is utilized in the subsequent higher level energy delivery.

[0013] According to a sixth aspect of the invention, an ablation catheter device is disclosed. The ablation catheter comprises an elongated, flexible, tubular body member having a proximal end, a distal end, and a lumen extending therebetween. A control shaft is coaxially disposed and is slidingly received within the lumen of the tubular body member. The catheter further comprises a flexible carrier assembly which includes at least two arms, each arm including at least one ablation element used to deliver energy to tissue. Each ablation element includes a relatively uniform triangle cross-section along its length, with a continuous or discontinuous perimeter or path. The cross section is preferably an isosceles triangle wherein the common base is opposite two sides that determine a vertex angle. This vertex angle is configured, based on the number of carrier arms of the particular carrier assembly, to allow a number of electrodes to be constrained into a volumetrically efficient circle or "pie" shape, the sum of all the vertex angles approximating 360 degrees, such that:

$$\text{Vertex Angle} = \frac{360 \text{ degrees}}{\text{Number of Carrier Arms}}$$

[0014] In an alternative embodiment, at least one cross section is dissimilar, and/or the cross sections do not include only isosceles triangle geometries. In these configurations, the relevant (vertex) angles are configured such that their sum approaches 360 degrees in total, similarly providing efficiently constrainable volumes when maintained within the lumen of carrier assembly.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] The accompanying drawings, which are incorporated in and constitute a part of this specification, illustrate various embodiments of the present invention, and, together with the description, serve to explain the principles of the invention. In the drawings:

[0016] Fig. 1 illustrates the treatment to be accomplished with the devices and methods described below.

[0017] Fig. 2a illustrates a perspective view of an ablation catheter consistent with the present invention in which the carrier element has four carrier arms, each including two ablation elements.

[0018] Fig. 2b is a sectional view of a finned electrode of Fig. 2a.

[0019] Fig. 3a is a sectional view of an ablation element consistent with the present invention.

[0020] Fig. 3b is a sectional view of multiple ablation elements of Fig. 3a shown constrained in the distal end of an ablation catheter of the present invention.

[0021] Fig. 3c is a perspective, partial cutaway view of the ablation catheter of Fig. 3b.

[0022] Fig. 4 illustrates a perspective, partial cutaway view of a preferred embodiment of an ablation catheter consistent with the present invention in which the carrier element has three carrier arms each including two ablation elements.

[0023] Fig 4a is a sectional view of a distal portion of the ablation catheter of Fig. 4.

[0024] Figs. 5a, 5b, 5c, 5d, 5e, and 5f are sectional end views of ablation elements consistent with the present invention, shown in associated contact with tissue during energy delivery.

[0025] Figs. 6a and 6b are sectional end views of ablation elements consistent with the present invention.

[0026] Fig. 6c is a side view of an ablation element consistent with the present invention.

DESCRIPTION OF THE EMBODIMENTS

[0027] Reference will now be made in detail to the present embodiments of the invention, examples of which are illustrated in the accompanying drawings. Wherever possible, the same reference numbers will be used throughout the drawings to refer to the same or like parts.

[0028] The present invention utilizes ablation therapy. Tissue ablation is often used in treating several medical conditions, including abnormal heart rhythms. Ablation can be performed both surgically and non-surgically. Non-surgical ablation is typically performed in a special lab called the electrophysiology (EP) laboratory. During this non-surgical procedure a catheter is inserted into a vessel such as a vein, and guided into the

heart using fluoroscopy for visualization. Subsequently, an energy delivery apparatus is used to supply energy to the heart muscle. This energy either "disconnects" or "isolates" the pathway of the abnormal rhythm. It can also be used to disconnect the conductive pathway between the upper chambers (atria) and the lower chambers (ventricles) of the heart. For individuals requiring heart surgery, ablation can be performed during coronary artery bypass or valve surgery.

[0029] The present invention provides catheters for performing targeted tissue ablation in a subject. In preferred embodiments, the catheters comprise a tubular body member having a proximal end and distal end and preferably a lumen extending therebetween. The catheter is preferably of the type used for performing intracardiac procedures, typically being introduced from the femoral vein in a patient's leg or a vein in the patient's neck. The catheter is preferably introducible through a sheath with a steerable tip that allows positioning of the distal portion to be used, for example, when the distal end of the catheter is within a heart chamber. The catheters include ablation elements mounted on a carrier assembly. The carrier assembly is preferably attached to a coupler, which in turn is connected to a control shaft that is coaxially disposed and slidingly received within the lumen of the tubular body member. The carrier assembly is deployable from the distal end of the tubular body member by advancing the control shaft, such as to engage one or more ablation elements against cardiac tissue, which is typically atrial wall tissue or other endocardial tissue. Retraction of the control shaft causes the carrier assembly to be constrained within the lumen of the tubular body member.

[0030] Arrays of ablation elements, preferably electrode arrays, may be configured in

a wide variety of ways and patterns. In particular, the present invention provides devices with electrode arrays that provide electrical energy, such as radiofrequency (RF) energy, in monopolar (unipolar), bipolar or combined monopolar-bipolar fashion, as well as methods for treating conditions (e.g., atrial fibrillation, supra ventricular tachycardia, atrial tachycardia, ventricular tachycardia, ventricular fibrillation, and the like) with these devices. Alternative to or in combination with ablation elements that deliver electrical energy to tissue, other forms and types of energy can be delivered including but not limited to: sound energy such as acoustic energy and ultrasound energy; electromagnetic energy such as electrical, magnetic, microwave and radiofrequency energies; thermal energy such as heat and cryogenic energies; chemical energy such as energy generated by delivery of a drug; light energy such as infrared and visible light energies; mechanical and physical energy; radiation; and combinations thereof.

[0031] As described above, the normal functioning of the heart relies on proper electrical impulse generation and transmission. In certain heart diseases (e.g., atrial fibrillation) proper electrical generation and transmission are disrupted or are otherwise abnormal. In order to prevent improper impulse generation and transmission from causing an undesired condition, the ablation catheters of the present invention may be employed.

[0032] One current method of treating cardiac arrhythmias is with catheter ablation therapy, which, to date, has been difficult and impractical to employ. In catheter ablation therapy, physicians make use of catheters to gain access into interior regions of the body. Catheters with attached electrode arrays or other ablating devices are used to create lesions that disrupt electrical pathways in cardiac tissue. In the treatment of cardiac

arrhythmias, a specific area of cardiac tissue having aberrant conductive pathways, such as atrial rotors, emitting or conducting erratic electrical impulses, is initially localized. A user (e.g., a physician such as an electrophysiologist) directs a catheter through a main vein or artery into the interior region of the heart that is to be treated. The ablating element is next placed near the targeted cardiac tissue that is to be ablated. The physician directs energy, provided by a source external to the patient, from one ore more ablation elements to ablate the neighboring tissue and form a lesion. In general, the goal of catheter ablation therapy is to disrupt the electrical pathways in cardiac tissue to stop the emission of and/or prevent the propagation of erratic electric impulses, thereby curing the heart of the disorder. For treatment of atrial fibrillation, currently available methods and devices have shown only limited success and/or employ devices that are extremely difficult to use or otherwise impractical.

[0033] The ablation catheters of the present invention allow the generation of lesions of appropriate size and shape to treat conditions involving disorganized electrical conduction (e.g., atrial fibrillation). The ablation catheters of the present invention are also practical in terms of ease-of-use and limiting risk to the patient, as well as significantly reducing procedure times. The present invention accomplishes these goals by, for example, the use of spiral shaped and radial arm shaped (also called umbrella shaped) carrier assemblies whose ablation elements create spiral, radial, or other simple or complex shaped patterns of lesions in the endocardial surface of the atria by delivery of energy to tissue or other means. The lesions created by the ablation catheters are suitable for inhibiting the propagation of inappropriate electrical impulses in the heart for prevention of reentrant arrhythmias.

[0034] Definitions. To facilitate an understanding of the invention, a number of terms are defined below.

[0035] As used herein, the terms "subject" and "patient" refer to any animal, such as a mammal like livestock, pets, and preferably a human. Specific examples of "subjects" and "patients" include, but are not limited, to individuals requiring medical assistance, and in particular, requiring atrial fibrillation catheter ablation treatment.

[0036] As used herein, the terms "catheter ablation" or "ablation procedures" or "ablation therapy," and like terms, refer to what is generally known as tissue destruction procedures.

[0037] As used herein, the term "ablation element" refers to an energy delivery element, such as an electrode for delivering electrical energy. Ablation elements can be configured to deliver multiple types of energy, such as ultrasound energy and cryogenic energy, either simultaneously or serially. Electrodes can be constructed of a conductive plate, wire coil, or other means of conducting electrical energy through contacting tissue. In monopolar energy delivery, the energy is conducted from the electrode, through the tissue to a ground pad, such as a conductive pad attached to the back of the patient. The high concentration of energy at the electrode site causes localized tissue ablation. In bipolar energy delivery, the energy is conducted from a first electrode to one or more separate electrodes, relatively local to the first electrode, through the tissue between the associated electrodes. Bipolar energy delivery results in more precise, shallow lesions while monopolar delivery results in deeper lesions. Both monopolar and bipolar delivery provide advantages, and the combination of their use is a preferred embodiment of this application. Energy can also be delivered using pulse width modulated drive signals, well

known to those of skill in the art. Energy can also be delivered in a closed loop fashion, such as a system with temperature feedback wherein the temperature modifies the type, frequency and or magnitude of the energy delivered.

[0038] As used herein, the term "carrier assembly" refers to a flexible carrier, on which one or more ablation elements are disposed. Carrier assemblies are not limited to any particular size, or shape, and can be configured to be constrained within an appropriately sized lumen.

[0039] As used herein, the term "spiral tip" refers to a carrier assembly configured in its fully expanded state into the shape of a spiral. The spiral tip is not limited in the number of spirals it may contain. Examples include, but are not limited to, a wire tip body with one spiral, two spirals, ten spirals, and a half of a spiral. The spirals can lie in a relatively single plane, or in multiple planes. A spiral tip may be configured for energy delivery during an ablation procedure.

[0040] As used herein the term "umbrella tip" refers to a carrier assembly with a geometric center which lies at a point along the axis of the distal portion of the tubular body member, with one or more bendable or hinged carrier arms extending from the geometric center, in an umbrella configuration. Each carrier arm may include one or more ablation elements. Each carrier arm of an umbrella tip includes a proximal arm segment and a distal arm segment, the distal arm segment more distal than the proximal arm segment when the carrier assembly is in a fully expanded condition. One or more additional carrier arms can be included which include no ablation elements, such as carrier arms used to provide support or cause a particular deflection. An umbrella tip

body is not limited to any particular size. An umbrella tip may be configured for energy delivery during an ablation procedure.

[0041] As used herein, the term "lesion," or "ablation lesion," and like terms, refers to tissue that has received ablation therapy. Examples include, but are not limited to, scars, scabs, dead tissue, burned tissue and tissue with conductive pathways that have been made highly resistive or disconnected.

[0042] As used herein, the term "spiral lesion" refers to an ablation lesion delivered through a spiral tip ablation catheter. Examples include, but are not limited to, lesions in the shape of a wide spiral, and a narrow spiral, a continuous spiral and a discontinuous spiral.

[0043] As used herein, the term "umbrella lesion" or "radial lesion," and like terms, refers to an ablation lesion delivered through an umbrella tip ablation catheter. Examples include, but are not limited to, lesions with five equilateral prongs extending from center point, lesions with four equilateral prongs extending from center point, lesions with three equilateral prongs extending from center point, and lesions with three to five non-equilateral prongs extending from center point.

[0044] As used herein, the term "coupler" refers to an element that connects the carrier assembly to the control shaft. Multiple shafts, or ends of the carrier assembly may connect to the coupler. Multiple carrier arms can have one or more of their ends attached to the coupler. The coupler may include anti-rotation means that work in combination with mating means in the tubular body member. Couplers may be constructed of one or more materials such as polyurethane, steel, titanium, and polyethylene.

[0045] As used herein, the term "carrier arm" refers to a wire-like shaft capable of

interfacing with electrodes and the coupler. A carrier arm is not limited to any size or measurement. Examples include, but are not limited to: stainless steel shafts; Nitinol shafts; titanium shafts; polyurethane shafts; nylon shafts; and steel shafts. Carrier arms can be entirely flexible, or may include flexible and rigid segments.

[0046] As used herein, the term "carrier arm bend point" refers to a joint (e.g., junction, flexion point) located on a carrier arm. The degree of flexion for a carrier arm bend point may range from 0 to 360 degrees. The bend portion can be manufactured such that when the carrier assembly is fully expanded, the bend point is positioned in a relatively straight configuration, a curved configuration, or in a discrete transition from a first direction to a second direction, such as a 45 degree bend transition. The bend portion can include one or more flexing means such as a spring, a reduced diameter segment, or a segment of increased flexibility.

[0047] The present invention provides structures that embody aspects of the ablation catheter. The present invention also provides tissue ablation systems and methods for using such ablation systems. The illustrated and various embodiments of the present invention present these structures and techniques in the context of catheter-based cardiac ablation. These structures, systems, and techniques are well suited for use in the field of cardiac ablation.

[0048] However, it should be appreciated that the present invention is also applicable for use in other tissue ablation applications such as tumor ablation procedures. For example, the various aspects of the invention have application in procedures for ablating tissue in the prostrate, brain, gall bladder, uterus, and other regions of the body,

preferably regions with an accessible wall or flat tissue surface, using systems that are not necessarily catheter-based.

[0049] The multifunctional catheters of the present invention have numerous advantages over previous prior art devices. The present invention achieves efficiency in tissue ablation by maximizing contact between electrodes and tissue, such as the atrial walls, while also achieving rapid and/or efficient transfer of heat from the electrode into the circulating blood ("cooling"), such as by maximizing electrode surface area in contact with circulating blood. To achieve this result, in a preferred embodiment the electrode has a projecting fin that is configured to act as a heat sink that provides rapid and efficient cooling of the electrode. In another preferred embodiment the electrode comprises two components such that one component, the electrode conductive portion, contracts tissue and the other component, the nonconductive portion, remains thermally conductive. The present invention includes electrodes with improved and miniaturized cross sectional geometries and carrier assemblies that "fold-up" efficiently to allow a smaller ablation catheter to be employed. These improved electrodes are preferably triangularly shaped as described in detail in reference to subsequent figures below. Because these triangular electrodes fold up efficiently, and can have either a "base" to contact tissue or a "point" to contact tissue, greater efficiency and versatility are achieved. The devices and systems are configured to minimize the amount of tissue ablated while still achieving the desired therapeutic benefit of the ablation therapy. Ablated lesions are created with a target depth, and minimal widths. System components monitor energy delivered, parameters associated with energy delivered and other system parameters. Energy delivered is prevented from achieving one or more threshold values.

[0050] Figs. 1-12 show various embodiments of the multifunctional catheters of the present invention. The present invention is not limited to these particular configurations.

[0051] Fig. 1 illustrates the treatment to be accomplished with the devices and methods described herebelow. Fig. 1 shows a cutaway view of the human heart 1 showing the major structures of the heart including the right atrium 2, the left atrium 3, the right ventricle 4, and the left ventricle 5. The atrial septum 6 separates the left and right atria. The fossa ovalis 7 is a small depression in the atrial septum that may be used as an access pathway to the left atrium from the right atrium. The fossa ovalis 7 can be punctured, and easily reseals and heals after procedure completion. In a patient suffering from atrial fibrillation, aberrant electrically conducive tissue may be found in the atrial walls 8 and 9, as well as in the pulmonary veins 10 and the pulmonary arteries 11. Ablation of these areas, referred to arrhythmogenic foci (also referred to as drivers or rotors), is an effective treatment for atrial fibrillation. Though circumferential ablation of the pulmonary vein usually cures the arrhythmia that originates in the pulmonary veins, as a sole therapy it is usually associated with lesions that have high risk of the eventual stenosis of these pulmonary veins, a very undesirable condition. The catheters of the present invention provide means of creating lesions remote from these pulmonary veins and their ostia while easily being deployed to ablate the driver and rotor tissue.

[0052] To accomplish this, catheter 100 is inserted into the right atrium 2, preferably through the inferior vena cava 20, as shown in the illustration, or through the superior vena cava 21. Catheter 100 may include an integral sheath, such as a tip deflecting sheath, or may work in combination with a separate sheath. When passing into the left atrium, the catheter passes through or penetrates the fossa ovalis 7, such as over a guide

wire placed by a trans-septal puncture device. The catheter 100 carries a structure carrying multiple ablation elements such as RF electrodes, carrier assembly 120, into the left atrium. Carrier assembly 120, which includes multiple electrodes 130, can be advanced and retracted out of distal end of catheter 100. Carrier assembly 120 is adapted to be deformable such that pressing carrier assembly 120 into left atrial wall 9 will cause one or more, and preferably all of electrodes 130 to make contact with tissue to be analyzed and/or ablated. Each of the electrodes 130 is attached via connecting wires to an energy delivery apparatus, RF delivery unit 200, which is also attached to patch electrode 25, preferably a conductive pad attached to the back of the patient.

[0053] RF delivery unit 200 is configured to deliver RF energy in monopolar, bipolar or combination monopolar-bipolar energy delivery modes. In a preferred embodiment, monopolar energy delivery is followed by bipolar energy delivery. In an alternative embodiment, the bipolar energy is then followed by a period without energy delivery; such as a sequence in which the three steps are have equal durations. In another preferred embodiment, RF delivery unit 200 is configured to also provide electrical mapping of the tissue that is contacted by one or more electrodes integral to carrier assembly 120. Electrodes 130, preferably with a triangular cross section, can also be configured to be mapping electrodes and/or additional electrodes can be integral to carrier assembly 120 to provide a mapping function. Carrier assembly 120 is configured to be engaged over an endocardial surface to map and/or ablate tissue on the surface. RF energy is delivered after a proper location of the electrodes 130 is confirmed with a mapping procedure. If the position is determined to be inadequate, carrier assembly 120 is repositioned through various manipulations at the proximal end of the ablation catheter 100. In another

preferred embodiment, RF delivery unit 200 is configured to deliver both RF energy and ultrasound energy through identical or different electrodes 130. In another preferred embodiment, RF delivery unit 200 is configured to accept a signal from one or more sensors integral to ablation catheter 100, not shown, such that the energy delivered can be modified via an algorithm which processes the information received from the one or more sensors. The improved electrodes and other catheter and system components of the present invention typically require only 3 to 5 watts of RF energy to adequately ablate the tissue. The minimal power requirements results in reduced procedure time as well as greatly enhanced safety of the overall procedure.

[0054] Figures 2a and 2b illustrate an exemplary embodiment of the ablation catheter 100 of the present invention. These ablation catheters have triangular electrodes 130, each with fin 133 configured to provide rapid and efficient cooling of electrode 130. The cooling efficiency prevents over-heating of the electrode and neighboring tissue during ablation, as well as a short transition time from an ablation temperature, preferably 60° C, to body temperature, typically 37° C after an ablation cycle has ceased. This rapid transition is typically less than 20 seconds, even when the electrode remains in contact with recently ablated tissue. Other benefits of the rapid and efficient cooling electrode configuration include reducing the risk of blood clotting.

[0055] The ablation elements of the present invention include RF energy delivery electrodes 130 of Figs. 2a and 2b, as well as other elements capable of delivering one or more forms of energy, described in detail hereabove, the electrodes and other system components configured in a manner sufficient to controllably ablate tissue. Electrodes 130 include conductive materials, such as a metal or metal-coated material. Metals and

combinations of metals are appropriate such as: platinum, iridium, gold, stainless steel and aluminum. Conductive polymers are also appropriate materials. Conductive surfaces may be painted, coated or plated surfaces, such as gold plated over a copper base. Electrode materials may also include foils such as aluminum or gold foils attached to a base. Electrodes 130 deliver RF energy in monopolar or bipolar mode as has been described in reference to Fig. 1. Electrodes 130 are designed to have small surface area, typically less than 2.5mm^2 and preferably approximating 0.56mm^2. Electrodes 130 are designed to have small volume, typically less than 3.0mm^3 and preferably approximating 1.3mm^3. Electrodes 130 are designed to have small mass, typically less than 0.05 grams, and preferably approximating 0.03 grams. These miniaturized electrodes, especially those with a triangular cross section, provide numerous advantages such as high ratio of energy to surface area (energy density) during ablation, as well as efficiently compact volume of carrier assembly 120 when constrained within the lumen of the ablation catheter in the retracted, undeployed state.

[0056] Figure 2a shows the structures of the ablation carrier assembly 120 and other portions of ablation catheter 100. The ablation carrier assembly 120 shown includes carrier arms 123 that extend radially out from the central axis of the distal end of catheter shaft 101, the carrier arms 123 positioned in a symmetric configuration with equal angles (ninety degrees in a four arm configuration between each arm). Carrier assembly 120 is shown with four carrier arms 123, however any number can be used, and each arm can carry one or more mapping or ablating electrodes 130, or be void of electrodes. Carrier arms 123 are resiliently biased, preferably constructed of a wire such as a ribbon wire, and may have segments with different levels of flexibility. Carrier arms 123 are shown

with multiple electrodes 130 fixedly mounted (such as with glues, soldering, welding, crimping or other attachment means) to its distal arm segment 127. In an alternative embodiment, different patterns of electrodes are employed, and one or more arms may be void of electrodes such as where carrier arm 123 provides support only. In a preferred embodiment, different types of ablation elements are mounted to one or more carrier arms 123, such as electrodes with different geometries, or ablation elements that deliver different forms of energy. Carrier arms 123 may also include mapping electrodes, thermal sensors or other sensors, with or without the inclusion of ablation elements. In a preferred embodiment, each carrier arm 123 includes at least one ablation element. In alternative embodiments, three or more arms can be separated by non-equal angles.

[0057] Each carrier arm 123 includes proximal arm segment 125 and distal arm segment 127. Electrodes 130 are mounted onto distal arm segment 127. During the ablation procedure, an operator presses distal arm segment 127 into tissue prior to and during energy delivery. Carrier assembly 120 is configured with specific rigidity such that the operator can exert a nominal force to cause the appropriate electrodes 130 to press and slightly "bury" into the tissue, without perforating or otherwise damaging the neighboring tissue. In a preferred embodiment, the distal arm segments contain thermocouples such as sensors embedded in the electrodes 130, or sensors mounted equidistant between two electrodes 130. Proximal arm segment 125 and distal arm segment 127 connect at a bendable joint, carrier arm bend point 121. In a preferred embodiment, proximal arm segment 125, distal arm segment 127 and bend point 121 are a continuous resiliently flexible wire. Each distal arm segment 127 bends radially inward from the bend point 121 toward the longitudinal axis of catheter shaft 101. The distal arm

segments 127 are shown also to tend proximally, to establish an acute angle with the proximal arm segment 125 from which it extends, and the angle is small such that the distal end of the distal arm segment 127 is proximal to the carrier arm bend point 121. Bend point 121 allows "folding out" of carrier assembly 120 during retraction, acting as a hinge in providing the means for rotably joining the distal arm segment 127 to the proximal arm segment 125. The proximal arm segment 125 of the carrier arm 123 may include temperature sensors, not shown, such as thermocouples to measure temperature of blood. In the configuration shown, the proximal arm segment 125 will not contact tissue during the ablation procedure. In an alternative embodiment, proximal arm segment 125 includes one or more electrodes, for ablation and/or for mapping, such that the opposite side of carrier assembly 120 can be used to map or ablate tissue and is configured to contact tissue, such as when carrier assembly 120 is deployed and catheter shaft 101 is in tension such as when pulled back by an operator.

[0058] Each distal arm segment 127 connects, at its end opposite bend point 121, to connection point 124, a mechanical joint such as a soldered, crimped or welded connection that stabilizes each distal arm segment 127 relative to the others. In a preferred embodiment, two continuous wires or ribbons are used to create the four distal arm segments 127. Each wire or ribbon comprises the pair of distal arm segments 127 that are linearly aligned, and the two wires are connected at their midpoint at connection point 124. These wires or ribbons are preferably constructed of Nitinol, but other materials such as stainless steel or a plastic may be used. In an alternative embodiment, the two connection wires are resiliently biased to deploy in the configuration shown in

Fig. 2a, but do not include connection point 124 such that the center portion of the two continuous wires can move relative to each other.

[0059] Referring to the ablation catheter 100 structures, Fig. 2a shows a tubular body member that is an elongated, flexible, hollow tube, catheter shaft 101, which connects at its proximal end to handle 110. The material used for the construction of the catheter shaft 101 and each component which resides or is configured to be inserted through a lumen integral to catheter shaft 101, are selected to provide the suitable flexibility, column strength and steerability to allow percutaneous introduction of ablation catheter 100 through the vasculature of the patient, entering the right atrium 2 through the septum 6 and into the left atrium 3. Catheter shaft 101 and other tubular conduits of ablation catheter 100 are constructed of materials such as Pebax, urethanes, nylons, thermoplastic elastomers, and polyimides. The shafts may be reinforced with wire or plastic braids and/or may include coil springs. Catheter shaft 101 is typically between 4 to 12 French and typically 6 to 8 French. In a preferred embodiment, catheter shaft 101 is introduced through a deflectable sheath where the sheath mechanism is already in place in left atrium 3. In an alternative embodiment, catheter 100 is inserted directly without the use of an outer sheath, and catheter 100 includes a deflectable tip assembly and deflection controls.

[0060] Handle 110 on the ablation catheter includes controls to operate the carrier assembly 120. Handle 110 is constructed of a rigid or semi-rigid material such as Delrin or polycarbonate, and includes button 116 that is connected to switch means, not shown, for starting and/or stopping the delivery of energy to one or more of electrodes 130. Handle 110 may include other controls, not shown, to perform numerous functions such

as change energy delivery settings. Handle 110 may include a retraction mechanism, not shown, to advance and retreat carrier assembly 120. In an alternative embodiment, handle 110 is attached to an inner shaft slidingly received within catheter shaft 101 such that retraction of the handle 110 causes the carrier assembly 120 to collapse and be constrained within the lumen at end of catheter shaft 101. Carrier arm 123 is resiliently biased in shown position so that it can be collapsed and withdrawn within lumen of catheter shaft 101 through manipulation of handle 110 on proximal end of catheter 100.

[0061] Handle 110 includes a plug 118 that attaches to an interface unit of the present invention, such as an RF energy generator that also includes mapping functions and display. Plug 118 is connected to electrical wires that extend distally with a lumen integral to catheter shaft 101 of carrier assembly 120, terminating at each of the electrodes 130.

[0062] Fig. 2b illustrates the cross section, preferably a uniform cross section, of one or more electrodes 130 mounted to distal arm segment 127 of Fig. 2a. A projecting member, fin 133, assists in the rapid and efficient cooling of electrode 130 during and after ablation energy application, acting as a heat sink and efficiently transferring heat energy to the neighboring blood, such as blood circulating in the left atrium 3 or the right atrium 2 depending upon where the carrier assembly 120 has been placed by the operator. The size, surface area and mass of fin 133 are chosen to effectively transfer the heat energy while allowing carrier assembly 120 to achieve a sufficiently compact configuration when constrained within the lumen of the ablation catheter. In a preferred embodiment, fin 133 is sized such that the portion of the surface area of electrode 130 that is in contact with circulating blood is at least 60%, and preferably 70% of the total

surface area of electrode 130. Fin 133 may change laminar and/or other non-turbulent flows to turbulent flow, such that heat is more efficiently transmitted away from electrode 130. In an alternative embodiment, illustrated and described in reference to Figs. 5c and 5d, fin 133 may be electrically isolated from the remainder of electrode 130, such that fin 133 does not deliver energy to the circulating blood. In another alternative embodiment, illustrated and described in reference to Fig. 6b, electrode 130 may include multiple fins.

[0063] First wire 134 is an energy delivery conduit that connects to electrode 130 to transfer ablation energy and preferably to also send and/or receive signals to map the tissue of the heart. Second wire 135 depicts an exemplary wire that connects to electrode 130, and may act as the return wire to first wire 134, for return of ablation energy and/or mapping signals. Wire 134 and wire 135 are typically 30 awg wire including a 0.003" polyamide insulating outer jacket, each parameter chosen to carry sufficient ablation currents and prevent voltage breakdown between neighboring wires. The efficiency of the electrodes of the present invention, as well as the efficient configuration of the other components of the system, allow greatly reduced wire gauge and insulation thickness, correlating to smaller diameter and more flexible ablation catheters.

[0064] Surface 136 is the base of the electrode that is the part of the structure that contacts tissue during ablation. In a preferred embodiment, surface 136 is a small surface area so that energy delivered per square area is maximized. Fin 133 projects from the apex opposite surface 136, and provides sufficient surface area such that the majority of the surface area of electrode 130 resides in the circulating blood when surface 136 is in contact with tissue and energy is being delivered. Within the triangular cross section of

electrode 130 passes each wire 134 and 135, as well as distal arm segment 127, to which electrode 130 is fixedly mounted.

[0065] Referring now to Figs. 3a through 3c, another preferred embodiment of the ablation catheter and components of the ablation system of the present invention is illustrated. Electrodes 130 have a triangular cross section with a continuous perimeter or path, preferably an isosceles triangle wherein the common base is opposite two sides that determine a vertex angle. This vertex angle is configured, based on the number of carrier arms of the particular carrier assembly, to allow a number of electrodes to be constrained into a volumetrically efficient circle or "pie" shape, the sum of all the vertex angles approximating 360 degrees, such that:

$$\text{Vertex Angle} = \frac{360 \text{ degrees}}{\text{Number of Carrier Arms}}$$

[0066] In an alternative embodiment, the cross sections are dissimilar, and/or the cross sections do not include only isosceles geometries, however the individual vertex angles are configured such that their sum approaches 360 degrees in total, providing efficient constrained volume of the carrier assembly. In addition to allowing compact constrained volume, and overall small surface area, volume and mass of electrodes 130, the electrodes of the present invention provide maximum flexibility in performing ablation procedures, such as by: minimizing energy delivered to blood; avoiding energy delivered to non-targeted tissue and/or minimizing tissue area receiving energy during ablation; maximizing energy density delivered to tissue; reducing procedure time, and other advantages. In a preferred embodiment, the ablation catheter and system of the

present invention includes multiple dissimilar electrodes, fixedly mounted to a single ablation catheter or mounted to multiple ablation catheters used sequentially or simultaneously in a single ablation procedure for a patient.

[0067] Referring specifically to Fig. 3a, electrode 130a is configured to deliver RF energy to tissue via surface 136. Electrode 130a of Fig. 3a is similar to electrode 130 of Fig. 2b with a smaller projecting fin 133, sized to allow a more compact constrained configuration of the carrier assembly while still increasing the surface area of electrode 130a in the circulating blood during ablation. Electrode 130a is fixedly mounted to distal arm segment 127 which comprises a Nitinol wire or ribbon but alternatively a non-conductive material such as nylon or other non-metal which does not require electrode 130a from being electrically isolated from distal arm segment 27, isolation means not shown. Electrode 130a includes within its triangular cross section wire 134 and wire 135 that are electrically connected to electrode 140a and travel proximally to an electrical connection point that attaches to an interface unit of the present invention. Wire 134 and 135 provide supply and return of RF power and potentially supply and return of mapping drive and record signals. Additional wires and other energy delivery or other conduits, not shown, may pass through the triangular cross section of electrode 130a, such as energy and/or signal delivery conduits that connect to sensors such as thermocouples, or other ablation or mapping elements. In a preferred embodiment, electrode 130a includes an embedded thermocouple, not shown but preferably a bimetallic thermocouple consisting of copper and alloy 11 or Constantan alloy. Each thermocouple is attached to 40 awg wire with a 0.001" insulating jacket, the wires traveling proximally and attaching to the interface unit of the present invention for converting signals to temperature values.

[0068] Referring to Fig. 3b, a partial cutaway view of the ablation catheter of the present invention is illustrated, including the multiple electrodes 130a of Fig. 3a constrained with a lumen of catheter shaft 101 of ablation catheter 100. Ablation catheter 100 may be configured to be inserted through a deflectable guide catheter, or include distal tip deflection means, not shown. Electrodes 130a are fixedly mounted to distal arm segments 127 which are attached to proximal arm segments via a bendable portion (both proximal arm segments and bendable portion not shown but described in detail in reference to Fig. 2a). The ablation element carrier assembly has been folded into the retracted state shown, by retraction of handle 110 and/or activation of a control of handle 110, not shown but preferably a sliding knob or lever on handle 110. Handle 110 includes connector 118 for electrical attachment to an energy delivery apparatus such as an RF generator and/or electrophysiology mapping unit, and further includes button 116 used by the operator to initiate an energy delivery event. Handle 110 may additionally include other functional components and assemblies such as other control or activation means, as well as audio and/or tactile transducers to alert the operator of alert conditions.

[0069] Referring additionally to Fig. 3c, the carrier assembly of Figs. 3b and 3c includes five electrodes 130a and five distal arm segments 127 that have been placed in a constrained condition within a lumen of catheter shaft 101 such that at least a portion of each of the triangle cross section of the five electrodes 130a lie in a single plane. Each electrode 130a has a similar isosceles triangle shaped cross section such that the vertex angle A approximates 75 degrees allowing the compact 360 circular or pie shaped configuration. In the constrained configuration shown, each vertex angle A is aligned radially outward from the central axis of shaft 101 such that the tissue contacting surface

136 of each electrode 130a is in relative contact with the inner wall of shaft 101. These triangle cross sections and relatively small projecting fins 133 are sized and configured to allow a compact constrained configuration that includes coupler 140 at its center. Coupler 140, described in detail in reference to Fig. 4, couples the carrier arms of the carrier assembly to a slidable shaft, not shown but operably attached to handle 110 and advanced and retracted by an operator to position the carrier assembly in its deployed (expanded) and constrained configurations respectively.

[0070] While the carrier assembly configuration of Figs. 3b and 3c illustrate a five carrier arm configuration that correlates to an electrode 130a cross section triangular vertex angle approximating 75 degrees, it can be easily derived from the equation above that a vertex angle of 120 degrees would correspond to three arm carrier assembly configurations and a vertex angle of 90 degrees would correspond to four arm configurations. It also should be easily understood that in embodiments in which electrode 130a cross sections are dissimilar, the sum of the vertex angles of the appropriate cross sections, those cross sections that are linearly aligned within the lumen of catheter shaft 101 in the retracted position, should approximate 360 degrees to minimize the overall constrained cross sectional area.X

[0071] Referring now to Figs. 4 and 4a, another preferred embodiment of ablation catheter 100 and ablation system of the present invention is illustrated. Catheter 100 includes carrier assembly 120 configured in another umbrella tip configuration. Carrier assembly 120 includes three carrier arms 123, each separated by 120 degrees from the neighboring arm when in the deployed condition, and each of which includes two ablation elements, electrodes 130. In an alternative embodiment, different patterns of electrodes

are employed, and one or more arms may be void of electrodes. Electrodes can take on one or more various forms, such as those described in detail in reference to Figs. 5a through 5f and Figs. 6a through 6c. The six electrodes 130 shown may have similar or dissimilar characteristics. They may be chosen to maximize cooling or maximize energy delivery to tissue. Each electrode 130 may be energized with one or more forms of energy such as RF energy in a sequence of monopolar and bipolar energy delivery. Referring back to Fig. 4, carrier arms 123 extend radially out from the central axis of the distal end of catheter shaft 101. Each carrier arm 123 includes proximal arm segment 125 and distal arm segment 127, these segments connected at a bendable joint, bend point 121. In a preferred embodiment, proximal arm segment 125 and distal arm segment 127 and bend point 121 are a continuous resiliently flexible wire, such as a "trained" Nitinol wire that creates the umbrella tip. Each electrode 130 is mounted to an insulator, insulating band 131 such that the electrode is electrically isolated from the wire segments of carrier assembly 120. Each electrode 130 is connected to wires that extend along shafts of carrier assembly 120, toward a lumen of catheter shaft 101, and proximally to handle 110. These wires, not shown but described in detail hereabove, include insulation to electrically isolate one wire from another. One end of each distal arm segment 127 is attached to a cylinder, coupler 140, which is sized to be slidably received within a lumen of catheter shaft 101.

[0072] Coupler 140 can be flexible or rigid, and may contain both rigid and flexible portions along its length. Coupler 140 may provide electrical connection means to connect wires extending from the handle to wires from carrier assembly 120 electrodes. The ends of the distal arm segments 127 and the ends of the proximal arm segments 125

can be attached to the outside of coupler 140, the inside of coupler 140 or both. Coupler 140 includes along its outer surface, a projection, projection 142, which has a cross section profile which mates with a recess, groove 106 of catheter shaft 101 which prevents undesired rotation of carrier assembly 120. In an alternative embodiment, catheter shaft 101 includes a projection, and coupler 140 includes a groove to accomplish a similar prevention of rotation. In another alternative embodiment, control shaft 150, which is slidingly received within a lumen of shaft 101, additionally or alternatively includes a projection or other means to mate with shaft 101 to prevent undesired rotation of carrier assembly 120. As depicted in Fig. 4a, control shaft 140 includes a thru lumen, lumen 152, such that ablation catheter 101 can be inserted over a guidewire (guidewire exit on handle 110 not shown). Additionally or alternatively, lumen 152 may include one or more wires or other filamentous conduits extending from proximal handle 110 a point more distal.

[0073] Control shaft 150 is mechanically attached to coupler 140. Control shaft 150 extends proximally to handle 110 and is operably connected to knob 115 such that rotation of knob 115 from a deployed position to a withdrawn position causes carrier assembly 120 to be constrained within a lumen of catheter shaft 101, and rotation of knob 115 from a withdrawn position to a deployed position causes carrier assembly 120 to extend beyond the distal end of catheter shaft 101 to be in an expanded condition. In a preferred embodiment, knob 115 is operably connected to control shaft 150 via a cam, or set of gears, not shown, to provide a mechanical advantage in the distance traveled by control shaft 150.

[0074] Catheter shaft 101 is preferably part of a steerable sheath, steering

mechanism not shown, and includes flush port 170, which is configured to be attachable to a flushing syringe, used to flush blood and other debris or contaminants from the lumen of an empty catheter shaft 101 (wherein control shaft 150, coupler 140 and carrier assembly 120 have been removed) or for flushing the space between control shaft 150 and the inner wall of catheter shaft 101. Catheter shaft 101 is not connected to handle 110, such that handle 110 can be withdrawn, removing control shaft 150, coupler 140 and carrier assembly 120 from catheter shaft 101. This configuration is useful when these components are provided in a kit form, including combinations of different versions of these components, the different combinations made available to treat multiple patients, or a single patient requiring multiple electrode patterns or other varied electrode properties such as tissue contact surface area, electrode cooling properties and temperature sensor location. A preferred example of a kit would include the catheter shaft 101 and flush port 170 of Fig. 6 acting as a sheath; kitted with the insertable shaft assembly comprising handle 110, control shaft 150, coupler 140 and umbrella tipped carrier assembly 120 of Fig. 6 as well as a second insertable shaft assembly. The second insertable shaft assembly preferably includes a different carrier assembly of ablation elements such as a different pattern of electrodes or electrodes with different properties that the first insertable shaft assembly. Electrode or other ablation element variations include but are not limited to: type of energy delivered; size; cross sectional geometry; cooling properties; heating properties; and combinations thereof. In another preferred embodiment of the kit, a catheter configured for creating lesions at or near the pulmonary veins of the left atrium is included.

[0075] Also depicted in Fig. 4 is a system of the present invention, including in

addition to ablation catheter 100, RF delivery unit 200, an interface unit of the present invention which connects to handle 110 with a multi-conductor cable 202 at RF attachment port 181. RF delivery unit 200 includes user interface 201, such as a user interface including data input devices like touch screens, buttons, switches, keypads, magnetic readers and other input devices; and also including data output devices like data and image screens, lights, audible transducers, tactile transducers and other output devices. User interface 201 is used to perform numerous functions including but not limited to: selecting electrodes to receive energy (electrodes 130 of carrier assembly 120); setting power levels, types (bipolar and monopolar) and durations; setting catheter and other system threshold levels; setting mapping and other system parameters; initiating and ceasing power delivery; deactivating an alarm condition; and performing other functions common to electronic medical devices. User interface 201 also provides information to the operator including but not limited to: system parameter information including threshold information; mapping and ablation information including ablation element temperature and cooling information; and other data common to ablation therapy and other electronic medical devices and procedures. In a preferred embodiment, RF delivery unit 200 attaches to a temperature probe, such as an esophageal temperature probe, determines the temperature from one or more sensors integral to the probe, and further interprets and/or displays the temperature information on user interface 201. In another preferred embodiment, RF delivery unit 200 also includes cardiac mapping means, such that mapping attachment port 182 can be attached to RF delivery unit 200 avoiding the need for a separate piece of equipment in the system. In another preferred embodiment, RF delivery unit 200 can also deliver ultrasound and/or another form of energy, such

energy delivered by one or more additional ablation elements integral to carrier assembly 120, additional ablation elements not shown. Applicable types of energy include but are not limited to: sound energy such as acoustic energy and ultrasound energy; electromagnetic energy such as electrical, magnetic, microwave and radiofrequency energies; thermal energy such as heat and cryogenic energies; chemical energy; light energy such as infrared and visible light energies; mechanical energy; radiation; and combinations thereof.

[0076] In a preferred embodiment, ablation catheter 100 includes an embedded identifier (ID), an uploadable electronic or other code, which can be used by RF delivery unit 200 to confirm compatibility and other acceptability of the specific catheter 100 with the specific RF delivery unit 200. The electronic code can be a bar code, not shown, on handle 110 which is read by RF delivery unit 200, an electronic code which is transferred to RF delivery unit 200 via a wired or wireless connection, not shown, or other identifying means, such as an RF tag embedded in handle 110. In another preferred embodiment, RF delivery unit 200 also includes an embedded ID, such as an ID that can be downloaded to catheter 100 for a second or alternative acceptability check. The embedded ID can also be used to automatically set certain parameters or certain parameter ranges, and can be used to increase safety by preventing inadvertent settings outside of an acceptable range for the specific catheter 100.

[0077] Handle 110 includes two push buttons, first button 116 and second button 117. These buttons can be used to perform one or more functions, and can work in cooperation with user input components of user interface 201 such that commands entered into user interface 201 set the action taken when either or both button 116 and

button 117 are pressed. In a preferred embodiment, both button 116 and button 117 must be pressed simultaneously to deliver energy to one or more ablation elements of catheter 100. At the distal end of catheter shaft 101 is a circumferential band, band 104. Band 104 is preferably a visualization marker, such as a radiographic marker, ultrasound marker, electromagnetic marker, magnetic marker and combinations thereof. In an alternative embodiment, band 104 transmits or receives energy, such as when the marker is used as a ground or other electrode during an ablation. In another alternative embodiment, band 104 is an antenna used to determine the position of the distal end of catheter shaft 101 or the location of another component in relation to band 104. In another preferred embodiment, band 104 is used to store energy, such as capacitively stored energy that can be used to generate a magnetic field or to deliver ablation energy.

[0078] While the ablation catheter of Figs. 4 and 4a is shown with an umbrella tip geometry, it should be appreciated that numerous configurations of carrier arms, such as spiral, zigzag, and other patterns could be employed. These carrier assemblies are configured to provide sufficient forces to maximally engage the appropriate ablation element with the tissue to be ablated, without adversely impacting neighboring structures and other tissues. While the carrier assembly 120 of Fig. 4 "folds in" during retraction of shaft 150, other collapsing configurations can be employed such as the "fold out" configuration of the catheter of Fig. 2a, or configuration in which the carrier assembly transforms from a spiral, zigzag, or other curvilinear shape to a relatively straight or linear configuration as it is retracted and captured by the lumen of catheter shaft 101. Electrodes 130 of carrier assembly of Fig. 4 are shown facing out from the distal end of shaft 101 such that advancement or "pushing" of carrier assembly 120 engages electrodes

130 with tissue. In an alternative embodiment, electrodes are positioned, alternatively or additionally, to face toward the distal end of shaft 101. These electrodes may be mounted to proximal arm segment 125 such that retraction or "pulling" of carrier assembly 120, once deployed, engages these rear facing electrodes with tissue.

[0079] Ablation catheter 100 and RF delivery unit 200 are configured to ablate tissue with minimal power and precise control. RF Power levels are preferably less than 10 watts per electrode, and preferably 3 to 5 watts. Electrodes 130 are powered to reach an ablation temperature of approximately 60° C. The electrode geometries of the present invention, described in detail in reference to Figs. 5a through 5f and Figs. 6a through 6c, provide numerous and varied benefits including enhanced cooling properties. Electrodes of the present invention are configured to transition from an ablation temperature of 60° C to body temperature of 37° C in less than 20 seconds and preferably less than ten seconds. These electrodes are further configured to increase from body temperature to ablation temperature in less than 5 seconds. In a preferred embodiment, bipolar RF energy is delivered subsequent to monopolar delivery. The electrodes and power delivery subsystems of the present invention are configured to allow the electrode and neighboring tissue to decrease in temperature during the bipolar RF energy delivery following the monopolar delivery. This bimodal, sequential power delivery reduces procedure time, allows precise control of lesion depth and width, and reduces large swings in ablation temperatures. In another preferred embodiment, the temperature in the tissue in proximity to the electrode actually continues to increase as the electrode temperature decreases, such as during the bipolar delivery following monopolar delivery. In an alternative embodiment, the monopolar delivery cycle, the bipolar delivery cycle, or both,

are followed by a period of time in which no RF energy is delivered. During this "off" time period, no energy may be delivered or an alternative energy may be delivered such as cryogenic energy that actually decreases the temperature of the tissue in order to ablate.

[0080] In a preferred embodiment, parameters associated with the bipolar and monopolar energy delivery are adjusted during the procedure, automatically by the system and/or manually by the operator. The energy delivery parameters are adjusted by measured, calculated or otherwise determined values include those relating to: energy delivered measurements such as voltage or current delivered to an electrode; force or pressure measurement such as the force exerted by the carrier assembly as measured by an integral strain gauge; other ablation catheter or ablation system parameter; temperature of tissue; rate of change of temperature of tissue; temperature of an electrode or other ablation element; rate of change of temperature of an electrode or other ablation element; EKG; tissue thickness; tissue location; cardiac flow-rate; other patient physiologic and other patient parameters; and combinations thereof. The energy delivery drive parameters may be adjusted by a combination of these determined values. In order to automatically modify an energy delivery parameter, or to notify an operator of a condition, these determined values are compared to a threshold, such as via a threshold comparator integral to the interface unit of the present invention. Threshold values can be calculated by the system or can be entered by the operator into a user interface of the system.

[0081] Energy delivered measurements, such as current, voltage and power measurements, which may be compared to a threshold value, include average energy; instantaneous energy; peak energy; cumulative or integrated energy amounts; and

combinations thereof. In the catheter and system of the present invention, average power is approximately 5 Watts and less, cumulative energy for a cycle of bipolar and monopolar delivery is typically less than 500 Watt-seconds and preferably less than 300 Watt-seconds (5 watts for 60 seconds). Each threshold value may change over time and may be adjustable by an operator such as via a password enabled user interface. Cumulative determined values, such as cumulative energy delivered and "time at temperature" values may be able to be reset, such as automatically by the system and/or manually by an operator. Automatic resets may occur at specific events such as each time an ablation element is repositioned on tissue or each time energy delivered changes states, including the switching of electrodes receiving energy or the completion of a monopolar-bipolar delivery cycle.

[0082] Determined values such as temperature measurements may be made from single or multiple sensors, such as multiple temperature sensors during a single ablation cycle. In a preferred embodiment, multiple sensors are used and the more extreme (e.g. a higher temperature) value is compared to a threshold. When the threshold comparator determines a particular threshold has been reached, the system can adjust or otherwise react in various ways. In a preferred embodiment, the system enters an alarm or alert state. In another preferred embodiment, the energy delivery transmitted to an ablation element is modified; such as to cease or reduce the amount of RF energy delivered to an electrode. Numerous energy delivery parameters can be modified including but not limited to: current level; voltage level; frequency (usually fixed at 500 KHz); bipolar delivery "on" times; monopolar delivery "on" times; no energy delivery "on" times; electrode selected such as bipolar return electrode selected; and combinations thereof.

[0083] The automatic and manual adjustments of the present invention are triggered by comparing a measured, calculated or otherwise determined value to a threshold. These adjustments improve numerous outcomes of the proposed ablation therapy including those associated with improved efficacy and reduced adverse events. Specific benefits include precision controlled depth and width of lesions through a combination of bipolar and monopolar sequential duty cycles. The system is adjustable by the operator to modify intended lesion geometry to safely avoid structures like pulmonary vein lumens and the esophagus, as well as work in portions of the atrial wall that require deep lesions to effectively interrupt aberrant pathways.

[0084] Referring now to Figs. 5a through 5f, multiple preferred embodiments of electrode-type ablation element of the present invention are illustrated. These electrodes are shown in sectional view in contact with tissue 30 just prior to or during delivery of energy to tissue 30 via the electrode. Each of the electrodes of Figs. 5a through 5f are intended to maximize cooling, minimize energy delivered to non-targeted tissue (e.g. blood), or both. Certain electrodes are configured to minimize "low flow" areas for blood, such blood more likely to absorb enough energy to clot during an energy delivery cycle. The electrode cross sections assume various geometries such as triangular, semi-circular and crescent shaped, and are all preferably relatively uniform along their length such as to simplify their manufacturing. Cross sectional geometries are configured to create lesions of specific widths and depths, and to otherwise minimize trauma to neighboring tissue such as when force is applied to press the electrode "into" the tissue to be ablated. In a preferred embodiment, each of the electrodes of Figs 5a through 5f

includes one or more temperature sensors, such as a thermocouple in a non-energy delivery portion.

[0085] Referring specifically to Fig. 5a, electrode 130b is displayed including a triangular cross section and configured to be placed by an operator with base 136 in contact with tissue 30. Electrode 130b includes an isosceles triangle cross section, with two equal sides, sides 137 and 138, each positioned in circulating blood when ablation energy, such as RF energy, is being delivered via wires 134 and 135. Electrode 130b is fixedly mounted to distal arm segment 127, as has been described in detail in reference to previous figures. Distal arm segment 127 is sufficiently rigid to allow the operator to apply a force to electrode 130b such that electrode 130b can be pressed, as shown, into tissue 30. The transition point from base 136 to side 137 and from base 136 to side 138 each are rounded such that although electrode 130b is slightly depressed into tissue 30, low blood flow area 31 (an area where blood will tend to heat up at a faster rate) is minimized as well as tension in the neighboring tissue. The surface area of sides 137 and 138 are sufficiently large (i.e. the combined lengths of sides 137 and 138 is sufficiently long) such that their combined surface area is greater than 60% of the overall total surface area of electrode 130b, preferably greater than 75% of the total. This high percentage of surface area in the circulating blood provides rapid and efficient cooling of electrode 130b.

[0086] Referring specifically to Fig. 5b, electrode 130c is displayed including a triangular cross section and configured to be placed by an operator with the majority of sides 137and 138 in contact with tissue 30. Electrode 130c includes an isosceles triangle cross section and base 136 positioned in circulating blood when ablation energy, such as

RF energy, is being delivered via wires 134 and 135. Electrode 130c is fixedly mounted to distal arm segment 127, as has been described in detail in reference to previous figures. Distal arm segment 127 is sufficiently rigid to allow the operator to apply a force to electrode 130c such that electrode 130c can be pressed, as shown, into tissue 30. The surface area of sides 137 and 138 are sufficiently large such that their combined surface area is greater than 60% of the overall total surface area of electrode 130c, preferably greater than 70% of the total. This high percentage of surface area in contact with tissue minimizes the amount of energy delivered by electrode 130c into the neighboring blood. The energy delivery parameters are chosen such as to prevent the blood residing in or near low flow area 31 from clotting.

[0087] Referring specifically to Fig. 5c, electrode 130d is displayed including a laminate construction with a triangular cross section and configured to be placed by an operator with the majority of sides 137and 138 in contact with tissue 30. Electrode 130d is configured to both improve cooling, and maximize energy delivered to tissue versus blood. Electrode 130d includes an isosceles triangle cross section, with base 136 positioned in circulating blood when ablation energy, such as RF energy, is being delivered via wires 134 and 135. Electrode 130d is fixedly mounted to distal arm segment 127, as has been described in detail in reference to previous figures. Distal arm segment 127 is sufficiently rigid to allow the operator to apply a force to electrode 130d such that electrode 130d can be pressed, as shown, into tissue 30. Electrode 130d has a laminate construction that includes a first portion that receives and delivers energy to tissue, electrical portion 132, a segment preferably constructed of standard RF electrode materials described hereabove. Electrical portion 132 makes up the majority of sides 137

and 138 and is sized such that all or nearly all of its surface area is in contact with tissue 30 during delivery of energy. Electrode 130d has a second portion that is thermally conductive, thermal portion 139. Thermal portion 139 is either electrically non-conductive, minimally electrically conductive, and/or electrically isolated from electrical portion 132 such that thermal portion 139 does not deliver energy when energy is applied to and delivered by electrical portion 132. Thermal portion 139 may be constructed of standard electrode materials but be electrically isolated from electrical portion 132 such as with insulating glue 146. In this configuration and in an additional embodiment, thermal portion 139 may also (in addition to electrical portion 132) independently be used to map or deliver energy with different drive wires not shown. Alternatively, thermal portion 139 may be a plastic with high thermal conductivity such as a Konduit™ thermally conductive thermoplastic compound manufactured by LNP Engineering Plastics of Exton, Pa. Thermal portion 139 makes up a small portion of each of side 137 and side 138, and the entirety of base 136 such that when electrode 130d is positioned 'into" tissue by the operator, most of thermal portion 139 is in the circulating blood, dissipating heat from electrical portion 132 and the neighboring tissue. Thermal portion 139 is sized such that no significant energy is delivered to low flow area 31, greatly reducing any chance of clot formation. Electrode 130d is configured to apply the great majority of the energy it receives into tissue and not blood, as well as provide enhanced cooling by having a thermal portion with significant surface area and/or efficient thermal mass that resides in the circulating blood during energy delivery. In an alternative embodiment, thermal portion 139 further includes a projecting fin to increase the transfer of heat from electrode 130d into the blood stream as has been described in reference to

Fig. 2b hereabove. In an alternative embodiment, not shown, electrode 130d is fixedly attached to distal arm segment 127 in the opposite (mirrored) orientation such that base 136 is in contact with tissue 30 during ablation, similar to the attachment configuration of electrode 130b of Fig. 5a. In this particular preferred embodiment, electrical portion 132 makes up the majority of base 136, and thermal portion 139 makes up both sides 137 and 138 as well as two small end portions of base 136, such that all of the energy delivered from base 136 is transferred to tissue 30, and a greatly increased surface area comprising sides 137 and 138 is in contact with circulating blood to cool electrode 130d.

[0088] Referring specifically to Fig. 5d, electrode 130e is displayed including a similar construction to electrode 130d of Fig. 5c with a semi-circular cross section instead of a triangular cross section and a portion which does not deliver energy but acts as a heat sink. The crescent shaped cross section of electrode 130e causes less tissue deflection per unit force than the triangular cross section of electrode 130d of Fig. 5c, and may be preferable for ablating a wider lesion, ablating in areas of thin or weakened tissue, or for other operator preferences or patient requirements. Electrode 130e is configured to be placed by an operator with a central portion of rounded side 137 in contact with tissue 30. Electrode 130e is configured to both improve cooling, and maximize energy delivered to tissue versus blood. Base 136 is positioned in circulating blood when ablation energy, such as RF energy, is being delivered via wires 134 and 135. Electrode 130e is fixedly mounted to distal arm segment 127, as has been described in detail in reference to previous figures. Distal arm segment 127 is sufficiently rigid to allow the operator to apply a force to electrode 130e such that electrode 130e can be pressed, as shown, into tissue 30. Electrode 130e has a laminate construction that includes a first portion that

receives and delivers energy to tissue, electrical portion 132, a segment preferably constructed of standard RF electrode materials described hereabove. Electrical portion 132 is sized such that all or nearly all of its surface area is in contact with tissue 30 during delivery of energy. Electrode 130e has a second portion that is thermally conductive, thermal portion 139. Thermal portion 139 is either electrically non-conductive or electrically isolated from electrical portion 132 such that thermal portion 139 does not deliver energy when energy is applied to and delivered by electrical portion 132. Thermal portion 139 is a plastic with high thermal conductivity such as a Konduit™ thermally conductive thermoplastic compound manufactured by LNP Engineering Plastics of Exton, Pa and is attached to electrical portion 132 at joint 147. Alternatively, thermal portion 139 may be constructed of standard electrode materials and be electrically isolated from electrical portion 132 such as with insulating glue, not shown. Thermal portion 139 is appropriately sized such that when the operator positions electrode 130d into tissue, most of thermal portion 139 is in the circulating blood, efficiently dissipating heat from electrical portion 132 and the neighboring tissue. Thermal portion 139 is sized such that no significant energy is delivered to low flow area 31, greatly reducing any chance of clot formation. Electrode 130e is configured to apply the great majority of the energy it receives into tissue and not blood, as well as provide enhanced cooling by having a thermal portion with significant surface area and/or efficient thermal mass that resides in the circulating blood during energy delivery. In an alternative embodiment, thermal portion 139 further includes a fin to increase the transfer of heat from electrode 130e into the blood stream.

[0089] Referring specifically to Fig. 5e, electrode 130f is displayed including a

crescent shaped cross section and configured to be placed by an operator with side 137 in contact with tissue 30. The crescent shaped cross section of electrode 130f causes less tissue deflection per unit force than the triangular cross section of electrode 130d of Fig. 5c, and may be preferable for ablating a wider lesion, ablating in areas of thin or weakened tissue, or for other operator preferences or patient requirements. The surface area of base 136, positioned in circulating blood when ablation energy is being delivered via wires 134 and 135, is less that the surface area of side 137, which causes the majority of energy delivered to electrode 130f to be delivered to tissue versus blood. The crescent shape of electrode 130f is chosen to minimize trauma as electrode 130f is being pressed into the tissue. Electrode 130f is fixedly mounted to distal arm segment 127, as has been described in detail in reference to previous figures. Distal arm segment 127 is sufficiently rigid to allow the operator to apply a force to electrode 130f such that electrode 130f can be pressed, as shown, into tissue 30. The crescent shape greatly reduces the volume of low flow area 31, minimizing the chance of blood clotting.

[0090] Referring specifically to Fig. 5f, electrode 130g is displayed including a crescent shaped cross section and configured to be placed by an operator with side 137 in contact with tissue 30. The crescent shaped cross section of electrode 130g causes less tissue deflection per unit force than the triangular cross section of electrode 130d of Fig. 5c, and may be preferable for ablating a wider lesion, ablating in areas of thin or weakened tissue, or for other operator preferences or patient requirements. As compared to electrode 130f of Fig. 5e, side 137 has a serpentine segment that greatly increases the surface area of side 137. In should be appreciated that numerous other configurations can be used to increase the length of side 137 and the resultant surface area, such as zigzag

segments and combinations of straight and non-straight line segments. The surface area of base 136, positioned in circulating blood when ablation energy is being delivered via wires 134 and 135, is much less that the surface area of side 137, which causes a great majority of energy delivered to electrode 130g to be delivered to tissue versus blood. The crescent shape of electrode 130g is chosen to minimize trauma as electrode 130f is being pressed into the tissue. Electrode 130g is fixedly mounted to distal arm segment 127, as has been described in detail in reference to previous figures. Distal arm segment 127 is sufficiently rigid to allow the operator to apply a force to electrode 130g such that electrode 130g can be pressed, as shown, into tissue 30. The crescent shape greatly reduces the volume of low flow area 31, minimizing the chance of blood clotting. In an alternative embodiment, electrode 130g is fixedly mounted to distal arm segment 127 in the opposite (mirrored) orientation such that the large surface area serpentine side 137 is in the circulating blood during ablation, providing a highly efficient cooling electrode configuration.

[0091] Referring now to Figs. 6a through 6cf, multiple preferred embodiments of electrode-type ablation element of the present invention are illustrated. Each of the electrodes of Figs. 6a through 6c are intended to maximize cooling, minimize energy delivered to non-targeted tissue (e.g. blood), or both. Certain electrodes are configured to minimize "low flow" areas for blood, such blood more likely to absorb enough energy to clot during an energy delivery cycle. The electrodes cross sections assume various geometries and are all preferably relatively uniform along their length such as to simplify their manufacturing. Cross sectional geometries are configured to create lesions of specific widths and depths, and to otherwise minimize trauma to neighboring tissue such

as when force is applied to press the electrode "into" the tissue to be ablated. In a preferred embodiment, each of the electrodes of Figs 6a through 6c includes one or more temperature sensors, such as a thermocouple in a non-energy delivery portion.

[0092] Referring specifically to Fig. 6a, electrode 130h, displayed in a sectional view, has a triangular cross section and is configured to be placed by an operator with base 136 in contact with tissue to be ablated. Electrode 130h includes an isosceles triangle cross section, with two equal sides, sides 137 and 138, each positioned in circulating blood when ablation energy, such as RF energy, is being delivered via wires 134 and 135. Electrode 130h is fixedly mounted to distal arm segment 127, as has been described in detail in reference to previous figures. Distal arm segment 127 is sufficiently rigid to allow the operator to apply a force to electrode 130h such that electrode 130h can be pressed into the tissue to be ablated. The transition point from base 136 to side 137 and from base 136 to side 138 each are rounded to reduce tissue trauma and low blood flow areas during ablation. The thickness of sides 137 and 138 as well as base 136 are chosen to have sufficient mass to effectively deliver energy to tissue without overheating, while minimizing a large thermal mass that would be difficult to cool. In a preferred embodiment, sides 137 and 138 have a smaller wall thickness than base 136, differentiation in thickness not illustrated. Side 137 and side 138 are not connected, leaving opening 148 opposite side 136, to provide enhanced cooling such as by increasing the effective surface area (allowing circulating blood to pass by the interior surfaces of sides 137 and 138 and potentially base 136). The surface area of sides 137 and 138 are sufficiently large (i.e. the combined lengths of sides 137 and 138 is sufficiently long) such that their combined surface area is greater than 60% of the overall total surface area of

electrode 130h, preferably greater than 75% of the total. In alternative embodiments, side 137 and/or side 138 comprises a non-straight segment such as a curved segment, serpentine segment, zigzag segment, or combinations of straight and non-straight segments. The high percentage of surface area in the circulating blood, in addition to the advantages provided by opening 148, provide rapid and efficient cooling of electrode 130h.

[0093] Referring specifically to Fig. 6b, electrode 130i, displayed in a sectional view, has a triangular cross section and is configured to be placed by an operator with base 136 in contact with tissue to be ablated. Electrode 130i includes an isosceles triangle cross section, with two equal sides, sides 137 and 138, each positioned in circulating blood when ablation energy, such as RF energy, is being delivered via wires 134 and 135. Electrode 130i is fixedly mounted to distal arm segment 127, as has been described in detail in reference to previous figures. Distal arm segment 127 is sufficiently rigid to allow the operator to apply a force to electrode 130i such that electrode 130i can be pressed into the tissue to be ablated. The transition point from base 136 to side 137 and from base 136 to side 138 each are rounded to reduce tissue trauma and low blood flow areas during ablation. The thickness of sides 137 and 138 as well as base 136 are chosen to have sufficient mass to effectively deliver energy to tissue without overheating, while minimizing a large thermal mass that would be difficult to cool. In a preferred embodiment, sides 137 and 138 have a smaller wall thickness than base 136, differentiation in thickness not illustrated. Side 137 and side 138 are not connected, leaving opening 148 opposite side 136, to provide enhanced cooling such as by increasing the effective surface area (allowing circulating blood to pass by the interior surfaces of

sides 137 and 138 and potentially base 136). Included on each of side 137 and side 138 is a projecting fin, fin 133a and 133b respectively, which increase the surface areas of sides 137 and 138. The surface areas of sides 137 and 138 are sufficiently large (i.e. the combined lengths of sides 137 and 138 is sufficiently long) such that their combined surface area is greater than 60% of the overall total surface area of electrode 130i, preferably greater than 75% of the total. The high percentage of surface area in the circulating blood provides rapid and efficient cooling of electrode 130i.

[0094] Referring specifically to Fig. 6c, electrode 130j, displayed in a side view, is configured to be placed by an operator with base 136 in contact with tissue to be ablated. Electrode 130j includes a rectangular cross-section, not illustrated, with four projecting fins 133a, 133b, 133c and 133d extending from a top surface 149. Top surface 149 and each projecting fin are each positioned in circulating blood when ablation energy, such as RF energy, is being delivered via wires 134 and 135. Electrode 130j is fixedly mounted to distal arm segment 127, as has been described in detail in reference to previous figures. Distal arm segment 127 is sufficiently rigid to allow the operator to apply a force to electrode 130j such that electrode 130j can be pressed into the tissue to be ablated. The thickness of base 136, top surface 149 and projections 133a, 133b, 133c and 133d are chosen to have sufficient mass to effectively deliver energy to tissue without overheating, while minimizing a large thermal mass that would be difficult to cool. In a preferred embodiment, top surface 149 and fins 133a, 133b, 133c, and 133d have a smaller wall thickness than base 136, differentiation in thickness not illustrated. The surface areas of top surface 149 and fins 133a, 133b, 133c and 133d are sufficiently large such that their combined surface area is typically greater than 60% of the overall total surface area of

electrode 130i, preferably greater than 85% of the total. The high percentage of surface area in the circulating blood provides rapid and efficient cooling of electrode 130j.

[0095] It should be understood that numerous other configurations of the systems, devices and methods described herein may be employed without departing from the spirit or scope of this application. The ablation catheter includes one or more ablation elements such as the electrodes described in reference to Figs. 5a through 5f and Figs. 6a through 6c. These electrodes include various cross-sectional geometries, projecting fins, energy delivering portions and non-energy delivering portions, and other features described in reference to these drawings. It should be appreciated that one or more features described in reference to one specific electrode can be combined with one or more features described in reference to a different electrode, in whole or in part, in any combination, without departing from the spirit and scope of this application. The electrodes can be configured to maximize tissue contact of the energy delivering portion(s), maximize cooling, or both. Clinician preferences, broad patient population requirements, and other treatment goals are likely to require catheters with different performance parameters, as are described in detail throughout this application, to both safely and effectively block an aberrant conductive pathway. The systems, catheters and ablation elements of the present invention are designed to achieve specific depths and widths of lesions, while preventing overheating that may damage more tissue than necessary and/or create dangerous embolus such as blood clots or fragmented tissue. The systems of the present invention are configured to automatically, semi-automatically or manually adjust the energy applied to the ablation elements such as by adjusting one or more of the following: the level or amount of energy delivered; type of energy delivered; drive signal supplied such as

monopolar and bipolar; phasing, timing or other time derived parameter of the applied energy; and combinations thereof.

[0096] The ablation elements of the present invention are attached to energy delivery conduits that carry the energy to the electrode that is supplied by the interface unit. RF electrodes are connected to wires, preferably in a configuration with individual wires to at least two electrodes to allow independent drive of the electrodes including sequential and simultaneous delivery of energy from multiple electrodes. Alternative or additional energy delivery conduits may be employed, such as fiber optic cables for carrying light energy such as laser energy; tubes that carry cryogenic fluid for cryogenic ablation or saline for saline mediated electrical energy ablation; conduits for carrying sound energy; other energy delivery conduits; and combinations thereof.

[0097] The system includes multiple functional components, such as the ablation catheter, and the interface unit. The interface unit preferably energy supply means and a user interface, as well as calculating means for interpreting data such as mapping data and data received from one or more sensors, as well as means of comparing measured, calculated or otherwise determined values to one or more thresholds. In a preferred embodiment, a low level energy delivery is performed prior to a higher level energy delivery. During or after the low energy delivery, one or more parameters are measured, calculated or otherwise determined that are used to determine a threshold for the second energy delivery, such as a second delivery of energy to the same relative tissue location.

[0098] The interface unit further includes means of adjusting one or more system parameters, such as the amount type, or configuration of energy being delivered, when a particular threshold is met. The ablation catheter includes at least one ablation element

for delivering energy to tissue such as cardiac tissue. Cardiac tissue applicable for ablation includes left and right atrial walls, as well as other tissues including the septum and ventricular tissue. The ablation catheter of the present invention includes a flexible shaft with a proximal end, a distal end, and a deployable carrier assembly with at least one, and preferably multiple ablation elements. The flexible shafts may include one or more lumens, such as thru lumens or blind lumens. A thru lumen may be configured to allow over-the-wire delivery of the catheter or probe. Alternatively the catheter may include a rapid exchange sidecar at or near its distal end, consisting of a small projection with a guidewire lumen therethrough. A lumen may be used to slidingly receive a control shaft with a carrier assembly on its distal end, the carrier assembly deployable to exit either the distal end or a side hole of the flexible shaft. The advancement of the carrier assembly, such as through a side hole, via controls on the proximal end of the device, allows specific displacement of any functional elements, such as electrodes, mounted on the carrier assembly. Other shafts may be incorporated which act as a rotational linkage as well as shafts that retract, advance or rotate one or more components. A lumen may be used as an inflation lumen, which permits a balloon mounted on a portion of the exterior wall of the flexible shaft to be controllably inflated and deflated. The balloon may be concentric or eccentric with the central axis of the shaft, it may be a perfusion balloon, and may include an in-line pressure sensor to avoid over-pressurizing. A lumen may be used to receive a rotating linkage, such as a linkage used to provide high-speed rotation of an array of ultrasound transducers mounted near the distal end of the linkage. Each device included in a lumen of the flexible shafts may be removable or configured to prevent removal.

[0099] The ablation catheter of the present invention may include one or more functional elements, such as one or more location elements, sensors, transducers, antennas, or other functional components. Functional elements can be used to deliver energy such as electrodes delivering energy for tissue ablation, cardiac pacing or cardiac defibrillation. Functional elements can be used to sense a parameter such as tissue temperature; cardiac signals or other physiologic parameters; contact with a surface such as the esophageal or atrial walls of a patient; an energy parameter transmitted from another functional element such as amplitude, frequency; phase; direction; or wavelength parameters; and other parameters. In a preferred embodiment of the present invention, the ablation catheter includes multiple functional elements. In another preferred embodiment, the ablation catheter includes a deflectable distal end; such as a deflected end that causes one or more functional elements to make contact with tissue. Deflection means may include one or more of: a pull wire; an expandable cage such as an eccentric cage; an expandable balloon such as an eccentric balloon; an expandable cuff; a deflecting arm such as an arm which exits the flexible catheter shaft in a lateral direction; and a suction port.

[00100] The ablation catheter of the present invention preferably includes a handle on their proximal end. The handle may be attached to an outer sheath, allowing one or more inner shafts or tubes to be controlled with controls integral to the handle such as sliding and rotating knobs that are operable attached to those shafts or tubes. Alternatively, the handle may be attached to a shaft that is slidingly received by an outer sheath, such that an operator can advance and retract the shaft by advancing and retracting the handle and

holding the sheath in a relatively fixed position. The handle may include one or more attachment ports, such as attachment ports which electrically connect to one or more wires; ports which provide connection to optical fibers providing laser or other light energies; ports which fluidly connect to one or more conduits such as an endoflator for expanding a balloon with saline or a source of cooling fluids; and combinations thereof. Other controls may be integrated into the handle such as deflecting tip controls, buttons that complete a circuit or otherwise initiate an event such as the start of energy delivery to an ablation element. In addition, the handle may include other functional components including but not limited to: transducers such as a sound transducer which is activated to alert an operator of a change is status; a visual alert component such as an LED, a power supply such as a battery; a lock which prevents inadvertent activation of an event such as energy delivery; input and output devices that send and receive signals from the interface unit of the present invention; and combinations thereof.

[0100] The interface unit of the present invention provides energy to the ablation elements of the ablation catheter. In preferred embodiments, one or more ablation elements are electrodes configured to deliver RF energy. Other forms of energy, alternative or in addition to RF, may be delivered, including but not limited to: acoustic energy and ultrasound energy; electromagnetic energy such as electrical, magnetic, microwave and radiofrequency energies; thermal energy such as heat and cryogenic energies; chemical energy; light energy such as infrared and visible light energies; mechanical energy; radiation; and combinations thereof. The ablation elements can deliver energy individually, in combination with or in serial fashion with other ablation elements. The ablation elements can be electrically connected in parallel, in series,

individually, or combinations thereof. The ablation catheter may include cooling means to prevent undesired tissue damage and/or blood clotting. The ablation elements may be constructed of various materials, such as plates of metal and coils of wire for RF or other electromagnetic energy delivery. The electrodes can take on various shapes including shapes used to focus energy such as a horn shape to focus sound energy, and shapes to assist in cooling such as a geometry providing large surface area. Electrodes can vary within a single carrier assembly, such as a spiral array of electrodes or an umbrella tip configuration wherein electrodes farthest from the central axis of the catheter have the largest major axis. Wires and other flexible energy delivery conduits are attached to the ablation elements, such as electrical energy carrying wires for RF electrodes or ultrasound crystals, fiber optic cables for transmission of light energy, and tubes for cryogenic fluid delivery.

[0101] The ablation elements requiring electrical energy to ablate require wired connections to an electrical energy power source such as an RF power source. In configurations with large numbers of electrodes, individual pairs of wires for each electrode may be bulky and compromise the cross-sectional profile of the ablation catheter. In an alternative embodiment, one or more electrodes are connected in serial fashion such that a reduced number of wires, such as two wires, can be attached to two or more electrodes and switching or multiplexing circuitry are included to individually connect one or more electrodes to the ablative energy source. Switching means may be a thermal switch, such that as a first electrodes heats up, a single pole double throw switch change state disconnecting power from that electrode and attaching power to the next electrode in the serial connection. This integral temperature switch may have a first

temperature to disconnect the electrode, and a second temperature to reconnect the electrode wherein the second temperature is lower than the first temperature, such as a second temperature below body temperature. In an alternative embodiment, each electrode is constructed of materials in their conductive path such that as when the temperature increased and reached a predetermined threshold, the resistance abruptly decreased to near zero, such that power dissipation, or heat, generated by the electrode was also near zero, and more power could be delivered to the next electrode incorporating the above switching means

[0102] The interface unit of the present invention includes a user interface including components including but not limited to: an ultrasound monitor such as an ultrasound monitor in communication with one or more ultrasound crystals near a temperature sensor of an esophageal probe or ultrasound crystals within an electrode carrier assembly of the ablation catheter; an x-ray monitor such as a fluoroscope monitor used to measure the distance between two or more location elements; other user output components such as lights and audio transducers; input components such as touch screens, buttons and knobs; and combinations thereof. In a preferred embodiment, the interface unit provides functions in addition to providing the energy to the ablation catheter including but not limited to: providing a cardiac mapping function; providing cardiac defibrillation energy and control; providing cardiac pacing energy and control; providing a system diagnostic such as a diagnostic confirming proper device connection; providing the calculating function of the present invention; providing a signal processing function such as interpreting signals received from one or more sensors of a probe, such as an esophageal probe, and/or the ablation catheter; providing drive signals and/or energy to one or more

functional elements of the ablation catheter; providing a second energy type to the ablation elements of the ablation catheter; and combinations thereof.

[0103] In a preferred embodiment, the interface unit provides an analysis function to determine one or more system parameters that correlate to ablation settings, the parameters including but not limited to: an energy delivery amount; an energy delivery frequency; an energy delivery voltage; an energy delivery current; an *energy delivery temperature; an energy delivery rate; an energy delivery duration; an energy delivery modulation parameter; an energy threshold; another energy delivery parameter; a temperature threshold; an alarm threshold; another alarm parameter; and combinations thereof. The analysis function compares a measured, calculated or otherwise determined function to a threshold value, such as a threshold value settable by an operator of the system. In a preferred embodiment, the interface unit receives temperature information from multiple sensors of the ablation catheter and/or other body inserted devices, and the highest reading received is compared to a temperature threshold such as a temperature threshold determined by the location of tissue being ablated. The analysis function includes one or more algorithms that mathematically process information such as signals received from sensors of the ablation catheter or other device; information entered into the user interface of the interface unit by the operator; embedded electronic information uploaded from the ablation catheter or other device such as information determined during the manufacture of the catheter or device; and combinations thereof. In a preferred embodiment, the ablation setting determined by the analysis function is provided to the operator via a display or other user interface output component.

[0104] The interface unit of the present invention performs one or more

mathematical functions, signal processing functions; signal transmission functions; and combinations thereof, to determine a system performance (e.g. during ablation) or other system parameter. A calculation may include a function performed by an operator of the system such as a distance value that is entered into the interface unit after a measurement is performed such as a measurement made from an IVUS monitor or a fluoroscopy screen. In a preferred embodiment, energy delivered , such as a maximum cumulative energy, maximum peak energy or maximum average energy is limited by a threshold. In a preferred embodiment, when a temperature reaches a threshold, one or more system parameters are modified. These modifications include but are not limited to: a threshold parameter such as an increased temperature threshold; an alarm or alert parameter such as an audible alarm "on" state; an energy parameter such as a parameter changing energy type or modifying energy delivery such as switching from RF energy to cryogenic energy or stopping energy delivery; a sensor parameter such as a parameter which activates one or more additional sensors; cooling apparatus parameter such as a parameter activating a cooling apparatus; a parameter that changes the polarity of energy delivery or the modulation of energy delivery such as a parameter that switches from monopolar to bipolar delivery or phased monopolar-bipolar to bipolar; and combinations thereof.

[0105] The system of the present invention preferably includes multiple functional elements integral to the ablation catheter and/or other system component. These functional elements may be mounted on the outer wall of the flexible shaft of the device. Alternatively or additionally, one or more functional elements may be mounted to a balloon, such as a perfusion balloon, eccentric balloon or concentric balloon and/or elements may be mounted to a carrier assembly such as a carrier assembly than exits the

distal end or a side hole of the flexible shaft. These functional elements may be covered with a membrane and multiple elements may be configured in an array such as an array that is rotated within a lumen of the flexible shaft. Functional elements may be placed on the patient's chest, such as EKG electrodes, pacing electrodes or defibrillation electrodes. Functional elements include but are not limited to: sensors such as temperature sensors; transmitters such as energy transmitting electrodes, antennas and electro-magnetic transmitters; imaging transducers; signal transmitters such as drive signal transmitters.

[0106] Functional elements may include sensing functions such a sensor to detect a physiologic parameter. In a preferred embodiment, one or more functional elements are configured as sensors to receive signals that are indicative of one or more cardiac functions of the patient. Sensors may include but are not limited to: an electrical signal sensor such as a cardiac electrode; a temperature sensor such as a thermocouple; an imaging transducer such as an array of ultrasound crystals; a pressure sensor; a pH sensor; a blood sensor, a respiratory sensor; an EEG sensor, a pulse oximetry sensor; a blood glucose sensor; an impedance sensor; a contact sensor; a strain gauge; an acoustic sensor such as a microphone; a photodetector such as an infrared photodetector; and combinations thereof. Functional elements alternatively or additionally include one or more transducers. The transducer may be a location element; a transmitter such as a transmitting antenna, an RF electrode, a sound transmitter; a photodiode, a pacing electrode, a defibrillation electrode, a visible or infrared light emitting diode and a laser diode; a visualization transducer such as an ultrasound crystal; and combinations thereof.

[0107] Numerous kit configurations are also to be considered within the scope of this

application. An ablation catheter is provided with multiple carrier assemblies. These carrier assemblies can be removed for the tubular body member of the catheter, or may include multiple tubular body members in the kit. The multiple carrier assemblies can have different patterns, different types or amounts of electrodes, and have numerous other configurations including compatibility with different forms of energy. Multiple sensors, such as EKG skin electrodes may be included, such as electrodes that attach to the interface unit of the present invention. A kit may include one or more catheters, such as an ultrasound catheter, which are configured to enter and extend distally in a lumen of the ablation catheter. One or more esophageal probes may be included such as probes with different tip or sensor configurations.

[0108] Though the ablation device has been described in terms of its preferred endocardial and percutaneous method of use, the array may be used on the heart during open-heart surgery, open-chest surgery, or minimally invasive thoracic surgery. Thus, during open-chest surgery, a short catheter or cannula carrying the carrier assembly and its electrodes may be inserted into the heart, such as through the left atrial appendage or an incision in the atrium wall, to apply the electrodes to the tissue to be ablated. Also, the carrier assembly and its electrodes may be applied to the epicardial surface of the atrium or other areas of the heart to detect and/or ablate arrhythmogenic foci from outside the heart.

[0109] Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims. In

addition, where this application has listed the steps of a method or procedure in a specific order, it may be possible, or even expedient in certain circumstances, to change the order in which some steps are performed, and it is intended that the particular steps of the method or procedure claim set forth herebelow not be construed as being order-specific unless such order specificity is expressly stated in the claim.

We Claim:

1. An ablation system for an operator to treat a patient, said system comprising:

an ablation catheter including at least one ablation element for delivering energy to tissue, said catheter comprising a flexible shaft with a proximal end and a distal end;

and

an interface unit for providing energy to the ablation catheter;

wherein the at least one ablation element is configured to rapidly transition from a first temperature to a second temperature wherein said first temp approaches a tissue ablation temperature and said second temp approaches body temperature.

2. The system of claim 1 wherein the at least one ablation element includes an outer surface and at least 60% of said surface is in contact with the patient's circulating blood when the energy is delivered.

3. The system of claim 1 wherein the at least one ablation element includes an outer surface and at least 75% of said surface is in contact with the patient's circulating blood when the energy is delivered.

4. The system of claim 1 wherein the at least one ablation element includes an outer surface and at least 85% of said surface is in contact with the patient's circulating blood when the energy is delivered.

5. The system of claim 1 wherein the ablation element includes a relatively uniform cross-section along its length.

6. The system of claim 5 wherein said cross-section has a first portion and a second portion, and wherein the first portion is relatively straight and the second portion is longer than said first portion.

7. The system of claim 6 wherein said cross-section has a triangular shape.

8. The system of claim 7 wherein the first portion comprises a base of the triangle and the second portion comprises the two opposing sides.

9. The system of claim 7 wherein the two opposing sides are not connected.

10. The system of claim 6 wherein said cross-section has a crescent shape.

11. The system of claim 6 wherein the second portion of the cross-section is semicircular.

12. The system of claim 6 wherein the second portion comprises a series of segments selected from the group consisting of: straight segments; curved segments; serpentine segments; zigzag segments; and combinations thereof.

13. The system of claim 6 wherein when the energy is being delivered to the tissue, the first portion of said cross-section is in contact with circulating blood and the second portion of said cross-section is in contact with the patient's tissue.

14. The system of claim 6 wherein the portion of said cross-section in contact with circulating blood when energy is being delivered to the tissue further comprises at least one projecting fin.

15. The system of claim 1 wherein the at least one ablation element causes the patient's blood flow to change from laminar flow to turbulent flow.

16. The system of claim 1 wherein the at least one ablation element has a mass of less than 0.05 grams.

17. The system of claim 16 wherein said ablation element includes an outer surface and at least 50% of said surface is in contact with the patient's blood when the energy is delivered.

18. The system of claim 1 wherein the first temperature approaches 60° C.

19. The system of claim 1 wherein the ablation element transitions from said first temperature to said second temperature in less than 20 seconds.

20. The system of claim 19 wherein the ablation element transitions from said first temperature to said second temperature in less than 10 seconds.

21. The system of claim 19 wherein the first temperature is approximately 60° C.

22. The system of claim 1 wherein the at least one ablation element subsequently transitions from said second temperature to a third temperature, wherein said third temperature approaches the tissue ablation temperature.

23. The system of claim 22 wherein the at least one ablation element transitions from said second temperature to said third temperature in less than 5 seconds.

24. The system of claim 1 wherein bipolar radiofrequency energy is delivered to the at least one ablation element when said ablation element transitions from the first temperature to the second temperature.

25. The system of claim 1 wherein at least a portion of tissue neighboring the at least one ablation element increases in temperature as said ablation element transitions from the first temperature to the second temperature.

26. The system of claim 1 wherein zero radiofrequency energy is delivered when the ablation element transitions from the first temperature to the second temperature.

27. The system of claim 26 wherein non-radiofrequency energy is delivered when the ablation element transitions from the first temperature to the second temperature.

28. The system of claim 27 wherein the non-radiofrequency energy delivered is selected from the group consisting of: ultrasound energy; cryogenic energy; and combinations thereof.

29. An ablation system for an operator to treat a patient, said system comprising:

an ablation catheter including at least one ablation element with an external surface area, said ablation element for delivering energy to tissue, and said catheter comprising a flexible shaft with a proximal end and a distal end;

and;

an interface unit for providing energy to the ablation catheter;

wherein a majority of the external surface area of said at least one ablation element is in contact with the tissue when energy is delivered to said tissue.

30. The system of claim 29 wherein the at least one ablation element includes an outer surface and at least 60% of said surface is in contact with the patient's tissue when the energy is delivered.

31. The system of claim 30 wherein at least 70% of said surface is in contact with

the patient's tissue when the energy is delivered.

32. The system of claim 29 wherein the ablation element includes a relatively uniform cross-section along its length.

33. The system of claim 32 wherein said cross-section has a first portion and a second portion, and wherein the first portion is relatively straight and the second portion is longer than said first portion.

34. The system of claim 33 wherein said cross-section has a triangular shape.

35. The system of claim 34 wherein the first portion comprises a base of the triangle and the second portion comprises the two opposing sides.

36. The system of claim 34 wherein the two opposing sides are not connected.

37. The system of claim 33 wherein said cross-section has a crescent shape.

38. The system of claim 37 wherein the second portion of the cross-section is semicircular.

39. The system of claim 33 wherein the second portion comprises a series of segments selected from the group consisting of: straight segments; curved segments; serpentine segments; zigzag segments; and combinations thereof.

40. The system of claim 33 wherein when the energy is being delivered to the tissue, the second portion of said cross-section is in contact with circulating blood and the first portion of said cross-section is in contact with the patient's tissue.

41. The system of claim 33 wherein the portion of said cross-section in contact

with circulating blood when energy is being delivered to the tissue further comprises at least one projecting fin.

42. The system of claim 29 wherein said majority of surface area is for minimizing amount of energy to ablate tissue.

43. The system of claim 29 wherein said majority of surface area is for minimizing the amount of energy delivered to the patient's blood.

44. The system of claim 29 further comprising a carrier assembly including the at least one electrode, said carrier assembly configured to maximize engagement with the tissue receiving the energy.

45. An ablation system for an operator to treat a patient with arrhythmia comprising:

a first ablation catheter including at least one ablation element for delivering energy to cardiac tissue, said catheter comprising a flexible shaft with a proximal end and a distal end;

a second ablation catheter including at least one ablation element for delivering energy to cardiac tissue, said catheter comprising a flexible shaft with a proximal end and a distal end;

and;

an interface unit for providing energy to the ablation catheter;

wherein the energy delivered does not exceed a threshold, said threshold set to a different value for said first ablation catheter and said second ablation catheter.

46. The system of claim 45 wherein the first ablation catheter has a different pattern of ablation elements than the second ablation catheter.

47. The system of claim 45 wherein the first ablation catheter delivers at least one form of energy not delivered by the second ablation catheter.

48. The system of claim 45 wherein the at least one ablation element of the first ablation catheter has a different surface area than the at least one ablation element of the second ablation catheter.

49. The system of claim 45 wherein the at least one ablation element of the first ablation catheter has a different cross-sectional geometry than the at least one ablation element of the second ablation catheter.

50. The system of claim 45 wherein the at least one ablation element of the first ablation catheter has different cooling properties than the at least one ablation element of the second ablation catheter.

51. The system of claim 45 wherein the at least one ablation element of the first ablation catheter has different heating properties than the at least one ablation element of the second ablation catheter.

52. An ablation system for an operator to treat a patient, said system comprising:

an ablation catheter including at least one ablation element for delivering energy to tissue, said catheter comprising a flexible shaft with a proximal end and a distal end;

and;

an interface unit for providing energy to the ablation catheter;

wherein the energy provided by the interface unit is configured to (1) achieve a target energy level at a target tissue depth; and (2) pulse energy such that the tissue surrounding the electrode does not exceed a threshold temperature.

53. The system of claim 52 wherein the energy delivered is radiofrequency energy.

54. The system of claim 53 wherein bipolar and monopolar energy are delivered.

55. The system of claim 53 wherein the interface unit automatically modifies the duration of one or more of: monopolar energy delivery time; bipolar energy delivery time; and time periods wherein zero energy is delivered.

56. The system of claim 52 wherein the interface unit adjusts an energy delivery parameter based on a value selected from the group consisting of: temperature of tissue; rate of change of temperature of tissue; temperature of the at least one ablation element; rate of change of temperature of the at least one ablation element; EKG; tissue thickness; tissue location; cardiac flow rate; and combinations thereof.

57. The system of claim 56 wherein the energy delivered is electrical energy.

58. The system of claim 57 wherein the energy delivery parameter adjusted is frequency.

59. The system of claim 57 wherein the energy delivery parameter adjusted is monopolar duty cycle.

60. The system of claim 57 wherein the energy delivery parameter adjusted is bipolar duty cycle.

61. The system of claim 57 wherein the energy delivery parameter adjusted is cumulative amount of energy delivered.

62. The system of claim 52 wherein the threshold is selected to minimize depth of the lesion created by delivering the energy to the tissue.

63. The system of claim 52 wherein the threshold is selected to minimize the width of the lesion created by delivering the energy to the tissue.

64. The system of claim 52 wherein the threshold is selected to minimize both the width and the depth of the lesion created by delivering energy to the tissue.

65. The system of claim 52 wherein the threshold is selected to achieve a desired depth of the lesion created by delivering energy to the tissue.

66. The system of claim 65 wherein said desired depth is dependent on the thickness of the tissue at the ablation location.

67. The system of claim 52 further comprising a temperature sensor configured to provide information regarding said tissue temperature.

68. The system of claim 67 wherein the temperature sensor is placed in a chamber of the heart.

69. The system of claim 67 wherein the temperature sensor is mounted on or near the at least one ablation element.

70. The system of claim 67 wherein the temperature sensor is placed in the esophagus of the patient.

71. The system of claim 67 further comprising a second temperature sensor configured to provide information regarding said tissue temperature.

72. An ablation system for an operator to treat a patient, said system comprising:

an ablation catheter including at least one ablation element for delivering energy to tissue, said catheter comprising a flexible shaft with a proximal end and a distal end;

and;

an interface unit for providing energy to the ablation catheter;

wherein the interface unit monitors at least one parameter of the system to prevent energy delivered from exceeding a threshold value, said threshold value determined by the at least one ablation element delivering energy.

73. The system of claim 72 wherein the ablation catheter further comprises a second ablation element for delivering energy to tissue.

74. The system of claim 73 wherein the ablation catheter is configured to monitor the temperature of the firs ablation element and the second ablation element.

75. The system of claim 74 wherein the higher of the first ablation element temperature and the second ablation element temperature is said at least one parameter monitored to prevent the energy delivered from exceeding said threshold value.

76. The system of claim 72 Wherein the monitored parameter is selected from the group consisting of: temperature such as temperature from a temperature sensor; a value of measured current; a value of measured voltage; a flow

measurement value; a force measurement value such as a measurement of strain; a pressure measurement value; and combinations thereof.

77. The system of claim 72 wherein the energy delivery threshold is a peak energy delivered threshold.

78. The system of claim 77 wherein the threshold is 10 Watts.

79. The system of claim 72 wherein the energy delivery threshold is an average energy delivered threshold.

80. The system of claim 79 wherein the threshold is 4 Watts.

81. The system of claim 72 wherein the energy delivery threshold is a cumulative energy delivered threshold.

82. The system of claim 81 wherein the threshold is 500 Watt-seconds.

83. The system of claim 81 wherein the threshold is 300 Watt-seconds.

84. The system of claim 72 further comprising a threshold comparator configured to compare a determined value to a threshold.

85. The system of claim 84 wherein said determined value represents an instantaneous amount of energy delivered to tissue.

86. The system of claim 84 wherein said determined value represents an integration of the amount of energy delivered to tissue.

87. The system of claim 86 wherein the determined value can be reset.

88. The system of claim 87 wherein the determined value is reset each time energy delivered to the at least one ablation element is switched from off to on states.

89. The system of claim 87 wherein the determined value is reset each time the at least one ablation element is repositioned by the operator.

90. The system of claim 84 wherein said determined value represents an average of the amount of energy delivered to tissue.

91. The system of claim 84 wherein the threshold comparator is further configured to compared a second determined value to a second threshold.

92. The system of claim 72 wherein said threshold value changes over time.

93. The system of claim 72 wherein said system is configured to deliver a first energy level followed by a second energy level, said first energy level of lesser magnitude than said second energy level.

94. The system of claim 94 wherein said threshold is modified after said first energy level is delivered.

95. The system of claim 1 or 29 or 45 or 52 or 72 wherein the patient is a human being.

96. The system of claim 1 or 29 or 45 or 52 or 72 wherein the ablation catheter further comprises a deployable carrier assembly fixedly attached to a control shaft, said carrier assembly including at least one ablation element.

97. The system of claim 96 wherein the carrier assembly is flexible.

98. The system of claim 97 wherein the carrier assembly is configured to conform with an endocardial surface of the heart.

99. The system of claim 96 wherein the ablation catheter further comprises a handle on its proximal end, said handle including means of deploying the catheter assembly.

100. The system of claim 96 wherein the carrier assembly is configured in an umbrella geometry.

101. The system of claim 96 wherein the carrier assembly is configured in a spiral geometry.

102. The system of claim 1 or 29 or 45 or 52 or 72 wherein the ablation catheter further comprises an integral functional element is selected from the group consisting of: a sensor; a transmitter; an imaging element; and combinations thereof.

103. The system of claim 102 wherein the functional element is a sensor selected from the group consisting of: an electrical signal sensor such as a cardiac electrode; a temperature sensor such as a thermocouple; an imaging transducer such as an array of ultrasound crystals; a pressure sensor; a pH sensor; a physiologic sensor such as a blood sensor; a respiratory sensor; an EEG sensor; a pulse oximetry sensor; a blood glucose sensor; an impedance sensor; a contact sensor; a strain gauge; an acoustic sensor; and combinations thereof.

104. The system of claim 1 or 29 or 45 or 52 or 72 wherein the at least one ablation element is an electrode.

105. The system of claim 104 wherein said electrode is constructed of materials

selected from the group consisting of: platinum; iridium; gold; and combinations thereof.

106. The system of claim 1 or 29 or 45 or 52 or 72 wherein the at least one ablation element comprises a thermally conductive energy delivery portion and a thermally conductive non-energy delivery portion.

107. The system of claim 106 wherein the energy deliver portion is electrically conductive and the non-energy delivery portion is not electrically conductive.

108. The system of claim 106 wherein energy delivery portion and the non-energy delivery portion are separated by an insulator.

109. The system of claim 106 wherein the energy delivery portion includes a temperature sensor.

110. The system of claim 106 wherein the non-energy delivery portion includes a temperature sensor.

111. The system of claim 1 or 29 or 45 or 52 or 72 wherein the at least one ablation element has a surface area less than 2.5 mm^2.

112. The system of claim 111 wherein the at least one ablation element is configured to ablate tissue when energized with less than 10 watts of energy.

113. The system of claim 111 wherein the at least one ablation element is configured to ablate tissue when energized with less than 5 watts of energy.

114. The system of claim 111 wherein the at least one ablation element has a surface area less than 0.75 mm^2.

115. The system of claim 114 wherein the at least one ablation element is configured to ablate tissue when energized with less than 10 watts of energy.

116. The system of claim 114 wherein the at least one ablation element is configured to ablate tissue when energized with less than 5 watts of energy.

117. The system of claim 1 or 29 or 45 or 52 or 72 wherein the at least one ablation element has a mass of less than 0.05 grams.

118. The system of claim 117 wherein the at least one ablation element is configured to ablate tissue when energized with less than 10 watts of energy.

119. The system of claim 117 wherein the at least one ablation element is configured to ablate tissue when energized with less than 5 watts of energy.

120. The system of claim 1 or 29 or 45 or 52 or 72 wherein the at least one ablation element has a volume of less than 3.0 mm^3.

121. The system of claim 120 wherein the at least one ablation element is configured to ablate tissue when energized with less than 10 watts of energy.

122. The system of claim 120 wherein the at least one ablation element is configured to ablate tissue when energized with less than 5 watts of energy.

123. The system of claim 1 or 29 or 45 or 52 or 72 wherein the at least one ablation element comprises a thermally conductive portion configured to reside in or near circulating blood during the delivering of energy to tissue.

124. The system of claim 123 wherein said at least one ablation element has a majority of its surface area in contact with circulating blood during the delivery of energy to tissue.

125. The system of claim 123 wherein said thermally conductive portion comprises a projecting fin.

126. The system of claim 125 wherein the projecting fin is electrically isolated from the remainder of the at least one ablation element.

127. The system of claim 123 wherein said thermally conductive portion comprises multiple projecting fins.

128. The system of claim 123 wherein said thermally conductive portion is configured to modify blood flow during the delivery of energy to tissue.

129. The system of claim 128 wherein said thermally conductive portion is configured to change non-turbulent blood flow to turbulent blood flow.

130. The system of claim 129 wherein a majority of said thermally conductive portion does not deliver energy.

131. The system of claim 1 or 29 or 45 or 52 or 72 wherein the ablation catheter further comprises two or more ablation elements.

132. The system of claim 131 wherein the ablation catheter includes a first energy delivery conduit and a second energy delivery conduit, each energy delivery conduit configured to independently deliver energy to a first ablation element and a second ablation element.

133. The system of claim 132 wherein the ablation catheter includes at least three ablation elements, and at least two ablation elements receive energy from the first energy delivery conduit.

134. The system of claim 131 wherein a first ablation element has a different

cross-sectional profile than a second ablation element.

135. The system of claim 131 wherein a first ablation element has a larger surface area contacting tissue during energy delivery than a second ablation element.

136. The system of claim 131 wherein a first ablation element has a larger percentage of its overall surface area in contact with tissue during energy delivery than a second ablation element.

137. The system of claim 1 or 29 or 45 or 52 or 72 wherein the at least one ablation element includes a temperature sensor.

138. The system of claim 137 wherein the temperature sensor is a thermocouple.

139. The system of claim 1 or 29 or 45 or 52 or 72 wherein the ablation catheter is configured to deliver multiple forms of energy.

140. The system of claim 139 wherein the at least one ablation element comprises an electrode and an ultrasound crystal.

141. The system of claim 139 wherein the catheter is configured to deliver a first energy that causes tissue to increase in temperature and a second energy that causes tissue to decrease in temperature.

142. The system of claim 1 or 29 or 45 or 52 or 72 wherein the ablation catheter includes an energy delivery conduit which transmits the energy to the at least one ablation element.

143. The system of claim 142 wherein the energy delivery conduit is a wire.

144. The system of claim 142 wherein the energy delivery conduit is a fiber optic

cable.

145. The system of claim 144 wherein the energy delivered is laser energy.

146. The system of claim 142 wherein the energy delivery conduit is a hollow tube.

147. The system of claim 145 wherein the hollow tube is configured to carry a flowing fluid during the delivery of energy to tissue.

148. The system of claim 147 wherein the fluid is nitrogen.

149. The system of claim 147 wherein the fluid is saline and the energy delivered is electrical energy.

150. The system of claim 142 wherein the ablation catheter further comprises a second energy delivery conduit, said second energy delivery conduit transmitting energy to said at least one ablation element.

151. The system of claim 150 wherein the second energy delivery conduit transmits a different form of energy than the first energy delivery conduit.

152. The system of claim 1 or 29 or 45 or 52 or 72 wherein the delivered energy is selected from the group consisting of: sound energy such as acoustic energy and ultrasound energy; electromagnetic energy such as electrical, magnetic, microwave and radiofrequency energies; thermal energy such as heat and cryogenic energies; chemical energy; light energy such as infrared and visible light energies; mechanical energy; radiation; and combinations thereof.

153. The system of claim 152 wherein multiple forms of energy are delivered.

154. The system of claim 152 wherein radiofrequency and ultrasound energy are delivered.

155. The system of claim 152 wherein radiofrequency energy is delivered.

156. The system of claim 155 wherein monopolar and bipolar radiofrequency energy are delivered.

157. The system of claim 156 wherein monopolar and bipolar energy are delivered sequentially.

158. The system of claim 156 wherein the power delivered to the at least one ablation element is less than ten watts.

159. The system of claim 1 or 29 or 45 or 52 or 72 wherein the tissue is cardiac tissue.

160. The system of claim 1 or 29 or 45 or 52 or 72 wherein the tissue is selected from the group consisting of: prostate; brain; gall bladder; uterus; tumor; and combinations thereof.

161. The system of claim 1 or 29 or 45 or 52 or 72 wherein the ablation catheter further comprises a second ablation element and the interface unit provides and directs energy to the first ablation element and the second ablation element independently.

162. The system of claim 161 wherein the interface unit provides energy to the first ablation element and the second ablation element simultaneously or sequentially.

163. The system of claim 1 or 29 or 45 or 52 or 72 wherein the interface unit is

configured to provide information relating to the temperature of the at least one ablation element.

164. The system of claim 163 wherein the information is rate of cooling information.

165. The system of claim 1 or 29 or 45 or 52 or 72 wherein the interface unit is configured to compare the temperature of the at least one ablation element to a threshold.

166. The system of claim 165 wherein the threshold is calculated by the system.

167. The system of claim 165 wherein the threshold is adjustable by the operator.

168. The system of claim 165 wherein an ablation parameter is modified when said threshold is reached.

169. The system of claim 168 wherein the ablation parameter results in a modification to the energy delivered to the at least one ablation element.

170. The system of claim 168 wherein the ablation parameter results in the activation of an alarm.

171. The system of claim 1 or 29 or 45 or 52 or 72 further comprising a thermal monitoring circuit.

172. The system of claim 171 wherein the thermal monitoring circuit includes a thermal sensor on or near the at least one ablation element.

173. The system of claim 171 wherein the thermal sensor is integral to the at least one ablation element.

174. The system of claim 171 wherein the thermal sensor is mounted to a distal portion of the ablation catheter at a location remote from the at least one ablation element.

175. The system of claim 174 wherein the ablation catheter further comprises a second ablation element and the thermal sensor is in between said first ablation element and said second ablation element.

176. The system of claim 171 wherein the thermal sensor provides a temperature information signal to the interface unit.

177. The system of claim 171 wherein the thermal monitoring circuit comprises multiple thermal sensors.

178. An ablation catheter device, comprising:

(a) an elongated, flexible, tubular body member having a proximal end, a distal end and a lumen extending therebetween;

(b) a control shaft coaxially disposed and slidingly received within the lumen of the tubular body member;

and;

(c) a flexible carrier assembly which includes at least two arms, each arm including at least one ablation element used to deliver energy to tissue;

wherein each ablation element includes a relatively uniform triangle shaped cross-section along its length.

179. The device of claim 178 wherein the triangular cross-section comprises a continuous path.

180. The device of claim 178 wherein the triangular cross-section comprises a discontinuous path.

181. The device of claim 180 wherein the discontinuity is at the junction of two sides of the triangular cross-section.

182. The device of claim 178 wherein retraction of the control shaft causes the carrier assembly to be constrained within the lumen of the tubular body member;

and;

wherein advancement of the control shaft causes the carrier assembly to extend beyond the distal end of the tubular body member.

183. The device of claim 178 wherein retraction of the control shaft causes the distal end of the carrier assembly to enter the lumen of the tubular body member prior to the mid-point of the carrier assembly to enter said lumen.

184. The device of claim 178 wherein retraction of the control shaft causes the mid-point of the carrier assembly to enter the lumen of the tubular body member prior to the distal end of the carrier assembly entering said lumen.

185. The device of claim 178 wherein the carrier assembly includes three arms, and each ablation element triangle shaped cross-section includes two sides defining an angle of approximately 120 degrees.

186. The device of claim 178 wherein the carrier assembly includes four arms, and each ablation element triangle shaped cross-section includes two sides defining an angle of approximately 90 degrees.

187. The device of claim 178 wherein the carrier assembly includes five arms, and each ablation element triangle shaped cross-section includes two sides defining an angle of approximately 75 degrees.

188. The device of claim 178 wherein the carrier assembly includes three or more arms, and each ablation element triangle shaped cross-section includes two sides defining an angle of x degrees, wherein x is approximately 360 divided by the number of arms.

189. A method of using any of the systems or devices of claims 1 through 188.

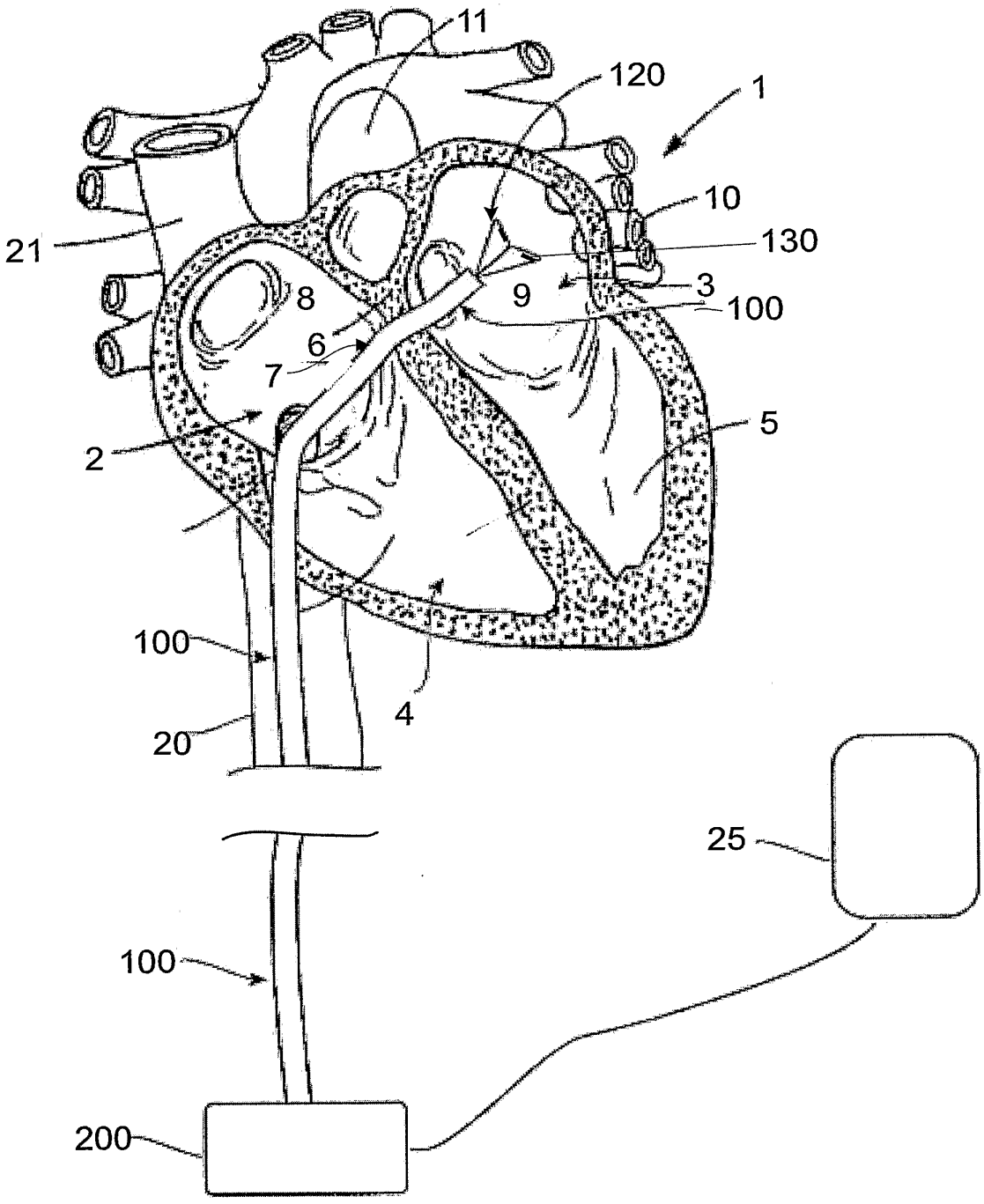


Figure 1

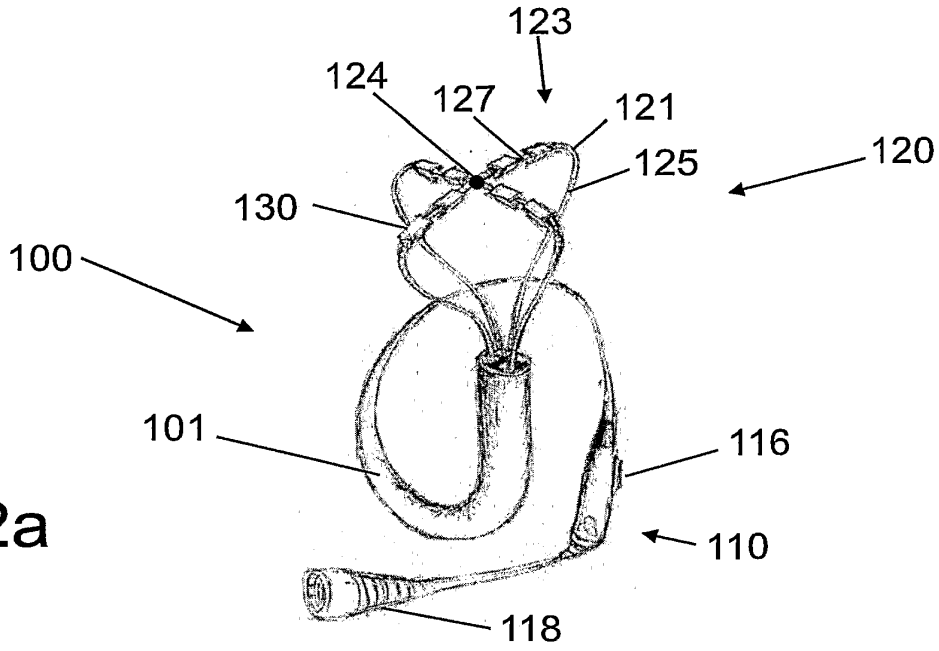


Figure 2a

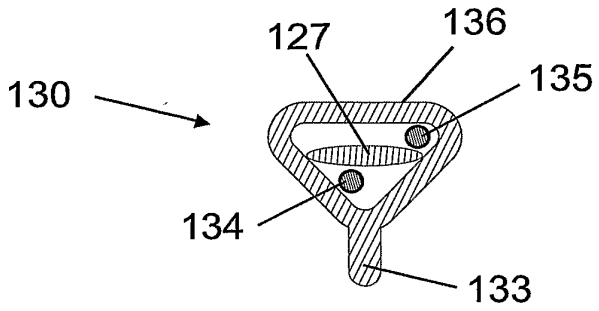


Figure 2b

Figure 3a

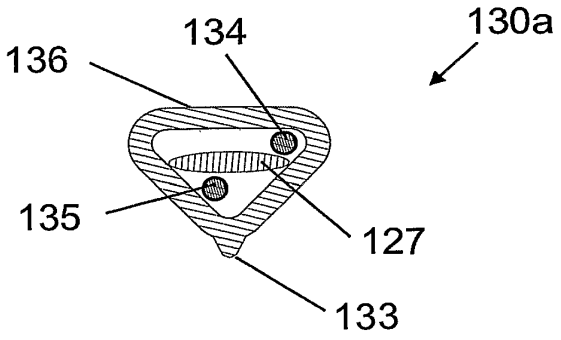


Figure 3b

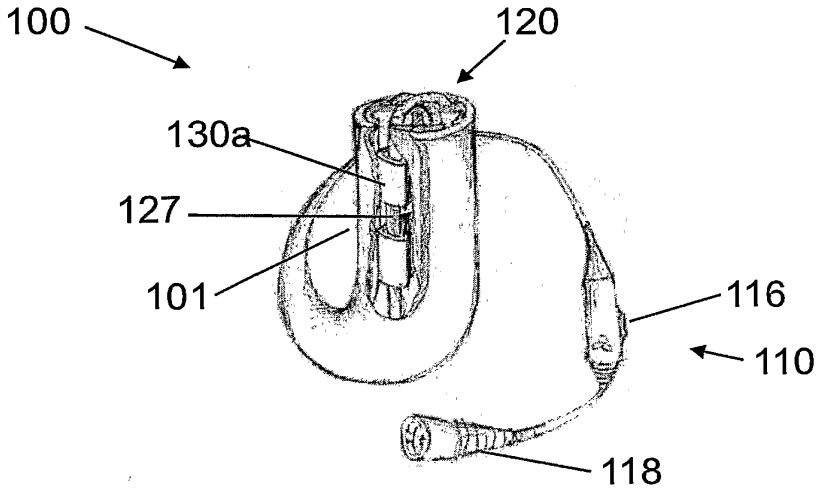
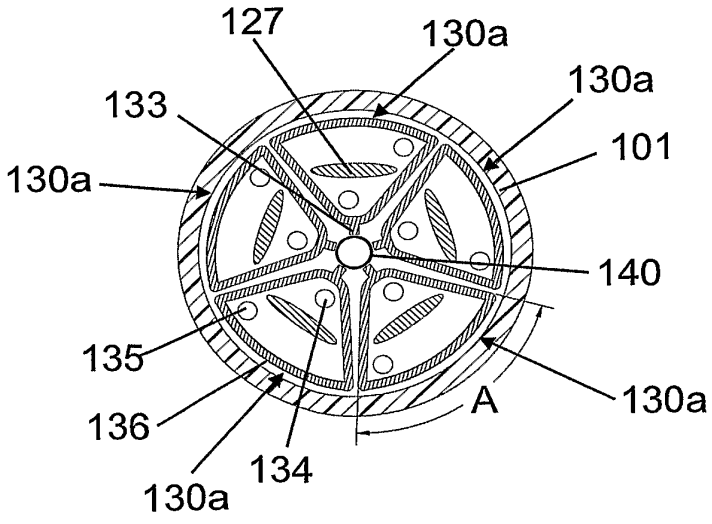


Figure 3c



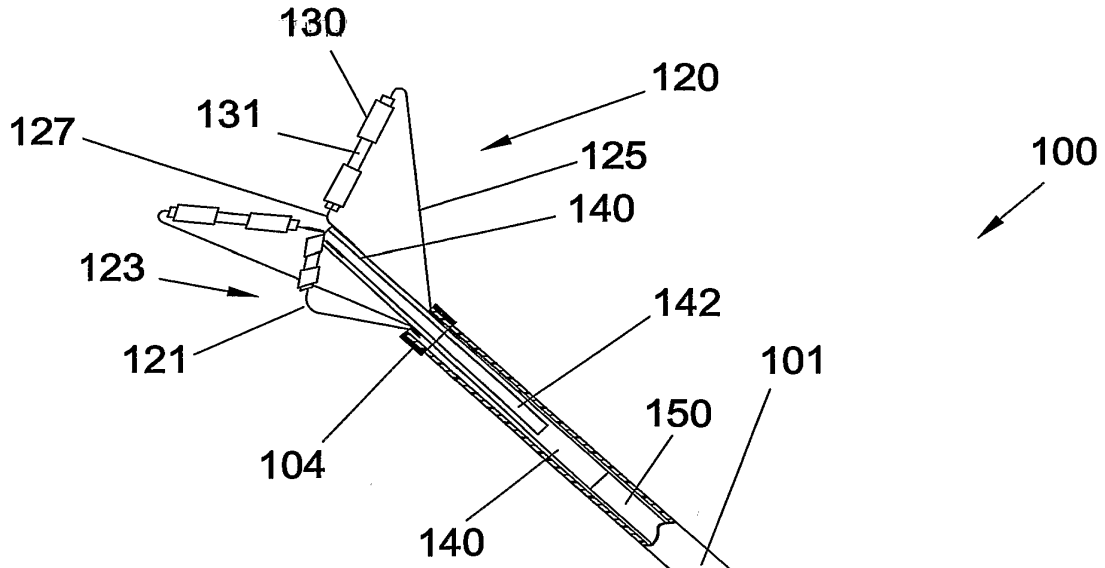

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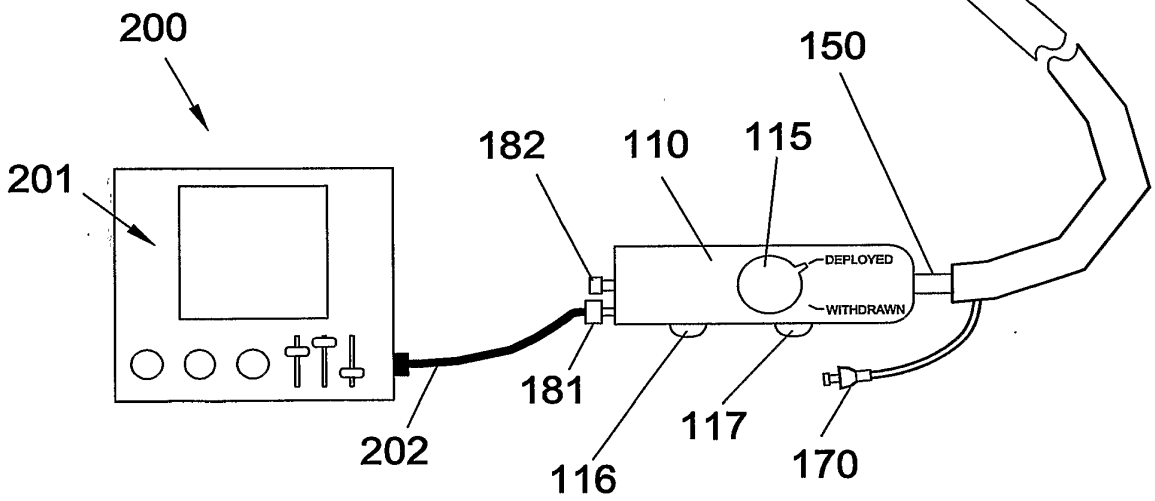
Fig. 4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WITHDRAWN
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Fig. 4a

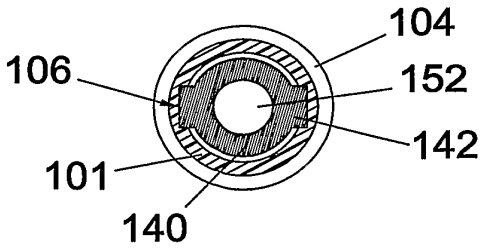
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Fig. 5a

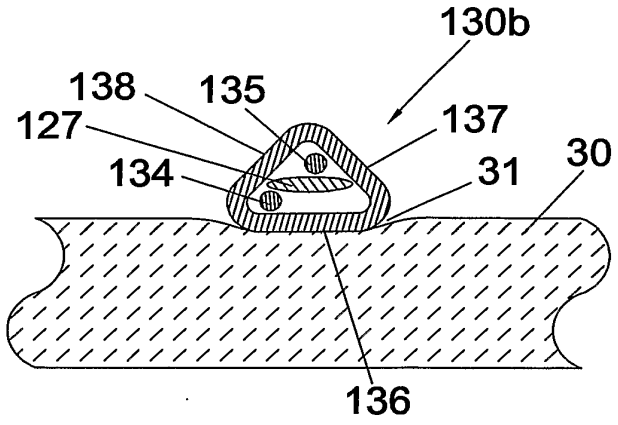


Fig. 5b

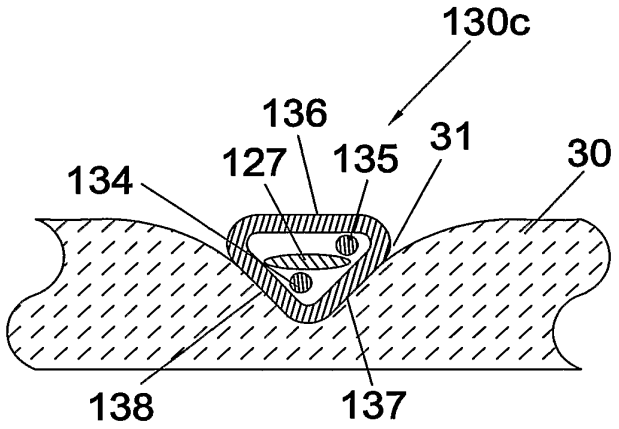


Fig. 5c

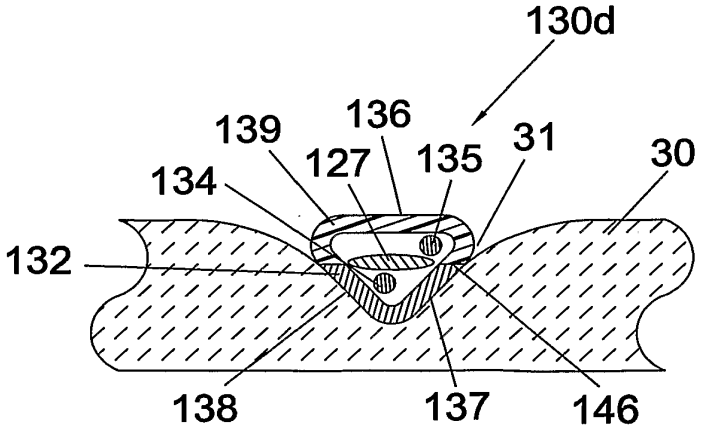


Fig. 5d

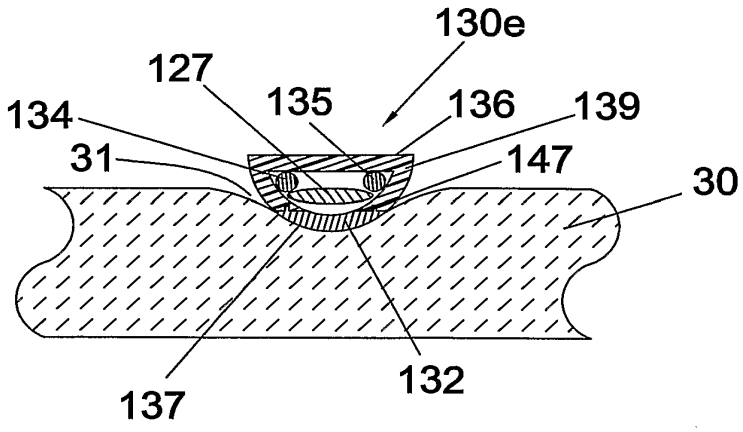


Fig. 5e

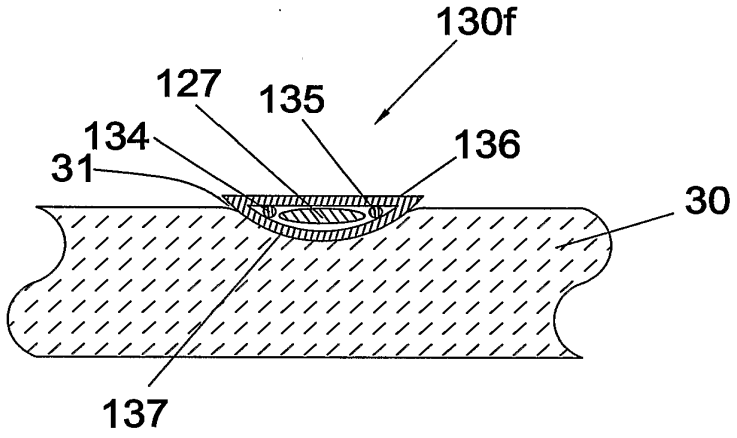


Fig. 5f

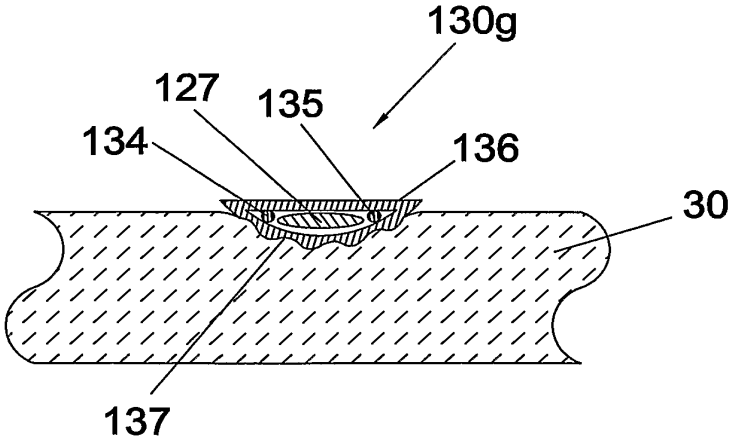


Fig. 6a

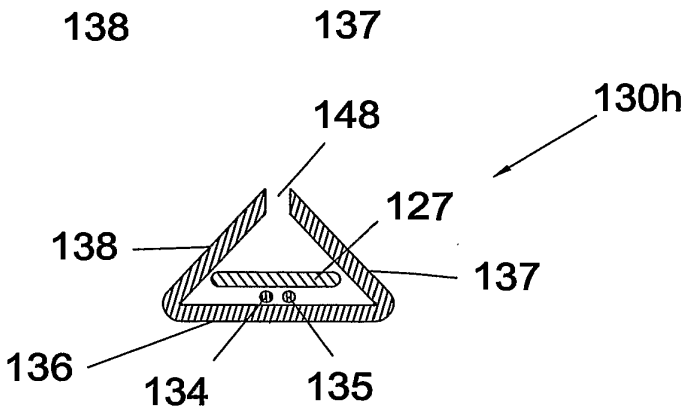


Fig. 6b

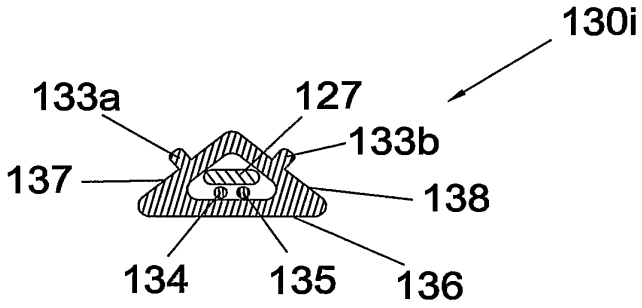
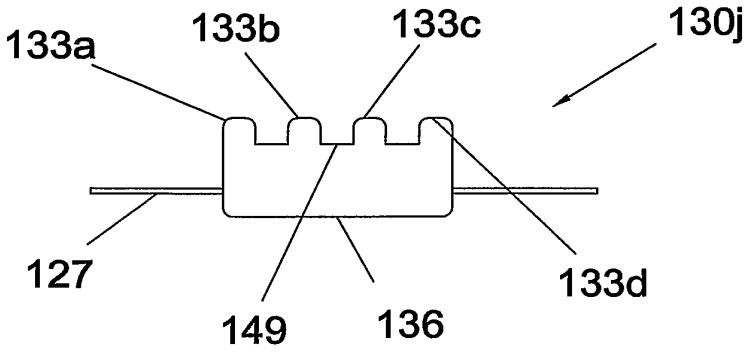


Fig. 6c



Espacenet

Bibliographic data: WO2015013252 (A1) — 2015-01-29

TREATMENT OF ALZHEIMER'S DISEASE

Inventor(s): SHANTHA TOTADA R [US] ± (SHANTHA, TOTADA R)

Applicant(s): WEDGE THERAPEUTICS LLC [US] ± (WEDGE THERAPEUTICS, LLC)

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Abstract of WO2015013252 (A1)

A safe and effective electrical impulses delivering device to stimulate the CNS by transmitting electrical impulses through olfactory nerves, sphenopalatine ganglion and its branches; cranial nerve III, IV, V, VI,; pituitary gland, hypothalamo hypophysial tract, thalamus, thalamic radiation, brain stem, and cerebellum for the treatment of Alzheimer's diseases is described.

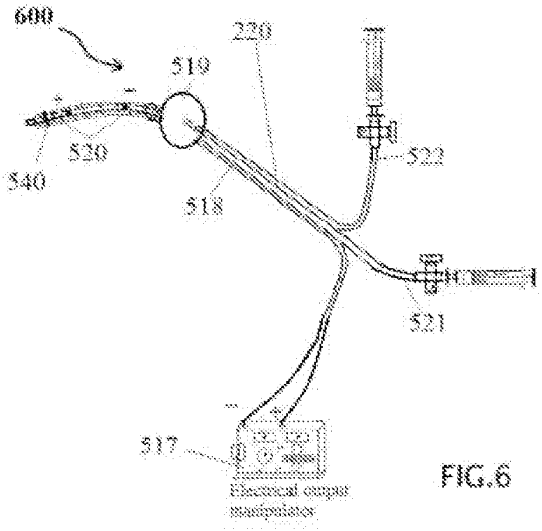

FIG.6

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(71) Applicant: **WEDGE THERAPEUTICS, LLC** [US/US]; 3218 Red Oak Drive, St. Paul, Minnesota 55121 (US).

(72) Inventor: **SHANTHA, Totada R.**; 1946 Carrington Court, Stone Mountain, Georgia 30087 (US).

(74) Agents: **SCHULTE, Daniel, C.** et al.; Kagan Binder, PLLC, Suite 200, Maple Island Building, 221 Main Street North, Stillwater, Minnesota 55082 (US).

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[Continued on next page]

(54) Title: TREATMENT OF ALZHEIMER'S DISEASE

(57) Abstract: A safe and effective electrical impulses delivering device to stimulate the CNS by transmitting electrical impulses through olfactory nerves, sphenopalatine ganglion and its branches; cranial nerve III, IV, V, VI,; pituitary gland, hypothalamo hypophysial tract, thalamus, thalamic radiation, brain stem, and cerebellum for the treatment of Alzheimer's diseases is described.

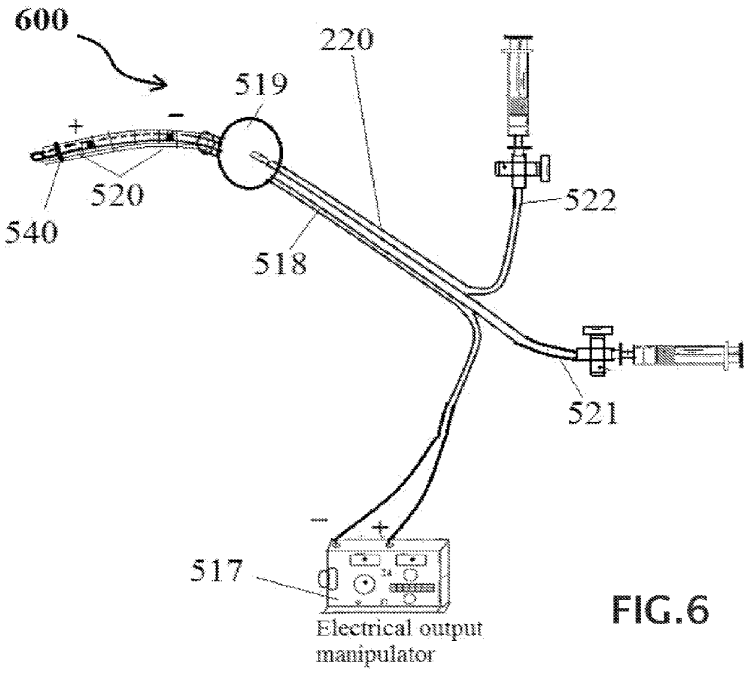

FIG.6

WO 2015/013252 A1

EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

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TREATMENT OF ALZHEIMER'S DISEASE

PRIORITY

This application claims the benefit of priority to U.S. Provisional Application No. 61/857,008 filed July 22, 2013 entitled "TREATMENT OF ALZHEIMER`S DISEASE" the entire disclosure of which is incorporated herein by reference for all purposes.

FIELD OF THE INVENTION

This invention disclosure relates to methods of treating Alzheimer's disease (AD) and other neurodegenerative diseases by electrical impulses delivered to the central nervous system (CNS) through one or more of the olfactory nerves (ORE), trigeminal nerve branches, sphenoid sinus with its 10 (five on each side) cranial nerves surrounding it, and pituitary-hypothalamic-hypophysis complex; and sphenopalatine ganglion, such as to be received at the central nervous system. The present disclosure involves a medical device and medical procedures that stimulate nerves by transmitting electrical energy to adjacent nerves From there the energy is transmitted to the central nervous system non-invasively to treat Alzheimer's and other neurodegenerative diseases. This medical procedure is defined as being non-invasive when no break in the skin (or other surface of the body, such as a wound bed) is created through use of the method, and when there is no contact with an internal body cavity beyond a body orifice (Examples: mouth, anus, external auditory meatus of the ear, nasal passages and its air sinuses). As compared to non-invasive methods described herein, invasive (including minimally invasive procedures) procedures do involve inserting a substance or device into, through the skin, or into an internal body cavity beyond a body orifice.

BACKGROUND OF THE INVENTION

Neural activity is controlled by electrical impulses or "action potentials" generated in and propagated by neurons. In an inactive dormant state, a neuron is negatively polarized, and exhibits a resting membrane potential that is typically between -70 and -60 mV. Through electrical or chemical connections known as synapses, any given neuron receives from other neurons excitatory and inhibitory input signals or stimuli. A neuron integrates the excitatory and inhibitory input signals it receives, and generates or fires a series of action potentials in the event that

the integration exceeds a threshold potential. A neural firing threshold may be, for example, approximately -55 mV Action potentials propagated to the neuron's synapses, then conveyed to other neurons to which the neuron is connected through the synapses connected by axons and dendrites.

Neural activity in the brain is influenced by electrical energy supplied from a waveform generator type of device as explained in this invention. Nerve stimulation is accomplished directly or indirectly by depolarizing a nerve membrane, causing the discharge of an action potential; or by hyperpolarization of a nerve membrane, preventing the discharge of an action potential. Such stimulation may occur after electrical energy, or also other forms of energy, transmitted to the vicinity of a nerve [Rattay, F. The basic mechanism for the electrical stimulation of the nervous system. Neuroscience Vol. 89, No.2, pp. 335-346,1999; Heimbur, T. G, Andrew D. Jackson. On soliton propagation in biomembranes and nerves. PNAS vol. 102 (no. 28, Jul. 12, 2005):9790-9795]. Nerve stimulation is measured directly as an increase, decrease, or modulation (inflection) of the activity of nerve fibers. It may be also secondary from the physiological effects that follow the transmission of electrical energy to the nerve fibers, its connected neurons, glia, and neuropil.

Electrical stimulation of the brain with implanted electrodes has been approved for the treatment of essential tremor and Parkinson's disease. The principle underlying these approaches involves disruption and modulation of hyperactive neuronal circuit transmission at specific sites in the brain by electrical stimulation by implanting electrodes at these sites. These electrical stimulation procedures are expensive, may not work as desired, and are invasive procedure conducted with the patient conscious and a participant in the surgery. Our method is used while the patient is awake and without invasive surgical procedure. The successful applications of modem electrophysiology are the cardiac pacemaker, electrical stimulation of nerves for the treatment of radiating pain in the lower extremities by stimulating the sacral nerve roots at the bottom of the spinal cord, and electrical stimulation of the vagus nerves for treatment of epilepsy and depression (U.S. Pat. No. 4, 702, 254).

Neural stimulation systems encompass a pulse generator and an electrode assembly as described here in this invention. The present disclosure involves such a

device and medical procedures that stimulate nerves (nerve fibers and neurons) by transmitting energy to nerves and tissue (neuropil) non-invasively with no break in the skin or mucus membrane. The neurons of the brain (central nervous system-CNS) communicate via a relay system (through synapses and nerve fibers) of electrical impulses and specialized molecules that play an important role in the generation and conduction of these conductive electrical pulses called neurotransmitters. A neuron generates an electrical impulse, causing the cell to release its neurotransmitters, which in turn, bind to adjacent neurons or synapses. Then the recipient neurons (through synapses) generate their own electrical impulses and release their neurotransmitters, triggering the process in more neurons and the processes continues until the impulse becomes to weak to be conducted, or no longer produced. This is how messages to and from the CNS to various structures are propagated with their effect felt all over the body. Researchers have found that the electrical stimulation causes the neurons to release adenosine triphosphate (ATP), a high-energy molecule essential to many biological processes including myelinization and nerve conduction. The invention described herein is intended to increase the ATP levels, which will in turn enhance all the activities of the neuron, its extensions, and synapses.

Insulin and other therapeutic agents are incorporated in the treatment of Alzheimer's disease, along with the inventive device described here as illustrated in U. S. Patent Application Publication Number US 2012/0323214 Al (Pub. Date: Dec. 20, 2012; Alzheimer's Disease Treatment With Multiple Therapeutic Agents Delivered To The Olfactory Region Through A Special Delivery Catheter And Iontophoresis by Totada R. Shantha). Other therapeutic agents to treat Alzheimer's disease along with electrical stimulation of the nerves (nerve fibers and neurons) by transmitting energy to nerve tissue non-invasively as described will augment and amplify each other's effect besides its own effects to increase the memory and cognition in AD. Both electrical energy and insulin have a trophic effect on the neurons, and the insulin is a mitogenic. They promote the glucose metabolism within the neuronal mitochondria, which increases the ATP production aerobically. The ATP enhances the protein, peptides, amino acid synthesis, and their output by the nucleus and endoplasmic reticulum by using the ATP energy provided by the

mitochondria. Thus, the combination enhances the protein-peptide-amino acid complex production of every kind, including tau proteins involved in the construction and maintenance of neurotubules, neurotrophic factors, neurotransmitters, enzymes, and hormones, that are also involved in memory and cognition. Electrical impulses and insulin augment the production of substrates needed to assemble neurotransmitters; and protein complexes to maintain the cell wall, the integrity of the neurons, and their extensions and synapses. Thus, electrical energy with insulin along with other therapeutic agents described in this invention prevents or delays further decay of the neurons afflicted by this disease, reduces the ROS damage to the remaining healthy nerve tissue, improves synaptogenesis, enhances the output of glutathione, and augments the production of acetylcholine and their functions as memory enhancer and neurotransmitter.

The cited patent publication, U. S. Patent Application Publication Number US 2012/0323214 Al (the '214 publication) contains information that overlaps with certain aspects of the present disclosure. But the present description includes certain additional features. The '214 publication involves stimulation to produce electroporation and inontphoresis, to cause membranes of nerve or other tissue more permeable to therapeutic agents, allowing improved delivery of therapeutic agents to the central nervous system by passing the blood-brain-barrier. Methods of and devices of the description may cause this same effect, but in a distinct manner transmit impulses to nerve fibers of up to fourteen nerve trunks, which cause or allow the impulse to spread to various centers of the brain and wake the brain to enhance memory, increase memory, and cure or curtail AD and other neurological diseases or one or more symptom thereof. The electrical activity generated may be similar to electrical activity associated with biological release of a neurotransmitter such acetyl choline, generating electrical activity that is translated into various neurological activities including memory and recall.

Electrical synapsis is the term used to describe the reaction in which the membranes of the two neurons or cells touch and share proteins. This allows the action potential to pass directly from one neuronal cell membrane to the next. Our invention will enhance the mechanism of electrical synapse.

Action potentials occur in several types of animal cells. Such cells are called excitable cells; for example neurons, muscle cells, and endocrine cells, and some plant cells. In neurons, action potential plays a fundamental role in cell-to-cell communication. In muscle cells, for instance, an action potential is the first step in the chain of events leading to contraction. Action potentials in the neurons are known as "nerve impulses" or "spikes", and the temporal sequence of action potentials generated by a neuron is called its "spike train". A neuron that emits an action potential is said to "fire".

Action potentials in neurons (other cells) are generated by special types of voltage-gated ion channels embedded in a cell's plasma membrane (Barnett MW, Larkman PM (June 2007). "The action potential". Pract Neurol 7 (3): 192–7). These channels shut when the membrane potential is near the resting potential of the cell, but they rapidly begin to open if the membrane potential increases to a precisely defined threshold value. When the channels open, they allow an inward flow of sodium ions, which changes the electrochemical gradient, which in turn produces a further rise in the membrane potential. This then causes more channels to open, producing a greater electric current, and so on. The process proceeds explosively until all of the available ion channels are open, resulting in a large upswing in the membrane potential. The rapid influx of sodium ions causes the polarity of the plasma membrane to reverse, and the ion channels then rapidly inactivate. As the sodium channels close, sodium ions can no longer enter the neuron, and they are actively transported out of the plasma membrane. Potassium channels are then activated, and there is an outward current of potassium ions, returning the electrochemical gradient to the resting state. After an action potential has occurred, there is a transient negative shift, called the after hyper-polarization or refractory period, due to additional potassium currents and this mechanism prevents an action potential traveling back the way it just came.

In animal cells including humans, there are two primary types of action potentials:

One type is generated by voltage-gated sodium channels; sodium-based action potentials usually last for less than one millisecond. The second type is generated by voltage-gated calcium channels; calcium-based action potentials may last for 100

milliseconds or longer. In some types of neurons, slow calcium spikes provide the driving force for a long burst of rapidly emitted sodium spikes. In cardiac muscle cells, on the other hand, an initial fast sodium spike provides a "primer" to provoke the rapid onset of a calcium spike, which then produces cardiac muscle contraction.

Almost all cells from animals, plants, and fungi function as batteries in the sense that they maintain a voltage difference between the interior and the exterior of the cell, with the interior being the negative pole of the battery. The voltage of a cell is measured in millivolts (mV), or thousandths of a volt. A typical voltage for an animal cell is –70 mV, approximately one-fifteenth of a volt. Because cells are so small, voltages of this magnitude give rise to very strong electric forces within the cell membrane.

A cell membrane consists of a layer of lipid molecules with larger protein molecules embedded in it. The lipid layer is highly resistant to movement of electrically charged ions, so it functions mainly as an insulator. The large membrane-embedded protein molecules, in contrast, provide channels through which ions can pass across the cell membrane, and some of the large molecules are capable of actively moving specific types of ions from one side of the membrane to the other. This is the basis of sodium and calcium pumps, which generate action potential to initiate cell activity and related function especially in the CNS neuronal complex as described in this invention.

As the membrane potential is increased, sodium ion channels on the cell membrane open, allowing the entry of sodium ions into the cell. This event is followed by the opening of potassium ion channels that permit the exit of potassium ions from the cell. The inward flow of sodium ions increases the concentration of positively charged cations in the cell and causes depolarization, where the potential of the cell is higher than the cell's resting potential. The sodium channels close at the peak of the action potential, while potassium continues to leave the cell. The efflux of potassium ions decreases the membrane potential or hyperpolarizes the cell. For small voltage increases from rest, the potassium current exceeds the sodium current and the voltage returns to its normal resting value, typically –70 mV. However, if the voltage increases past a critical threshold, typically 15 mV higher than the resting value, the sodium current dominates. This results in a runaway condition

whereby the positive feedback from the sodium current activates even more sodium channels. Consequently, the cell "fires," producing an action potential propagated along the nerve fibers to the next relay and so on. Currents produced by the opening of voltage-gated channels in the course of an action potential are typically significantly larger than the initial stimulating current. Thus, the amplitude, duration, and shape of the action potential are determined largely by the properties of the excitable membrane and not the amplitude or duration of the stimulus.

The all-or-none property of the action potential sets it apart from graded potentials such as receptor potentials, electrotonic potentials, and synaptic potentials, which scale with the magnitude of the stimulus. A variety of action potential types exist in many cell types and cell compartments as determined by the types of voltage-gated channels, leak channels, channel distributions, ionic concentrations, membrane capacitance, temperature, and other factors.

The principal ions involved in an action potential are sodium and potassium cations; sodium ions enter the cell, and potassium ions leave, restoring equilibrium. Relatively few ions need to cross the membrane for the membrane voltage to change drastically. The ions exchanged during an action potential, therefore, make a negligible change in the interior and exterior ionic concentrations. The few ions that do cross are pumped out again by the continuous action of the sodium–potassium pump, which, with other ion transporters, maintains the normal ratio of ion concentrations across the membrane. Calcium cations and chloride anions are involved in a few types of action potentials, such as the cardiac action potential and the action potential in the single-cell alga Acetabularia, respectively.

Although action potentials are generated locally on patches of excitable membrane, the resulting currents can trigger action potentials on neighboring stretches of membrane, precipitating a domino-like propagation. In contrast to the passive spread of electric potentials (electrotonic potential), action potentials are generated anew along excitable stretches of membrane and propagate without decay. Myelinated sections of axons are not excitable and do not produce action potentials and the signal is propagated passively as electrotonic potential. Regularly spaced unmyelinated axons, called the nodes of Ranvier, generate action potentials to boost the signal. Known as saltatory conduction, this type of signal propagation provides a

favorable exchange of a signal velocity and axon diameter. Depolarization of axon terminals, in general, triggers the release of neurotransmitters into the synaptic cleft. In addition, back propagating action potentials have been recorded in the dendrites of pyramidal neurons, which are ubiquitous - everywhere in the neocortex. These are thought to have a role in spike-timing-dependent plasticity.

Nevertheless, the main excitable cell is the neuron, which also has the simplest mechanism for the action potential. Neurons are electrically excitable cells composed, in general, of one or more dendrites, a single soma, a single axon and one or more axon terminals. The dendrite is one of the two types of synapses, the other being the axon terminal boutons. Dendrites form protrusions in response to the axon terminal boutons. These protrusions or spines are designed to capture the neurotransmitters released by the presynaptic neuron. They have a high concentration of ligand-activated channels. It is, therefore, here where synapses from two neurons communicate with one another. These spines have a thin neck connecting a bulbous protrusion to the main dendrite. This ensures that changes occurring inside the spine are less likely to affect the neighboring spines. The dendritic spine can, therefore, with rare exception, act as an independent unit. The dendrites then connect onto the body of the neurons. The neuron houses the nucleus, which acts as the regulator for the neuron. Unlike the spines, voltage activated ion channels populate the surface of the soma, these channels help transmit the signals generated by the dendrites. Emerging out from the soma is the axon hillock. This region is differentiated by having an incredibly high concentration of voltage-activated sodium channels. In general, it is considered a spike initiation zone for action potentials. Multiple signals generated at the spines and transmitted by the soma all converge here. The present inventive device will initiate and activate the electrical signal and conductivity in these neuronal components, which are silenced in the neurons of Alzheimer's.

An axon is a thin tubular protrusion traveling away from the soma of a neuron. The axons are insulated by a myelin sheath. Myelin is composed of Schwann cells that wrap themselves multiple times around the axonal segment in the peripheral nerves, and it is formed by the oligodendroglia in the CNS. This forms a thick fatty layer that prevents ions from entering or escaping the axoplasm and their

coming in contact with adjacent axons. This insulation also prevents significant signal decay as well as ensuring faster signal speed. This insulation, however, has the restriction that no channels can be present on the surface of the axon. There are, therefore, regularly spaced patches of membrane, (nodes of Ranvier) which have no insulation. These nodes of Ranvier are considered to be 'mini axon hillocks', as their purpose is to boost the signal in order to prevent significant signal decay. At the furthest end, the axon loses its insulation and begins to branch into several axon terminals. These axon terminals then end in the second class of synapses, axon terminal buttons. These buttons have voltage-activated calcium channels, which come into play when signaling other neurons. Our invention of delivering the electrical impulses helps in activation of voltage activated ion channels.

The action potential generated at the axon hillock propagates as a wave along the axon. The currents flowing inwards at a point on the axon during an action potential spread out along the axon, and depolarize the adjacent sections of its membrane. If sufficiently strong, this depolarization provokes a similar action potential at the neighboring membrane patches. This basic mechanism was demonstrated by Alan Lloyd Hodgkin in 1937. This mechanism discovered by Hodgkin is one of the basis and foundation of our invention to treat Alzheimer's and other neurological - neurodegenerative diseases.

The Na and K ions play a major role in the production of electrical impulses in the neurons and nerve fibers. The concentration of potassium ions inside a cell is ten times greater than the extracellular K+ concentration, and vice versa for sodium ions. A special protein in the cell and nerve fiber membrane (the Na-K pump) actively transports K+ into the cell and Na+ out of the cell, using ATP as the source of energy in the resting axon membrane. There is a selective permeability to K+ ions, allowing the net efflux of a small number of K+ ions and leaving the axoplasm electrically negative (polarized) while making the outside electrically positive. This accounts, for the most part, for the cell's "resting potential" which typically equals -70 millivolts.

Inward currents, carried by Na+ ions, depolarize the cell whereas outward currents, carried by K+ ions repolarize the cell. Repolarization of the membrane to the negative resting value occurs because of three factors: 1. The force moving Na+

into the cell diminishes as the axoplasmic potential becomes less negative; 2. the sodium channels ultimately close during a depolarization; 3. new potassium channels open and allow a large, outward K+ current that returns the axoplasmic potential toward its resting value. Sodium ions tend to flow in to the axon because it is now electrically negative inside and the Na+ ions are more concentrated outside. The selective permeability to Na^+ takes place when specific "sodium channels" in the axon membrane are opened. That means the impulses have a depolarization phase and a repolarization phase.

In order to initiate an impulse in the CNS, conditions must exist wherein a net inward current occurs. This requires that a sufficient number of sodium channels are opened in order to overcome the actions of the outward current pathways. A small depolarization of 15 to 20 mV is sufficient to initiate an impulse in a resting axon and neuron. However, a larger stimulating depolarization current is needed shortly after a preceding impulse. Our invention transmits both small and large depolarization electrical impulses without the use of ATP energy and the least or no active participation of sodium and potassium channels in the cell membrane for initiation of an electrical impulse, for example to bring back memory to silent Alzheimer's brain to resume activity.

Once an action potential has taken place at a patch of membrane, the membrane patch needs time to recover before it can fire again. At the molecular level, this absolute refractory period corresponds to the time required for the voltage-activated sodium channels to recover from inactivation, i.e., to return to their closed state. There are many types of voltage-activated potassium channels in neurons, some of them inactivate fast (A-type currents) and some of them inactivate slowly or do not inactivate at all; this variability guarantees that there will be always an available source of current for repolarization, even if some of the potassium channels are inactivated because of preceding depolarization. On the other hand, all neuronal voltage-activated sodium channels are inactivated within several milliseconds during strong depolarization, thus making following depolarization impossible until a substantial fraction of sodium channels have not returned to their closed state. Although it limits the frequency of firing, the absolute refractory period ensures that the action potential moves in only one direction along an axon. The

currents flowing in due to an action potential spread out in both directions along the axon. However, only the unfired part of the axon can respond with an action potential; the part that has just fired is unresponsive until the action potential is safely out of range and cannot restimulate that part.

In the usual orthodromic conduction, the action potential propagates from the axon hillock towards the synaptic knobs (the axonal termini); propagation in the opposite direction—known as antidromic conduction—is very rare. However, if a laboratory axon is stimulated in its middle, both halves of the axon are "fresh", i.e., unfired; then two action potentials will be generated, one traveling towards the axon hillock and the other traveling towards the synaptic knobs. This can happen with our device described here to activate the Alzheimer's disease affected neuronal complex.

Our invention activates the generation and propagation of action potential as described above and below without much participation of sodium, potassium, and calcium ion pumps, thus helping the neuronal action through axons and dendrites into the synapses and nerve cell itself, which translates into various functions of the brain including memory, recall, and cognition with augmentation effect on the neurotransmitters.

In the nervous system, the generation of electrical impulses and propagation of these impulses is due to neurotransmitters' mediated electrical activity which must be in place in order to activate the nerve conduction, which is important for proper functioning of CNS and all the functions including motor, sensory, memory, cognition, and related functions. The electrical generation takes place due to changes in the ionic concentration in the sodium and potassium at the cell membrane. If there is no generation of electrical impulses within the neurons and their processes, transmitted through the synapses, and conduction of these electrical impulses generated due to the activity of neurotransmitters such as acetylcholine which brings changes in the neuronal body, synapses, nerve fibers and terminals, the function of the CNS decreases is not carried out. The part of the brain that lacks such electrical activity becomes silent as seen in Alzheimer's. This is what also happens in patients with many other degenerative diseases of the CNS. Our inventive device and method of use enhance the electrical activity of the CNS,

augments the effect of remaining residual neurotransmitters, and thus restores function in Alzheimer's disease afflicted patients.

The life and functioning of the brain, whether a person is living, functioning normal or not functioning as expected (such as loss of memory seen in Alzheimer's) is evaluated based on the electrical activity of the brain. In modern medicine, the person is pronounced dead if there is no electrical activity of the brain-brain stem based on electroencephalogram (EEG). This tells us how important it is to maintain the electrical activity of the brain for proper functioning of all the neuron-related activities all the time including memory and cognition as well as various CNS initiated motor, sensory, and autonomic nerve functions. This electrical potential generation and its propagation is the lifeline of the brain functioning in totality. Because of low or no neurotransmitter acetylcholine in diseases such as Alzheimer's, the electrical activity is reduced, not generated, defective, or deficient. It is said to be both cause and effect due to synaptic and neuronal decline, associated with reduced acetylcholine neurotransmitter, which is needed to generate and transfer electrical activity of the CNS and make changes to store and retrieve the old and new memories. The present inventive method activates the electrical signals, augments and amplifies the effects without the help of the neurotransmitters, and/or helps it even when the neurotransmitters are very low in concentrations in the CNS, to restore the normal function to the neurons and their synapses. Thus, the invention elaborated in this application will curtail the diseases such as Alzheimer's, senile dementia and others neurodegenerative afflictions, thus restoring the memory and other functions of the CNS.

All cells in the body (tissues and organs) are electrically polarized; in other words, they maintain a voltage difference across the cell's plasma membrane, known as the membrane potential. This electrical polarization results from a complex interplay between protein structures embedded in the membrane, called ion pumps and ion channels. In neurons, the types of ion channels in the membrane usually vary across different parts of the cell, giving the dendrites, axon, and cell body different electrical properties. As a result, some parts of the membrane of a neuron may be excitable (capable of generating action potentials), whereas others are not. The most excitable part of a neuron is usually the axon hillock (the point where the

axon leaves the cell body), but the axon and the rest of neuronal cell body are also excitable.

Each excitable piece of neuronal membrane has two important levels of membrane potential: the resting potential, which is the value the membrane potential maintains as long as nothing perturbs the cell, and a higher value called the threshold potential. At the axon hillock of a typical neuron, the resting potential is around -70 mV and the threshold potential is around -55 mV. Synaptic inputs to a neuron cause the membrane to depolarize or hyperpolarize; that is, they cause the membrane potential to rise or fall. Action potential is triggered when enough depolarization accumulates to bring the membrane potential up to threshold. When an action potential is triggered, the membrane potential abruptly shoots upward; often reaching as high as +100 mV, then equally abruptly shoots back downward, often ending below the resting level, where it remains for some period. The shape of the action potential is stereotyped; that is, the rise and fall usually have approximately the same amplitude and time course for all action potentials in a given cell. In most neurons, the entire process takes place in less than a thousandth of a second. Many types of neurons emit action potentials constantly at rates of up to 10-100 per second; some types, however, are much quieter, and may go for minutes or longer without emitting any action potentials. Our invention helps the neurons to emit action potential to improve the sensory and motor function of the CNS especially related to memory, recall, and cognition.

THE BLOOD BRAIN BARRIER (BBB) AND ITS IMPLICATIONS IN THE TREATMENT OF CNS DISEASES SUCH AS ALZHEIMER'S

The problem in the treatment of CNS diseases including Alzheimer's is that 98% of therapeutic agents are not transported to, delivered to, or reach the site of pathology in the brain. The BBB is responsible for creating such a barrier to the delivery of therapeutic agents to the brain and spinal cord. This is how the brain is protected from the extraneous assault from various substances and cells that travel all over the body in the blood. The BBB is located in 400 miles of capillaries within the brain and has a unique histological make up compared to the other capillaries in other regions of the body. The endothelial cells of the blood vessels (BV) of the

CNS differ from the peripheral capillary endothelial cells due to many structural differences such as:

i. Lack of fenestration in the endothelial cells: The endothelial cells are joined by tight junctions, which block the protein molecule movement from within. In addition, they block the hydrophilic transfer of substances from the capillary to the CNS.

ii. These tight endothelium junctions in the BBB are 100 times tighter than similar junctions of other systematic capillary endothelium (Butte AM, Jones HC, Abbot NJ. Electrical resistance across the blood-brain barrier in anaesthetized rats; a development study. J Physiol 1990; 429:47-62.), thus creating a formidable barrier, which blocks almost 98% of the therapeutic agents delivered to the systemic circulation reaching the neuropile and neurons of the CNS. That is why the olfactory nerve mucosal delivery (ORE) of therapeutic agents is the most important method of bypassing these tight junctions of the BBB, delivering the therapeutic agents directly to the CNS for the treatment of Alzheimer's disease and other neurodegenerative diseases.

iii. The endothelial cells contain a specific receptor transport system for given molecules, such as insulin, glucose, glucagon etc. but not for most of the therapeutic agents used.

iv. They display a net negative charge inside the endothelial cell and basement membrane impeding anionic molecules to cross the membrane.

v. They show paucity of pericytes in the wall of these BV.

vi. There are hardly any pinocytotic vesicles in the cytoplasm of the endothelial cells compared to peripheral endothelial blood vessels cells that are involved in uptake and transport of various substances.

vii. Astrocytes foot process covers 95% of the endothelium outer surface.

viii. There is a thick basement membrane encasing these brain capillaries completely.

ix. The cerebral vascular endothelial cell possesses a transcellular lipophilic pathway, allowing diffusion of small lipophilic compounds such as insulin, transferrin, glucose, purines, and amino acids.

x. The BBB prevents passage of ionized water-soluble compounds with a molecular weight greater than 180 Daltons. Many new neuro therapeutic agents have been discovered, but because of a lack of suitable strategies for drug delivery across the

BBB, these agents are fruitless and only effective if methods to break the BBB are discovered.

xi. The concentration gradients also play a role in transport of therapeutic agents across the systemic BV, but make hardly any such effect across BBB blood vessels of the CNS.

Due to the above-described histological differences in the histological features, the brain blood vessels form a formidable 400 miles of BBB capillaries within the brain. The brain capillaries prevent transport of most of the therapeutic agents (98%) from inside the BV; they also prevent and / or inhibit clearance of neurotoxin compounds such as beta amyloid and their precursor in Alzheimer's; reactive oxygen species, toxic metabolites and their derivatives from the CNS entering the systemic circulation for clearance and to provide homeostatic neuropil milieu functional. Hence, the brain keeps on accumulating toxins with no path or passage to exit from the brain contributing to the CNS afflictions such as beta amyloid in Alzheimer's.

Attempts have been made to break the BBB by shrinking or expanding for disrupting adhesions (mannitol, bradykinin), or by local application of ultrasound. These methods are difficult to adopt by a patient without going to a clinic or hospital. This invention of transmitting the electrical impulses does not have any such barrier. It helps to overcome some of these obstacles posed by the CNS for the treatment of Alzheimer's by generating electrical impulses and breaking the BBB by vascular dilatation to allow therapeutic agents to reach the site of pathology to curtail the disease.

Even today, there is no cure for Alzheimer's disease; the cause and progression of Alzheimer's disease is not well understood and the disease progresses unabated. So is also the case with senile brain atrophy. Symptoms can include confusion, irritability, and aggression, mood swings, trouble with language, and long-term memory loss. As the sufferer declines, they often withdraw from family and society. Gradually, bodily functions are lost, ultimately leading to death in about 7 years (Average lifespan after diagnosis). The disease is associated with plaques and tangles in the brain (Tiraboschi P, Hansen LA, Thal LJ, Corey-Bloom J. The

importance of neuritic plaques and tangles to the development and evolution of AD. Neurology. 2004;62(11):1984.

Current treatments only help with the symptoms and there are no cures to stop or reverse the progression of the disease. As of 2008, more than 500 clinical trials have been conducted to find ways to treat the disease, but it is unknown if any of the tested treatments will work. At present, the treatment is to use Cholinesterase inhibitors to increase the level of acetylcholine in the CNS. The approved drugs for the management of Alzheimer's symptoms are donepezil (Aricept™), galantamine (Razadyne™), and rivastigmine (branded as Exelon and Exelon Patch™). Mental stimulation, exercise, statins to control cholesterol, and a balanced diet have been recommended as possible ways to delay symptoms in healthy older individuals, but they have not been proven as effective. It is one of the most costly diseases to society, becoming more burdensome with the increasing aged population.

The newest treatment for Alzheimer's is Bexarotene (Targretin®), a vitamin A derivative, used in skin for cutaneous T cell lymphomas, off label used for lung cancer, breast cancer, and Kaposi's sarcoma show promising results in mice studies. Bexarotene is a member of a subclass of compounds called retinoids. Certain retinoids are believed to selectively activate retinoid X receptors (RXRs). A chemical name for bexarotene is 4-[I-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl) ethenyl] benzoic acid. Mice studies showed that a single dose lowered the most toxic form of the amyloid beta peptide by 25 percent within six hours, an effect that lasted for up to three days in experimental mice according to Dr. Paige Cramer of Case Western Reserve University School of Medicine. Bexarotene quickly and dramatically improved brain function and social ability and restored the sense of smell in mice bred with a form of Alzheimer's disease. One example of the improved behaviors involved the typical nesting instinct of the mice. When Alzheimer's-diseased mice encountered tissue paper material suited for nesting, they did nothing to create a space to nest. This reaction demonstrated that they had lost the ability to associate the tissue paper with the opportunity to nest. Just 72 hours after the bexarotene treatment, however, the mice began to use the paper to make nests. Administration of the drug also improved the ability of the mice to sense and respond to odors.

The plaques in the CNS of Alzheimer's are compacted aggregates of amyloid that form in the brain and are the pathological hallmark of Alzheimer's disease. It appears that the bexarotene reprogrammed the brain's immune cells to phagocytose the amyloid deposits they encountered. This observation demonstrated that the drug addresses the amount of both soluble and deposited forms of amyloid beta within the brain and reverses the pathological features of the disease.

Bexarotene does not act directly on the β amyloid; instead, it activates retinoid receptors on brain cells that increase production of a fat-protein complex, apolipoprotein E, that helps to clear excess β amyloid in the fluid-filled space (neuropile, subarachnoid space, cerebrospinal fluid, Virchow-Robin space) between neurons. Dr. Landreth and his colleagues at Case Western Reserve University at Cleveland, Ohio; chose to explore the effectiveness of bexarotene for increasing ApoE expression. The elevation of brain ApoE levels, in turn, speeds the clearance of amyloid beta from the brain. Bexarotene acts by stimulating retinoid X receptors (RXR), which control how much ApoE is produced in the CNS. The invention described here can activate retinoid receptors on brain cells that increase production of a fat-protein complex, apolipoprotein E that helps to clear excess β amyloid to curtail Alzheimer's disease. Bexarotene also appears to enhance another cleanup process called phagocytosis, in which the brain immune cells engulf amyloid and move it away from the neuropile (Cramer P E, et al. (9 February 2012). "ApoE-Directed Therapeutics Rapidly Clear β-Amyloid and Reverse Deficits in AD Mouse Models". doi:10.1126/science.1217697: Science Express.). Human trials are underway to determine whether the drug crosses the blood-brain barrier and clears amyloid, as it does in mice. These researchers were struck by the speed with which bexarotene improved memory deficits and behavior even as it also acted to reverse the pathology of Alzheimer's disease. The present view of the scientific community is that small soluble forms of amyloid beta cause the memory impairments seen in animal models and humans with the disease. Within six hours of administering bexarotene, however, soluble amyloid levels fell by 25 percent; even more impressive, the effect lasted as long as three days. Finally, this shift was correlated with rapid improvement in a broad range of behaviors in three different mouse models of Alzheimer's.

It is important to note that insulin has been touted as a hormone in the treatment of Alzheimer's, because it is labeled as third diabetes of the brain (Steen E, Terry BM, Rivera EJ; et al. Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease—is this type 3 diabetes? J Alzheimers Dis. 2005;7(1):63-80). The latest study by Craft et al. whose findings are incorporated herein in its entirety; showed that Insulin has a number of important functions in the central nervous system and plays a major role in Alzheimer's (Craft S. et al. Intranasal Insulin Therapy for Alzheimer Disease and Amnestic Mild Cognitive Impairment. Arch Neurol. published online September 12, 2011, Pages 1-13). Brain insulin receptors are heavily and thickly localized in the hippocampus, the entorhinal cortex (olfactory bulb connected), and the frontal cortex. They are found primarily in synapses, where insulin signaling contributes to synaptogenesis and synaptic remodeling (Chiu SL, Chen CM, Cline HT. Insulin receptor signaling regulates synapse number, dendritic plasticity, and circuit function in vivo. Neuron. 2008;58 (5):708-719. Zhao WQ, Townsend M. Insulin resistance, and myloidogenesis as common molecular foundation for type 2 diabetes and Alzheimer's disease. Biochim Biophys Acta. 2009;1792(5):482-496.). Insulin also modulates glucose utilization in the hippocampus and other brain regions and facilitates memory at optimal levels in normal metabolism. The importance of insulin in normal brain function is underscored by evidence that insulin dysregulation contributes to the pathophysiology of Alzheimer's disease (AD), a disorder characterized in its earliest stages by synaptic loss and memory impairment. Our study on people with memory and cognition showed that olfactory nerve delivery through olfactory mucosa resulted in rapid recovery of cognition, and many of the depressed patients became normal. Studies show that Insulin levels and insulin activity in the central nervous system are reduced in AD. Insulin has a close relationship with the β-amyloid peptide, a toxic peptide produced by endoproteolytic cleavage of the amyloid precursor protein. Insoluble Aβ deposits in the brain's parenchyma and vasculature in Alzheimer's is an important pathology found in Alzheimer's disease. Soluble Aβ species, particularly oligomers of the 42 amino acid species (Aβ42), also have synaptotoxic effects (Selkoe DJ. Soluble oligomers of the amyloid beta-protein impair synaptic plasticity and behavior. Behav Brain Res.

2008;192 (1):106-113.). We believe that bexarotene acts by removing the soluble Aβ species, particularly oligomers of the 42 amino acid species (Aβ42), which has synaptotoxic effects and improves the memory almost within hours after the administration of bexarotene. Insulin will augment and amplify the effects of bexarotene and at the same time reduce the excitotoxic effects of glutamate, make easier to synthesize glutathione, which is neuroprotective, and facilitate to remove the effects of ROS. Its effects can be further augmented by insulin administered to olfactory mucosa and olfactory nerves. Insulin modulates the levels of Aβ and protects against the detrimental effects of Aβ oligomers on synapses. Thus, reduced levels of insulin and of insulin activity contribute to a number of pathological processes that characterize Alzheimer's disease. Restoring insulin to normal levels in the brain may therefore provide therapeutic benefit to adults with Alzheimer's disease and other degenerative brain afflictions.

Peripheral administration of insulin is not possible owing to the risk of hypoglycemia or induction and/or exacerbation of peripheral insulin resistance. In contrast, intranasal administration of insulin provides rapid delivery of insulin to the central nervous system via bulk flow along olfactory and trigeminal subperineural epithelial space, to the SAS of the CNS, CSF and is then distributed to the rest of the brain (Shantha T.R. and Yasuo Nakajima. Histological and Histochemical Studies on the Rhesus Monkey (Macaca Mulatta) Olfactory Mucosa. Yerkes Regional Primate Research Center, Emory University, Atlanta, Georgia: Z. Zellforsch. 103, 291—319 (1970). Shantha T.R.: Peri-vascular (Virchow - Robin) space in the peripheral nerves and its role in spread of local anesthetics, ASRA Congress at Tampa, Regional Anesthesia 17 (March-April, 1992). Shantha T.R. and Bourne G.H.: The "Perineural Epithelium": A new concept. Its role in the integrity of the peripheral nervous system. In Structure and Function of Nervous Tissues. Volume I. pp 379-458. (GH Bourne, Ed.). Academic Press, New York. 1969. U. S. Patent Application Publication Number: 201110020279 Al Rabies cure by T. R. Shantha, U. S. Patent Application Publication Number: US 2012/0323214 Al Pub. Date: Dec. 20, 2012; Alzheimer's Disease Treatment With Multiple Therapeutic Agents Delivered To The Olfactory Region Through a Special Delivery Catheter And Iontophoresis by Totada R. Shantha). The delivery of therapeutic agents including

insulin is a slower delivery via olfactory bulb axonal transport. Olfactory nerve and olfactory mucosal delivery will not adversely affect blood insulin or glucose levels unless it is delivered to the respiratory mucosa of the nasal cavity. In rodent models, intranasally administered insulin binds to receptors in the hippocampus and the frontal cortex within 60 minutes.

In human studies, intranasal insulin increases insulin levels in cerebrospinal fluid (CSF) within a similar period and acutely enhances memory. Furthermore, a 3-week trial of daily administration of intranasal insulin improved delayed story recall and caregiver-rated functional status in a small sample of adults with AD and in adults with amnestic mild cognitive impairment (aMCI), a condition thought to represent prodromal AD in most cases. Insulin improves memory in normal adults and patients with Alzheimer's disease without altering blood glucose. Energy metabolism in the CNS is dependent upon glucose uptake and is regulated by insulin in key brain regions. It has long been known that glucose uptake and utilization are deficient in patients with Alzheimer's disease. Recently, the gene expression levels of insulin, IGF-1, and their receptors were shown to be noticeably reduced in the brains of patients with Alzheimer's disease. Consequently, ability to deliver insulin to the CNS without altering blood glucose could provide an effective means to improve glucose uptake and utilization, and reduce cognitive deficits in patients with memory disorders. The benefit of olfactory mucosal insulin treatment was seen primarily for Alzheimer's patients without the apolipoprotein E (APOE) g4 allele. Longer treatment with olfactory mucosal insulin (21 days) enhanced memory, attention, and functioning compared with placebo in patients with either early stage Alzheimer's disease or mild cognitive impairment. Our own study of olfactory spray of dilute insulin in healthy volunteers resulted in better performance in tests scores.

Alzheimer's is a neurodegenerative dementia related to aging. It is characterized by the accumulation of neurofibrillary tangles and neuritic plaques (tau –τ– protein) in the brain affecting especially the degeneration of neurons in the olfactory bulb and its connected brain structures - the hippocampal formation, amygdaloid nuclei, nucleus basalis of Meynert, locus ceruleus, and the brainstem raphe nuclei, all of which project to the olfactory bulb (Figs. 14, 15). These degenerative alterations result in the loss of memory and cognitive function. There

is a major loss of cortical and hippocampal choline acetyltransferase activity and degeneration of basal forebrain cholinergic neurons. Loss of smell in Alzheimer's is due to necrosis and apoptosis of olfactory neurons, olfactory bulbs, olfactory tracts and the pre-pyriform cortex.

Alzheimer's is the most common form of dementia that demonstrates hardly any or no electrical pulse or action potential generation in the afflicted neurons due to low or the lack of neurotransmitter acetylcholine, which is associated with death and degeneration of neurons. Alzheimer's is a complex, slow evolving disease, and there is no cure. It worsens as it progresses with advancing age, and eventually leads to death in a vegetative state.

The incidences of Alzheimer's increase with age. In the United States, the prevalence of Alzheimer's was estimated to be 1.6% in 2000 both overall and in the 65–74 age group, with the rate increasing to 19% in the 75–84 group and to 42% in the greater than 84 age group (Hebert LE, Scherr PA, Bienias JL, Bennett DA, Evans DA (2003). "Alzheimer disease in the US population: prevalence estimates using the 2000 census". Arch. Neurol. 60 (8): 1119–22). Alzheimer's is found in about 10% of the population over the age of 65 and 47% of the population over the age of 85 affecting about 4 million people in the USA and 20 million people worldwide (Evans DA, Funkenstein HH, Albert MS, et al. Prevalence of Alzheimer's disease in a community population of older persons: higher than previously reported. JAMA. 1989;262:2551-2556). The World Health Organization estimated that in 2005, 0.379% of people worldwide had dementia, and that the prevalence would increase to 0.441% in 2015 and to 0.556% in 2030. Another study estimated that in 2006, 0.40% of the world population (range 0.17–0.89%; absolute number 26.6 million, range 11.4–59.4 million) were afflicted by Alzheimer's, and that the prevalence rate would triple and the absolute number would quadruple by 2050 and is expected to affect 1 in 85 people worldwide by then. The disease affects not only the person, but also the person's entire family, care givers and proves to be very burdensome financially and to the health care system.

The list of diseases treated using this inventive method described herein with or without insulin are endless but the most important ones include, among others, neurological conditions associated with memory loss, cognitive impairment and

dementia, including Alzheimer's, Parkinson's-type dementia, Huntington's-type dementia, Pick's-type dementia, Lewy body disease, MS, ALS, pain, PTSD, cerebral palsy, autism and those listed and unlisted. This electrical activation of the neuropil in the brain due to neurotransmitter-mediated activity is intricately involved in memory, attention, learning, cognitive processes and including various autonomic, sensory and motor function of the CNS. Besides delivering the electrical impulses; this present invention augments, and amplifies, the effects on existing neurotransmitters and any therapeutic agents inside the CNS. Note, however, that methods of the invention can be therapeutic methods of delivering the electrical impulses without delivery of any therapeutic device (active agent) other than saline or non-metabolically active agent to a location of the nasal cavity. Embodiments of methods can involve delivery of electrical impulses that are therapeutic in themselves, without the need for metabolically active agents such as a pharmaceutical or other biologically active agent. Similarly, devices as described can be useful for delivery of the electrical impulses but need not be capable of delivering a therapeutic agent to a location of the nasal region such as the olfactory mucosa, the sphenoid sinus, both of these locations, or other locations of the sinus cavity, with the insertion end of the device being located in a trans-nasal location. An apparatus that need not deliver a therapeutic fluid does not require and may exclude one or more ejection ports such as an opening or orifice located at a surface of the device shaft at the insertion end at the insertion end, in fluid communication with the proximal end, and through which fluid can be delivered externally of the device shaft to a region of the nasal cavity such as at the olfactory mucosa or the sphenoid sinus, with the insertion end located at the trans-nasal location. Exemplary methods do not require and may exclude delivery of a therapeutic agent (e.g., any described herein for treatment of Alzheimer's Disease or another condition) to a region of a nasal cavity, e.g., olfactory mucosa or sphenoid sinus.

Alzheimer's is the most common form of senile and pre-senile dementia in the world. It is known clinically as the progressive loss of memory, intellectual function, and disturbances in speech (Merritt, 1979, A Textbook of Neurology, 6th edition, pp. 484-489, Lea & Febiger, Philadelphia). Alzheimer's disease starts with inappropriate behavior, gullible statements, irritability, and a tendency towards

grandiosity, euphoria, and deteriorating performance at work. It progresses to deterioration in operational judgment, loss of insight, depression, loss of recent memory, and it ends in severe disorientation and confusion, apraxia of gait, generalized rigidity, and incontinence (Gilroy & Meyer, 1979, Medical Neurology, pp. 175-179, MacMillan Publishing Co.).

Pathological changes in Alzheimer's disease for example, involve degeneration of cholinergic neurons (nerves activated by acetylcholine or that release it) in the subcortical regions and of neuronal pathways that project from the basal forebrain, particularly Meynert's nucleus basalis to the cerebral cortex and hippocampus (Robert P H et al. 1999. "Cholinergic Hypothesis and Alzheimer's: The Place of Donepezil (Aricept), " Encephale 5:23-5 and 28-9). Alzheimer's is characterized by the accumulation of insoluble, 10 nm filaments containing β amyloid (Aβ) peptides, localized in the extracellular space of the cerebral cortex and vascular walls. There is dense accumulation of neuro fibrillary tangles of the tau (τ) protein observed intracellular in this dementia. The chief constituent of the cores is a peptide of 39 to 42 amino acids called the amyloid β protein, or Aβ. Although the Aβ protein is produced by the intracellular processing of its precursor (APP), the amyloid deposits forming the core of the plaques are extracellular. Both plaques and tangles are found in the same brain regions affected by nerve cell and synaptic loss. It is a known fact that the Alzheimer's is associated with degeneration of cholinergic neurons, in the basal forebrain, which play a primary role in memory and cognitive functions; decreased cholinergic function may be a fundamental cause of cognitive decline seen in Alzheimer's patients. This invention will activate the electrical activity and will restore the memory to functional level, acting at the basal forebrain, and at the same time restore the acetylcholine function.

Neuro fibrillary tangles are found within the cell bodies of dying neurons as well as some dystrophic neurites in the halo surrounding neuritic plaques of the Alzheimer's afflicted brain. The tangles are composed of paired-helical filaments whose biochemical analyses revealed that the main component is composed of hyper-phosphorylated form of the microtubule associated protein Tau (τ).

The factor that contributes to the occurrence or cause of the Alzheimer's is unknown. Familial incidence of the disease indicates genetic contribution.

Alzheimer's disease is typified by the following neuro pathological features, which display the huge loss of neurons, and synapses in the brain regions involved in higher cognitive functions (association cortex, hippocampus, and amygdala). Cholinergic neurons are particularly affected. The Alzheimer's plaques in the neuropil of the brain are composed of a core of amyloid material surrounded by a halo of dystrophic neurites, reactive astrocytes, and microglial cells. Even more, diminished cholinergic function may be an underlying cause of cognitive decline seen in Alzheimer's patients. No acetylcholine means no electrical pulse generation, with the loss of neuronal function, and loss of memory. This invention will remedy this deficiency.

Dementia testing is made by early measurement of cognitive testing. Standardized testing in humans can be performed using the Reye Auditory Verbal Learning Test, the Mini-Mental State Exam (MMSE), the Schier Logical Memory Test, or the Selective Reminding Test, among others. The cognitive subscale is also a major indication in the Alzheimer's Assessment Scale (ADAS-cog), and simultaneously assesses short-term memory, orientation in place and time, attention span, verbal ability and praxis. ADAS-cog testing is done for diagnosis of the condition and is used to evaluate success in treatment. Testing higher scores indicates cognitive impairment. Reduced scores, following treatment with tacrine, donepezil and the longer-acting rivastigmine are noted.

Scanning of the brain is in order whenever the cognition problems are detected. Although the neuronal and synaptic loss are universally recognized as the primary cause of the decline of cognitive functions, the cellular, biochemical, and molecular events responsible for this neuronal and synaptic loss are contentious and debated. There is global shrinkage of the brain mass and the brain of Alzheimer's patients weighs less than the non-Alzheimer's brain.

The delivery of therapeutic molecules across the blood brain barrier (BBB) has proven to be a major obstacle in treating various brain disorders including Alzheimer's disease. This invention describes transmitting the electrical nerve impulses through nerves that can include one or more of the olfactory nerves, sphenopalatine ganglion (SPG) nerve complex, trigeminal nerves, five cranial nerves in the cavernous sinus, pituitary gland to the hypothalamo - hypophysial system

complex, cerebral cortex, brain stem, and cerebellum. Therefore, it improves nerve conduction, restores lost cerebral function, delays, and curtails Alzheimer's and other neurological diseases by dilating the cerebral blood vessels to deliver the therapeutic agents to the neuropil.

This invention of electrical stimulation application can be adopted to deliver electrical current to create Iontophoresis and electroporation effect on the olfactory mucosa and lining of the sphenoid sinus. This enhances the permeability, uptake, and transport of therapeutic agents from the ORE and sphenoid sinus bypassing the BBB, by creating elecroporation and iontophoresis effects of olfactory mucosa and sphenoid sinus lining.

US 7,640,062 B2 (the entirety of which is incorporated herein by reference) describes the stimulation of the parasympathetic sphenopalatine ganglion to dilate the cerebral blood vessels to break the BBB and deliver therapeutic agents across the BBB. The '062 patent describes complex invasive surgical procedures to place a stimulator on the anatomical location of the sphenopalatine ganglion to archive the results. The '062 patent does not describe stimulation of various complex nerve structure and blood vessels of sphenoid sinus, pituitary gland or olfactory nerves that are easily accessible for widespread stimulation of the brain as described in the present inventive methods.

There are reported cases of cancer pain treated by removing the pituitary gland or destroying it with an alcohol injection. The subsequent autopsies demonstrate that the removal or destruction of the gland was not needed to obtain pain relief. Stimulation of the pituitary gland by alcohol injection or electrical stimulation has the same effect of relieving pain. See T.R. Shantha US patents 5,7 35,8 17, and 5,7 79,2,100, the entireties of which are incorporated herein by reference.

There are methods of application of electrical stimulation of nerves for treatment of epilepsy and depression by vagus nerve stimulation (VNS) described in U.S. Pat. No. 4,702,254; and U.S. Pat. No. 6,341,236. U.S. Pat. No. 5,299,569 entitled Treatment of neuropsychiatric disorders by left vagus nerve stimulation, at a location on the neck by first implanting an electrode there, then connecting the electrode to an electrical stimulator.

U. S. Patent Application Publication Number: US 2011/10152967 A1 discloses method and devices for the non-invasive treatment of neurodegenerative diseases through delivery of energy to target nervous tissue, particularly the vagus nerve. The devices used is a magnetic stimulator having coils with toroidal windings, which are in contact with an electrically conducting medium that is adapted to conform to the contour of a target body surface of a patient. These coils induce an electric current and/or an electric field within the patient, thereby stimulating nerve fibers within the patient. The stimulation brings about reduction of neuroinflammation in patients suffering from conditions comprising Alzheimer's disease, Parkinson's disease, Multiple Sclerosis, postoperative cognitive dysfunction and postoperative delirium. This is also one of the mechanisms the inventive device described here in uses to curtail Alzheimer's bringing about the reduction of neuroinflammation in the afflicted brain. The present invention described here is more effective in bringing down the neuroinflammation, because the electrical impulses are transmitted directly to many centers of the brain by thousands of nerve fibers projecting to periphery. This reduction in inflammation is effected by enhancing the anti-inflammatory capability of cytokines such as TGF-beta, wherein a retinoid or component of the retinoic acid signaling system provide an anti-inflammatory predisposition, by enhancing anti-inflammatory activity of a neurotrophic factor such as NGF, GDNF, BDNF, or MANF, and/or by inhibiting the activity of pro-inflammatory cytokines such as TNF -alpha.

A more efficient approach to selecting stimulation parameters might be to select a stimulation waveform that mimics electrical activity in the region of the brain that one is attempting to stimulate, in an effort to entrain the naturally occurring electrical waveform, as suggested in U.S. Pat. No. 6,234,953, and US2009/0299435. The patient may be more psychologically prepared to experience a procedure that is non-invasive and may therefore be more cooperative, resulting in a better outcome. Non-invasive procedures avoid damage to tissues that can result in bleeding, infection, skin or internal organ injury, blood vessel injury, and vein or lung blood clotting and are mostly painless. Less training may be required for use of non-invasive procedures by medical professionals. The procedures may be suitable for use by the patient or family members or caregiver at home or by a medical clinic

trained technician. The cost of non-invasive procedures is considerably less compared to invasive procedures.

Because the present inventive device can be inserted with ease, non-invasively, into the olfactory region (ORE), the sphenoid sinus and its actions controlled by delivering measured electrical pulses, this inventive device has application in the treatment of Alzheimer's disease. Other CNS affliction where it can be applied are as follows: Autism, cerebral palsy, chronic fatigue syndrome, PTSD, senility, hypo pituitary and hyper pituitary function, intractable pain including thalamic pain, various kinds of headaches, Lewy body dementia, Parkinson's disease, multiple sclerosis, ALS, spastic paraplegia, Down's Syndrome, psychological illnesses, addiction, phantom limb syndromes, reflex sympathetic dystrophy, Vascular dementias (or multi-infarct dementia), Frontal lobe dementias (such as Pick's disease) , Subcortical dementias (such as Huntington, or progressive supranuclear palsy), Focal cortical atrophy syndromes (such as primary aphasia), Metabolic-toxic dementias (such as chronic hypothyroidism or B12 deficiency), Infections (such as syphilis, neuro-AIDS or chronic meningitis), and such others.

A pharmaceutic agent or drugs administered along with neural stimulation as described herein can be selected based on the condition, e.g., disease, being treated. Examples include the following: the chemotherapeutics, insulin, IGF-1; levodopa (5-10% crosses BBB) combined with a dopa decarboxylase inhibitor or COMT inhibitor, dopamine agonists and MAO-B inhibitors (selegiline and rasagiline), dopamine agonists (include bromocriptine, pergolide, pramipexole, ropinirole, piribedil, cabergoline, apomorphine and lisuride), non-steroidal anti-inflammatory drugs, acetyl cholinesterase inhibitors such as tacrine, donepezil and the longer-acting rivastigmine; antibiotics, 2,4-dinitrophenol, glutamate receptor antagonist, glutathione, NMDA-receptor blocker such as ketamine, β amyloid inhibitor, Alzheimer's vaccine, non-steroidal anti-inflammatory drug including COX-2 inhibitor, deferoxamine, hormones, enzymes, erythropoietin, Intranasal fibroblast growth factor, epidermal growth factor, microglial activation modulator, cholinesterase inhibitor, stimulant of nerve regeneration, nerve growth factor, non-steroidal anti-inflammatory drugs, antioxidants, hormone, vitamin B_{12}, A, E, D_3, and

B complexes, and inhibitor of protein tyrosine phosphatase and others as they evolve.

This invention described herein restores and facilitates to overcome a number of obstacles posed by the CNS for the treatment of Alzheimer's;

1. By generating electrical impulses and transmitting them to the brain, activating neurons, and neuronal transmission through the synapses. Thus, activating the inactive neurons and activating the acetylcholine and their function to conduct nerve impulses that have become silent due to loss of acetylcholine neurotransmitter with abnormal accumulation of neurofibrillary tangles (amyloid (Aβ) deposits) and neuritic plaques (tau -τ – protein) in the neurons of the CNS is the one of the fundamental principle of this invention. It is also intent of this invention of using bexarotene, acetylcholine esterase inhibitors and insulin to remove or reduce the amyloid plaques, increase acetyl cholin neurotransmitter activity in the brain; thus, treat the fundamental factors that contribute to the disease.
2. By making the olfactory mucosa and sphenoid sinus lining more permeable to therapeutic agents by Iontophoresis and electroporation and transport the therapeutic agents to CNS by passing the BBB to deliver them to the site of pathology. The therapeutic agents we have selected are bexarotene, insulin, acetyl-cholin-esterase inhibitors, and ketamine delivered through the olfactory mucosa.
3. By breaking the BBB to allow therapeutic agents to reach the site of pathology to curtail Alzheimer's disease at the same time remove the toxic metabolites from neuropile to systemic circulation away from the brain.

SUMMARY OF THE INVENTION

The present invention disclosure involves a medical device and medical procedures that stimulate nerves by transmitting energy to adjacent nerves to be transmitted to the central nervous system non-invasively to treat Alzheimer's and other neurodegenerative diseases. This medical procedure is defined as being non-invasive when no break in the skin (or other surface of the body, such as a wound bed) is created through use of the method, and when there is no contact with an internal body cavity beyond a body orifice (e.g., Mouth, anus, external auditory meatus of the ear, eyes, and the nose). On the other hand, the invasive procedures (including minimally invasive procedures) procedures do involve inserting a

substance or device into, through the skin, or into an internal body cavity beyond a body orifice.

Advantages of our non-invasive medical methods and devices relative to comparable invasive procedures described in this invention are as follows. 1. The patient may be more psychologically complaint to use the procedure that is non-invasive and may therefore be more cooperative, ensuing in a better outcome. 2. Non-invasive procedures of inserting this device avoid damage to tissue it comes in contact such as bleeding, infection, skin or internal organ injury, blood vessel injury, and vein or lung blood clotting. 3. Non-invasive procedures of inserting this device are almost painless or minimally painful. 4. The inventive device described herein may be positioned without the need for local or general anesthesia. 5. Less training may be required for use of this non-invasive device by medical professionals. 6. This device may be continued to be used by the patient or family members at home with brief training. 7. The cost of non-invasive device and procedures is relatively less compared to invasive procedures. 8. This inventive device can be used as therapeutic, prophylactic, and diagnostic objectives in the management of Alzheimer's disease (Alzheimer's-AD) and other neurodegenerative diseases of the CNS. 9. This device can be easily mass-produced using non-reacting, non-allergic or hypo allergic synthetic, semi synthetic composite material.

The present invention discloses methods and devices for the non-invasive delivery of electrical impulses for the treatment of neurodegenerative conditions such as Alzheimer's disease. It makes use of an energy source that transmits energy non-invasively to nervous tissue. In particular, the devices can transmit energy to, or in close proximity to the CNS of the patient, in order to stimulate, block, and/or modulate electrophysiological signals in the CNS involved in Alzheimer's disease. The neurodegenerative diseases that can be treated with the present invention include Alzheimer's disease, Parkinson's disease, multiple sclerosis, AIDS dementia complex, Creutzfeldt-Jakob disease , Huntington disease, Tay- Sachs disease, toxic encephalopathy, transmissible spongiform encephalopathy, Vascular dementia, ALS, and many such neurodegenerative diseases. Though many of these above diseases differ from each other, but their pathogenesis share common features, which makes it possible to treat them with similar therapeutic agents and methods.

One of the important common features of these diseases is the presence of inflammation [Sandra Amor, Fabiola Puentes, David Baker and Paul van der Valko, Inflammation in neuro-degenerative diseases. Immunology, 129 (2010), 154-169}. Excessive and prolonged inflammation ultimately destroys the nervous tissue that is associated with the neurodegenerative disease. The neuroinflammation modulated by cytokines that are small signaling proteins or peptide molecules that are secreted by glial cells of the CNS, by numerous types of immune system cells. It is known that electrical stimulation brings about the reduction of neuroinflammation by enhancing the anti-inflammatory neurotrophic factors such as : Nerve growth factors (NGF), fibroblast growth factor (bFGF), glial-derived neurotrophic factor (CNTF), pigment epithelium-derived factor (PEDF), glial-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), erythropoietin's, insulin, IGF-1, platelet derived growth factor (PDGF), and/or by inhibiting the activity of pro-inflammatory cytokines such as TNF -alpha. Hence, in the treatment of these diseases be directed to reduce the cytokine effect and restore the brain function as we propose in this invention.

It is an object of the present invention to provide methods and apparatus for delivery of measured electrical impulses to the CNS neuropil, neurons and their connections which are involved in and affected by Alzheimer's disease.

It is an object of the present invention to develop a device to treat Alzheimer's and other neurodegenerative diseases.

It is an object of this invention to develop a device for stimulating the surface of the sphenoid sinus and its adjacent structures: pituitary gland, five cranial nerves and the internal carotid artery; olfactory mucosa; sphenopalatine ganglion (its afferents and efferent connection), using electrical impulses as described herein to activate the inactive neurons and their connections involved in Alzheimer's disease.

It is a further object of this invention to develop a device for stimulating the sphenopalatine ganglion located immediately below the sphenoid sinus on the lateral wall of the uppermost part of the nasal roof and send electrical impulses and signals to inactive neurons though its extensive CNS connections.

It is a further object of this invention to develop a device for stimulating the olfactory mucosa with its connection of olfactory nerves connecting the olfactory bulb and its connection to the CNS involved in Alzheimer's disease.

It is a further object of this invention to develop a device for stimulating the anterior ethmoidal nerve, which emerges from the roof of the nose in front of the olfactory mucosa, branch of the ophthalmic division of the trigeminal nerve.

It is a further object of this invention to develop a device for stimulating the surface of the sphenoid sinus, which will transmit the electrical impulses (stimulus, pulse, signals) to neurological structures, BV, and pituitary gland, hypothalamus, thalamus, and thalamic radiation; which the patient uses while engaging in normal activities and being ambulatory, to treat Alzheimer's.

Applicant has invented a device for stimulating the interior surface of the sphenoid sinus, its walls, and surrounding neuronal structure. The apparatus consists of an insertion body having a flexible outer surface adapted for insertion into the sphenoid sinus. The insertion body is constructed of a flexible material, which contracts and conforms to the interior surface of the sphenoid sinus. The insertion body is an inflatable outer membrane or balloon. This balloon attached to flexible tubing through which air or fluid can be pumped to inflate the balloon to position the balloon against the surface of the sphenoid sinus.

The inflatable balloon is inserted in the uninflated state into the hollow sphenoid sinus through the sphenoid foramina, which communicates with the nose. The balloon is then inflated with liquid or air under slight pressure.

In some cases it may be desirable to cool the liquid depending on the purpose for which the device is being used (e.g., to lower the activity of the hyperactive pituitary gland).

The device is provided with an electrical impulse transmitter on the catheter as it passes to the sphenoid sinus to stimulate the olfactory bulb and its cortical and subcortical connections in treating Alzheimer's and other neurodegenerative diseases.

The device is provided with electrical impulse transmitter on the catheter as it passes to the sphenoid sinus to stimulate the sphenopalatine ganglion.

Electrical stimulator wires are placed along the outer surface of the inflatable balloon for stimulating the pituitary gland and other nerve structures surrounding the sphenoid sinus in the cavernous sinus.

Temperature sensors are placed on the outer surface of the balloon to determine the temperature, which will approximate the temperature of the surface of the sphenoid sinus.

The interior shape of the balloon can be examined by using a fiber optic connection. By visual inspection through the fiber optic connection, the approximate size and shape of the sphenoid sinus can be determined and whether the balloon is filling that space or not to transmit the electrical impulses through the sidewalls and the roof of the sinus.

It is also an object of the present invention to provide methods and apparatus inserted to the anatomical sites explained below to deliver electrical impulses with a minimally invasive approach to treat CNS diseases such as Alzheimer's disease.

Means are provided for the quick detachment of the balloon from the rest of the apparatus. Under those circumstances, the balloon is left in the sphenoid sinus cavity and its activities controlled by a controller, outside the body through radio transmission, to a receiver located in the balloon. The battery-powered receiver, then directs that current to be provided to electrical stimulators on the outside of the balloon or to heating elements inside the balloon to heat the fluid to a desired temperature. This device will allow full mobility by the patient while being stimulated.

The apparatus and method of this invention is useful in the treatment of acute and chronic pain of headaches besides treating Alzheimer's and other neurological diseases. It also stimulates the structures surrounding the sphenoid sinus, and particularly the pituitary gland, which may be useful in treating various diseases that arise from the central and peripheral systems. A fluid able to be heated or cooled can be pumped into the balloon to enhance the output or decrease the output of pituitary hormones including growth hormone from the pituitary gland.

Thermocouples applied at the tip of the catheter inside the balloon are inserted into the sphenoid sinus. They are connected to the N-doped and P-doped legs of the semiconductor material which when connected to the direct current can

heat or cool the thermocouples depending on the direction of current flow. This heating and cooling is called the Peltier effect and was discovered in 1831 by a Swiss Scientist. The same principle is used in the heat pump. Devices embodying the Peltier effect are currently being used to cool and heat the tissue and fluids in the body. Instead of using the heating or cooling circulating pump to heat or cool the fluid inside the inflated balloon as desired to treat various conditions and to increase or decrease the pituitary function. In some applications, it is desirable simply to use the inflated balloon with its pressure and stimulating the sphenoid sinus surrounding structures with electrical conductive wires.

A catheter in this invention can be attached to the balloon through which drugs may be infused into the sphenoid sinus for absorption by the central nervous system directly across the sphenoid bone and its perforating blood vessels around the cavernous sinus.

It is a further object of the present invention to provide such methods and apparatus to be able to facilitate delivery of electrical impulses to the CNS BBB. This is through the sphenopalatine ganglion and carotid artery -Circle of Willis parasympathetic nerves located close to sphenoid sinus to make them dilate and become leaky (breaking of BBB), thus improve the delivery of systemic administration of therapeutic agents to the CNS.

It is another object of this invention, by dilating the BBB BV to allow the toxic material to pass from the neuropil which has no passage to exit once formed adding to the causation of Alzheimer's and other neurological diseases.

It is yet a further object of the present invention to provide cost effective methods and apparatus for delivery of electrical pulses, which will help to deliver compounds through the BBB and improve the electrical activity in the neuropil to enhance the brain function.

It is still a further object of the present invention to provide improved methods and apparatus for remedying or modifying neuronal dysfunction and their synaptic activities through electrical impulse deliverance.

It is an additional object of the present invention to provide a superior method and apparatus for treating and preventing neurological diseases, whose prognosis and development of pathological symptoms are influenced by electrical

impulses and neurotransmitters, which also improve with increased cerebral blood flow by activating the parasympathetic system.

It is still an additional object of some aspects of the present invention to provide improved methods and apparatus for treating and/or preventing Alzheimer's by improving the oxygen delivery to the brain by vasodilatation effect.

It is yet a further object of some aspects of the present invention to provide an insertable apparatus, which improves the function of the brain, without being implanted in the brain or in the nose.

These and other objects of the invention will become evident from the description of preferred embodiments thereof provided herein. In the preferred embodiments of the present invention, an electrical stimulator drives electrical pulses or current into the olfactory mucosal nerves, sphenopalatine ganglion, trigeminal nerves, cranial nerves III, IV, V, VI, pituitary gland with hypothalamo hypophysial tracts and into related neuro anatomical structures including neural tracts originating from these structures. Typically, the stimulator drives the current in order to control and/or modify these structures to induce changes in nerve conductivity within the neuropile and increase cerebral blood flow with more permeability for circulating therapeutic agents by modulating permeability of the BBB.

This invention is used in many medical applications by way of illustration and not with any limitation are as follows. The list of diseases that be treated by using this electrical simulator invention with or without adjuvant therapeutic agents , as well as other pharmaceutical, biochemical, nutraceuticals, and biological agents or compounds are many. They are: Alzheimer Disease, Arachnoiditis, Autism, Brain Ischemia, CNS Infections, Cerebral Palsy, senile dementias, ALS, Cerebrovascular Disorders, Corticobasal Ganglionic Degeneration (CBGD) (not on MeSH), Creutzfeldt-Jakob Syndrome, Dandy-Walker Syndrome, Dementia, Encephalitis, Encephalomyelitis, Epilepsy, Essential Tremor, Friedreich Ataxia, Huntington Disease, Hydrocephalus, Hypoxia Brain damage, Lewy Body Disease, Multiple sclerosis, Myelitis, Olivopontocerebellar Atrophies, PTSD, traumatic injury to the brain -blunt or otherwise, mental illnesses, Pantothenate Kinase Associated Neurodegeneration, Parkinson Disease, Parkinsonian Disorders,

Postpoliomyelitis Syndrome, Prion Diseases, Pseudotumor Cerebri, Shy-Drager Syndrome, Spinal Cord Diseases, Stroke, Thalamic Diseases, Tic Disorders, Truett Syndrome, Uveomeningoencephalitic Syndrome, psychological disorders, addictions, in the treatment of cerebrovascular disorders such as stroke, PTSD, for the treatment of migraine, cluster and other types of headaches, and pain and other diseases listed below, most importantly in the treatment of neurodegenerative diseases such as Alzheimer's.

For the facilitation of drug, transport across the BBB by effective cerebral BV dilatation and by bypassing the BBB for delivery of therapeutic agents and large molecules across the olfactory and trigeminal nerve complexes by Iontophoresis and electroporation modality is incorporated into the device to treat the above listed diseases.

In the specification of the present patent application, unless indication to the contrary is stated, stimulation of the olfactory mucosal nerves, sphenopalatine ganglion, trigeminal nerves, pituitary gland with hypothalamo hypophysial region, thalamus complex, brain stem and cerebellum is used. It is to be understood to alternatively or additionally to include stimulation of the complex afferent and efferent nerve connections of the sphenopalatine ganglion, olfactory bulb, pituitary gland complex, five cranial nerves, and both afferent and efferent nerve tracts including autonomic nervous system components.

It is also to be understood that the electrical "stimulation," as provided by preferred embodiments of the present invention by electrical pulse catheter placement close to the region, is placed where it is going to stimulate conductive neural pathways. The parameters of stimulation is described herein by way of illustration and not limitation, and that the scope of the present invention includes other possibilities, which would be obvious to someone of ordinary skill in the art who has read the present patent application. Further, the parameters of stimulation include substantially any form of the current application to designated tissue, even when the current application is configured to block or inhibit the activity of hyperactive nerves.

It is to be appreciated that preferred embodiments of the present invention are described with respect to driving current into the neural structures, directly and

to other sites in the brain, which upon stimulation modulate, enhance and restore the neuronal and synaptic function with improved conduction of nerve impulses; thus, restoring the brain function, especially in treating Alzheimer's and senile dementias.

It is yet further to be valued that while chosen embodiments of the invention are generally described herein with respect to electrical transmission of power and electrical stimulation of tissue, other modes of energy transport may be used as well. Such energy includes, but is not limited to, direct, or induced electromagnetic energy, RF transmission, ultrasonic transmission, optical power, and low power laser energy delivered through a fiber optic transmission cable.

The preferred embodiments of the present invention are described with regard to application of electrical currents to tissue, equivalent to applying an electrical field e.g., by creating a voltage drop between two electrodes.

With the neuronal center located, we send electrical impulses by this inventive device situated in the prefrontal, frontal cortex, hypothalamus, hippocampus, and amygdaloid nucleus, basal ganglion, cerebellum, and brain stem nuclei in the brain above and behind the nose. It is important to note the activation of these neuronal structures by electrical impulses causes restoration and improvement of their function. Circle Willis BV stimulation results in the opening of pores in the BBB vessel walls due to the dilatation effect of parasympathetic innervations, causing plasma proteins and therapeutic agents to extravasate which were unable to break the BBB thus allowing the large therapeutic molecules from within the blood vessels to the cerebral tissue to be substantially increased. Thus, this invention acts as a neurological drug delivery facilitator, without altering the molecular weight.

The added benefit of the use of this invention is due to the vasodilatation resultants improvement in oxygen supply to the CNS tissues.

It is also to be valued that electrical "stimulation," as provided by preferred embodiments of the present invention, is meant to include substantially any form of current application (galvanic) to designated tissue, even when the current configured to activate or to block or inhibit the activity of nerves. A voltage drop between two electrodes creates an electrical field.

It is another object of the present invention, a method for treating Alzheimer's and other neurodegenerative diseases, to cause an increase in clearance of an Alzheimer's related constituent CNS of the subject. This helps to remove from the neuropil of the subject to a systemic blood circulation of the subject, so as to treat the Alzheimer's or other neurodegenerative disease by electrical stimulation of one or more of the olfactory mucosal nerves, cranial nerves, sphenopalatine ganglion, trigeminal nerves, pituitary gland with hypothalamo hypophysial system, resulting and due to dilatation of BBB blood vessels.

There is therefore provided, in accordance with a preferred embodiment of the present invention, apparatus for modifying a property of a brain of an afflicted patient using one or more electrodes adapted to be applied directly to one or more olfactory nerves, other cranial nerves, sphenopalatine ganglion, trigeminal nerves, pituitary gland with hypothalamo hypophysial site separately or in combination.

Embodiments of devices can include an electrical delivery control unit adapted to drive one or more electrodes to apply a current or other electrical signal to a site, e.g., one or more nerve as described herein, capable of stimulating the CNS of the patient. The electrical conduction wires and one or more (e.g., proximal and distal) electrodes are connected to the electrical output manipulator. As a preferred embodiment, the apparatus has a catheter with balloons, which includes conductive wires adapted to connect the control unit to the one or more electrodes, wherein the control unit is adapted to drive the one or more electrodes from a position at a proximal end of the device and external to the patient.

Applying an electrical signal, as described herein separately or in a combined device to treat Alzheimer's or another neurological condition, to the olfactory nerves results in transmission of electrical pulses from the olfactory nerves to the olfactory bulb. From the olfactory tract, the pulses are delivered to subarachnoid space (SAS) to the cerebrospinal fluid (CSF) then to various centers of the brain and cerebral cortex, especially temporal and frontal lobes.

Applying an electrical signal as described herein separately or in a combined device to the olfactory nerve, the electrical stimulus reaches the CNS through the olfactory bulb, and then to the olfactory tract to prefrontal cortex, medial olfactory

area, to temporal lobe ,to lateral olfactory area, hippocampus, hypothalamus ,brain stem nuclei, and to cerebellum.

Transmitting electrical impulses as described to treat Alzheimer's or another neurological condition separately or in a combined device to the sphenopalatine ganglion results in transmission of electrical pulses to all its connecting branches. Electrical impulses from a device as described are transmitted to the CNS through the anterior, and posterior ethmoidal nerves, the communicating branch between them, the retro-orbital branch of an sphenopalatine ganglion of the subject, greater and lesser palatine nerve, sphenopalatine, communicating branch between a maxillary nerve and sphenopalatine ganglion, nasopalatine nerve, posterior nasal nerve, infraorbital nerve, otic ganglion of the subject, an afferent fiber going into the otic ganglion, Vidian nerve, greater and lesser superficial petrosal nerve, and deep petrosal nerve of the subject.

Transmitting the electrical impulses as described herein to treat Alzheimer's and other CNS diseases through the sphenoid sinus results in transmission of the electrical pulses to the pituitary gland. From this anatomical site, the electrical impulses are transmitted to one or more cranial nerve, e.g., I, III, IV, V, VI, to the brain stem nuclei, and other neurons in the brain stem, cerebellum; and parasympathetic plexus on the carotid artery in the cavernous sinus, basilar and posterior cerebral arteries on the brain stem (circle of Willis). The electrical impulses from the pituitary gland are relayed to the hypothalamo-hypophysial tract to the hypothalamus, the thalamus, thalamic radiation, basal ganglion, hippocampus, amygdala, Cingular gyrus, brain stem, and cerebral cortex, and cerebellum.

Yet another objective of described devices and methods to treat Alzheimer's is to deliver adjuvant therapeutic agents directly to olfactory mucosa and sphenoid sinus tissue in combination with electrical nerve stimulation as described, allowing the therapeutic agent to enter the brain due to iontophoresis, and electroporation electrical effects or otherwise on the olfactory mucosa and sphenoid sinus. Thus, this invention will facilitate the uptake and transport of these therapeutic agents from ORE to the CNS bypassing BBB through the olfactory nerves and other cranial nerves, enumerated. It is the intent of this invention to deliver the therapeutic agents

we have selected such as bexarotene, insulin, acetyl-cholin-esterase inhibitors, monoclonal antibodies and ketamine delivered through the olfactory mucosa.

Yet another objective of this invention to treat Alzheimer's is to deliver adjuvant therapeutic agents directly delivered to ORE and sphenoid sinus, such as bexarotene, dissolved in DMSO at 65 mg/mL or in ethanol at 10 mg/mL, which is instilled, with insulin and acetyl cholinesterase inhibitors in Alzheimer's patient's olfactory mucosa.

Applying electrical signals to olfactory mucosal nerves, sphenopalatine ganglion, trigeminal nerves, pituitary gland with hypothalamo hypophysial tract causes an increase in molecular passage between cerebrospinal fluid of the subject and another body fluid of the subject, to facilitate a diagnosis of Alzheimer's.

The stimulation of the neuropil by using this device also brings about reduction of neuroinflammation in patients suffering from conditions comprising Alzheimer's disease, Parkinson's disease, Multiple Sclerosis, postoperative cognitive dysfunction, and postoperative delirium as such. This also one of the mechanisms by which the inventive device described herein curtails Alzheimer's disease bringing about the reduction of neuroinflammation in the afflicted brain.

This invention delivers electrical impulses to the olfactory nerves, sphenopalatine ganglion, trigeminal nerves, pituitary gland with hypothalamo hypophysial tract, five cranial nerves in the sphenoid sinus wall (in the cavernous sinus). This results in stimulation of circle of Willis BV with its parasympathetic autonomic nerve supply which causes an increase in passage of therapeutic agents from systemic circulation or from the olfactory mucosal area of the nose of the subject into a central nervous system. Therapeutic agents are delivered by passing the BBB, besides the electrical stimulation of Alzheimer's disease afflicted patient's brain.

Therapeutic agents can be administered orally, intravenously or intranasally along with this inventive device in operation.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention will be completely implicit from the following detailed description of preferred embodiments thereof taken together with the drawings, in which:

FIG. 1 is the diagrammatic presentation 100 of the olfactory mucosa covering the medial and lateral walls of the nose, sphenopalatine ganglion, and anterior ethmoidal nerve.

FIG. 1a is the diagrammatic presentation of 100a showing head position and the olfactory mucosa when the device needs to be placed in the nose.

FIG. 2 is the diagrammatic presentation of the lateral wall 200 of the nerve structures in the nose.

FIG. 3 is the diagrammatic presentation of the medial wall 300 of the nerve structures in the nose.

FIG. 4 presents the views of diagram 400 showing structure stimulated by electrical impulses transported to the CNS.

FIG. 5 is the diagrammatic presentation 500 showing structure that may be stimulated by electrical impulses to be transmitted to the CNS.

FIG. 6 is the diagrammatic drawing 600 showing an embodiment of the inventive device used to stimulate olfactory mucosa.

FIG. 7 is the drawing 700 showing an embodiment of the inventive device with an insertion end located at a location to deliver electrical stimulation, a proximal electrode at olfactory mucosa and a distal electrode at the sphenoid sinus.

FIGS. 8 includes diagram 800 showing an embodiment of the inventive device with an insertion end located at a location to deliver electrical stimulation, a proximal electrode at olfactory mucosa and a distal electrode at a sphenoid sinus with anchoring balloon.

FIG. 9 is the diagrammatic presentation 900 of an embodiment of electrical simulator inventive device as described herein, incorporating olfactory mucosal, sphenoid sinus, pituitary gland, sphenopalatine ganglion stimulators in one device.

FIG. 10 is the diagrammatic presentation 1000 of an embodiment of a completely assembled electrical impulse delivering catheter as described, including

balloon and inflating syringes, useful to treat Alzheimer's and other neurological diseases.

FIG. 11 is the diagrammatic presentation 1100 showing the longitudinal section of the olfactory bulb, which conducts electrical impulses to the cortical centers, e.g., to treat Alzheimer's and other diseases delivered through the olfactory nerves from the olfactory mucosa.

FIG. 12 is the diagrammatic presentation 1200 showing an embodiment of a sphenoid sinus balloon as described herein, located in the sphenoid sinus, and the surrounding structures to which electrical impulses can be transmitted.

FIG. 13 is the diagrammatic presentation 1300 showing the sagittal section of the sphenoid sinus with an embodiment of inventive device in the sphenoid sinus, and the surrounding cavernous sinus structures to which electrical impulses can be transmitted.

FIG. 14 is the diagrammatic presentation 1400 showing the spread of electrical impulses from the olfactory nerves to the olfactory bulb and to the rest of the centers in the brain involved in the Alzheimer's and other disease processes.

FIG. 15 is the diagrammatic presentation 1500 of the medial wall with an insertion end of an embodiment of an electrical impulse delivering device as described herein in place in electrically-stimulative contact with the olfactory mucosa, olfactory bulb, sphenopalatine ganglion, pituitary gland, other neurological structures, and BV in the cavernous sinus.

FIG.16 is the diagrammatic presentation of catheter device in the sinus and the nose.

FIG.17 is the diagrammatic presentation shows the electrical stimulator catheter device in place

FIG. 18 is the diagrammatic presentation shows an example of an assembled catheter in position with an insertion end located at a trans-nasal location.

FIG.19 is the diagrammatic presentation shows various embodiments of the electrical stimulation catheter that can be incorporated.

FIG.20 is the diagrammatic presentation shows another embodiment of the electrical stimulation catheter placed in a trans-nasal location.

FIG. 21 is the diagrammatic presentation shows another embodiment of electrical stimulation with two balloon expanding syringes and electrical cell output monitor.

DETAILED DESCRIPTION

The term "Alzheimer's" means Alzheimer's disease, Alzheimer's afflicted brain. The term is used to allude to "neurodegenerative diseases" "neurological diseases" "CNS diseases" such as Parkinson's, senile brain atrophy, stroke, PTSD, Tumors, vascular disorders, and other such afflictions.

The terms "apparatus" "device" "inventive device" are used interchangeably.

The terms "therapeutic," "therapeutically effective doses," and their cognates refer to doses of a substance, e.g., of a protein, e.g., insulin, of an IGF-l, that result in prevention or delay of onset, or amelioration of one or more symptoms of a neurodegenerative disease such as Alzheimer's, Parkinson's, or another as described herein.

As used herein, the term "treating" or "treatment" and "example" refers to both therapeutic treatment, prophylactic or preventative measures and method of use.

A "subject," "individual" or "patient" used interchangeably herein, which refers to a vertebrate, preferably a mammal, more preferably a human.

The term "mammal (s)" include but are not limited to, humans, mice, rats, monkeys, farm animals, sport animals, and pets.

The term "neuropil" in the following description refers to an intricate, complex network of axons, dendrites, and glial branches that form the bulk of the central nervous system's grey matter with Microglial cells with BV endowed with BBB and in which nerve cell bodies are embedded.

The term "BBB" (blood brain barrier) refers to the 400 miles of blood vessels in the form of capillaries that supply the neuropil and form the bulk of the blood supply (20% of the cardiac output) of the central nervous system's gray matter in which the nerve cell bodies lay surrounded and embedded in the neuropil. Fortunately, the olfactory nerves provide a route bypassing the BBB, presenting the select therapeutic agents directly to the neuropil of the brain to the site of pathology to treat CNS diseases.

The term "Circle of Willis," "Cerebral BV," or brain "BV" includes anterior cerebral arteries, anterior communicating arteries, internal carotid arteries, posterior cerebral arteries, the basilar artery and middle cerebral arteries supplying the brain and give branches to from the BBB capillaries inside the brain, brain stem, and spinal cord.

The term "olfactory region" (ORE) includes olfactory mucosa, sphenopalatine ganglion and its branches, branches from the trigeminal nerve, olfactory nerve fasciculi as they enter the olfactory bulb, and the communicating blood vessels of this region to the CNS. It is located in the upper third of the medial and lateral wall of the nose (figs. 1, 2, 3) and covers the entire roof of the nose (cribriform plate of the ethmoid bone).

The term "olfactory mucosa" (OM) refers to the olfactory area in the upper part of the nose, which contains olfactory receptor bipolar neurons, that forms about 20 bundles of olfactory nerve fasciculi (Figs. 1,2,3). Olfactory neuro-epithelium is the only area of the body in which an extension of CNS meets the external environment.

The terms "tumor necrosis factors," (TNF), or "cytokines" refers to a naturally occurring cytokines present in humans or mammals, which play a key role in the inflammatory immune response and in the response to infection.

The term "perineural epithelium" (PE) means a histological structure of continuous flat squamous cell layers completely surrounding the nerve fasciculi (axons bundles) and separating the axons from the tissue space around the nerve bundle and protecting them.

The term "sub perineural epithelial space" (sub PE) is used to describe the tissue space between the nerve bundles of axons (fasciculi) and below the perineural epithelium (Fig. 11).

The terms "antibodies" and "immunoglobulins" mean the proteins produced by one class of lymphocytes (B cells) in response to specific exogenous foreign molecules (antigens, infections). They can be also be synthesized.

The term "monoclonal antibodies" (mAB) means the identical immunoglobulins which recognize a single antigen that are derived from clones

(identical copies) of a single line of B cell which can be a cytokine blocker, or a cytokine inhibitor, or as a cytokine antagonist.

The terms Alzheimer's and related diseases, and neurodegenerative disease, are interchangingly used.

The term electrical "pulse," "signal," and "impulse," are used interchangeably.

"Brain" and "CNS" signify the same structures and are used interchangeably.

The terms "treat," "treating," "treatment," "curtail" as used herein and unless otherwise specified, are used to mean that which reduces or retards or slows the progression or severity of a disease or condition.

The present invention disclosure relates to devices and medical procedures that stimulate nerves by transmitting electrical energy to nerves and tissue, preferably non-invasively. Described methods of treatment of Alzheimer's disease relate to stimulation of one or more cranial nerve, CN I (also referred to as the olfactory nerve), III, IV, V, and VI, (a total of 12 cranial nerves which include both sides of the sphenoid sinus and ORE). In accordance with particular embodiments of the invention, neural stimulation (multiple cranial nerves) may correspond to transcranial (through sphenoid sinus), cortical, subcortical, cerebellar, deep brain, spinal column, cranial or other peripheral nerve, and/or other types of stimulation.

Electrical stimulation impulses described herein are capable of various effects, as described, such as reducing neuroinflammation, wherein pathways involving anti-inflammatory cytokines, the retinoic acid signaling system, and/or neurotrophic factors enhanced, and/or pathways involving pro-inflammatory cytokines are inhibited with enhancement of neurotransmitters and memory related protein and amino acid output in the neurons.

ANATOMY OF THE SITES WHERE A DEVICE AS DESCRIBED CAN BE POSITIONED TO TREAT ALZHEIMER'S AND OTHER CNS DISEASES

Before we describe this invention, it is important to describe the anatomical regions we intend use this device to stimulate to treat or curtail Alzheimer's and other neurological diseases; and why these anatomical regions were selected to use this inventive device. Such knowledge also facilitates the insertion and placement of

this inventive device (especially an "insertion end" thereof) at a useful and therapeutic anatomical site. For these reason, we consider in detail:

a) The anatomy of the sphenoid sinus and its relation to five cranial nerves, pituitary gland, and hypothalamic and thalamic radiation,

b) Anatomy of the olfactory mucosa with olfactory neurons, its connection to the olfactory bulb, and its relay of electrical impulses to the CNS and entorhinal cortex,

c) Anatomy of the sphenopalatine ganglion and its sensory, motor, and autonomic nerve system connections.

ANATOMY OF THE SPHENOID SINUS, PITUITARY GLAND, HYPOTHALAMUS, THALAMUS AND CAVERNOUS SINUS (FIGS. 1-5,12-15) INVOLVED IN THE TREATMENT OF ALZHEIMER'S AND OTHER NEUROLOGICAL CONDITIONS

The sphenoid sinus is located within the body of the sphenoid bone posterior to the upper point of the nasal cavity. The sphenoid sinus consists of two large irregular cavities separated by a bony septum. The middle of the anterior wall of the sphenoid bone forms a crest, which articulates with the perpendicular plate of the ethmoid bone, which forms part of the nasal septum (FIG.13). On each side of the sphenoid crest, a rounded opening called the sphenoid foramina (Fig. 13 arrows 524) about 4 mm in diameter opens into the sphenoid sinus from the posterosuperior part of the nasal cavity. The hypophyseal fossa commonly known as sella turcica (shape of Turkish saddle) is located in a depression in the body of the sphenoid bone. The sella turcica forms a bony caudal border for the pituitary gland. Completing the formation of the saddle posteriorly is the dorsum sellae, continuous with the clivus, inferoposteriorly. The pituitary gland is encased in this thin boney fossa (Figs. 3-5, 12, 13, 15) surrounded by the cavernous sinus 541 with five cranial nerves 503-507, internal carotid artery 510, and is easily accessible for electrical stimulation as described in our invention through the sphenoid sinus.

The sphenoid sinus is about 2 cm high, 2 cm wide and 2.1 cm antero-posteriorly. The sphenoid sinus communicates with the sphenoid-ethmoidal recess behind the olfactory mucosa (Fig. 3, 4, 13) in the upper part of the nose through this ostium. It is through this ostium that a distal portion of the device as described herein, i.e., a distal portion of the insertion end of the described device, can be

inserted for treatment of various neurological diseases including Alzheimer's. If needed, the ostium diameter can be enlarged with a dilator without damage to any vital structures which are not in close proximity to the ostium, to facilitate the entry and placement of a distal portion of the inventive device. The posterior ethmoidal blood vessels supply the sphenoid sinus. The lymph is drained by retropharyngeal lymph nodes. The sphenoid sinus is innervated by the posterior ethmoidal nerve and orbital branch of the sphenopalatine ganglion. It is related to the pituitary gland and hypothalamus above and on each side of the sinus and is walled by the cavernous sinus containing carotid arteries, perforating blood vessels, internal carotid artery and the five cranial nerves.

The pituitary gland is located inside the sella turcica in a round bony cavity that is separated from the sphenoid sinuses by a thin plate of bone; the floor of the sella turcica forms part of the roof of the sphenoid sinuses (Figs. 2-5, 12, 13, and 15). On either side of the sphenoid sinus is located a pair of intercommunicating venous channels called the cavernous sinuses connected to the brain stem and orbital part of the brain around the infundibulum. Several important nerves and vascular structures pass through the cavernous sinus between the venous channels; these play an important role in conduction of electrical impulses from our inventive device from the sphenoid sinus to the brain and brain stem: They are:

i. The internal carotid artery (#510) which forms a major part of the Circle of Willis
ii. The ophthalmic division of the trigeminal nerve (V1-505)
iii. The maxillary division of the trigeminal nerve (V2-507)
iv. The occulomotor nerve (III 503)
v. The trochlear nerve (IV-504)
vi. The abducens nerve (VI-506)

Immediately below the sphenoid sinus embedded in the upper most part of lateral wall is the sphenopalatine ganglion with extensive connections (Figs. 2, 3). Above the sinus is the pituitary gland with infudibulum connected to the hypothalamus, thalamus, and the rest of the brain through the thalamic radiation, which transmit electrical impulses delivered through a device and method as described.

The pituitary gland is connected to the hypothalamus, thalamus, central gray, reticular system, hippocampus, parahippocampal gyrus, cingulate gyrus, and cortical centers through the thalamic projections. The basal ganglion, red nucleus, and substantia nigra are in close proximity to the hypothalamus and are inter-linked. The electrical impulses imparted to the pituitary gland spread to the above brain structures and play an important role in the treatment of Alzheimer's, and other nervous system diseases.

The pituitary gland rests immediately above the thin sphenoid bone, which will allow the electrical impulses to be transmitted to the surrounding above described brain structures.

In recent years, a number of devices have been developed for insertion into the human body cavities, and hollow tubes (BV) to treat a particular problem including the dilation of coronary blood vessels and stimulation of the heart and spinal cord. The miniaturization of various devices has made this possible. This inventive device, once described as to its structure, utility, and details of use and operation, is of a type that can be manufactured using known methods and materials and as now described herein can be useful to treat Alzheimer's and other neurodegenerative diseases.

ANATOMY OF THE OLFACTORY MUCOSA, OLFACTORY NERVES AND OLFACTORY BULB AND ITS CONNECTION TO CNS CORTICAL CENTERS FOR THE TREATMENT OF ALZHEIMER'S AND OTHER NEURODEGENERATIVE DISEASES, USING THE DESCRIBED DEVICE

The olfactory epithelium is a specialized epithelial tissue inside the nasal cavity that is involved in perception of smell located in the dorsoposterior aspect of the nasal vault. Because the olfactory neural cells are the only surface neural cells in the body, olfactory mucosa is considered in this aspect, as a "window to the brain."

Interestingly, the human adult olfactory mucosa is a potential source of olfactory ensheathing cells and multipotent neural stem cells. They have been used in autologous transplantation therapies aimed at the treatment of degenerative or traumatic conditions of the central nervous system, spinal cord injury or Parkinson's disease (Mackay-Sim A et al (2008) Autologous olfactory ensheathing cell transplantation in human paraplegia: a 3-year clinical trial. Brain 131(Pt 9):2376–

2386. Murrell W et al (2005) Multipotent stem cells from adult olfactory mucosa. Dev Dyn 233(2):496–515). It is demonstrated that the anatomical configuration of the nasal cavities affects the olfactory airflow, and the fraction of the air stream entering the naris that reaches the olfactory cleft is only between 10 and 15% (Hornung DE (2006) Nasal anatomy and the sense of smell. Adv Otorhinolaryngol 63:1–22. Hahn I, Scherer PW, Mozell MM (1993) Velocity profiles measured for airflow through a large-scale model of the human nasal cavity. J Appl Physiol 75(5):2273–2287). That is why to deliver most of the therapeutic agents to olfactory mucosa, a special delivery catheter and ordinary sprays result in depositing in respiratory mucosa, not in olfactory mucosa.

Humans have about 10 cm^2 (1.6 sq inch) of olfactory epithelium. Olfactory mucosa in humans lies on the roof of the nasal cavity about 7 cm above and behind the nostrils. The human olfactory mucosa consists of a pseudo-stratified columnar epithelium resting on a highly cellular lamina Propria. Olfactory epithelium consists of 4 distinct cell types:

1. Olfactory cells of the epithelium are bipolar neurons, which congregate to form the olfactory nerve (cranial nerve I). They are responsible for conducting the electrical impulses to the olfactory bulb and rest of the CNS. As they emerge to the lamina propria, they form up to 20 olfactory nerve fasciculi surrounded by Perineural epithelium and sub Perineural epithelial space, which conduct the therapeutic agents to the SAS and CSF surrounding the olfactory bulb. From there, the therapeutic agents are transported to the rest of the CNS (Shantha T.R. and Yasuo Nakajima. Histological and Histochemical Studies on the Rhesus Monkey (Macaca Mulatta) Olfactory Mucosa. Yerkes Regional Primate Research Center, Emory University, Atlanta, Georgia: Z. Zellforsch. 103, 291-319 (1970).
2. Supporting cells: Analogous to neural glial cells are the supporting cells (sustentacular cells) of the olfactory epithelium.
3. Microvillar cells: They were first described in 1982, and hypothesized as a second morphologically distinct class of chemoreceptor in the human olfactory mucosa. However, their putative role in the olfaction has not yet been definitely demonstrated.
4. Basal cells divided into two types.

a. The horizontal basal cells line the olfactory epithelium and the slightly more superficial globose basal cells thought to be the primary stem cell.
b. Brush Cells resting on the basal lamina of the olfactory epithelium, are stem cells capable of division and differentiation into either supporting or olfactory cells. The constant divisions of the basal cells lead to the olfactory epithelium replaced every 2-4 weeks.

Bowman's (olfactory) Glands deliver a protenacious secretion via ducts onto the surface of the mucosa. The role of the secretions is to trap and dissolve odiferous as well as therapeutic agents to transport to the bipolar neuronal pathways, Perineural epithelium, sub Perineural epithelial space to the olfactory bulb, SAS and CSF.

Stimulation of the olfactory nerves in the olfactory mucosa (see FIGS. 2-5, 13-15) results in transmission of electrical impulses to the olfactory neurons, olfactory nerve fasciculi, olfactory bulb, and olfactory tract to various nuclei in the CNS as shown in the figure 14. Examples of devices capable of delivering therapeutic agents to treat Alzheimer's and other neurological diseases with adjuvant therapeutic agents and insulin delivered to the olfactory mucosa, is described in U. S. Patent Application Publication Number: 2012/0323214 AD by Dr. Shantha, the entirety of which is incorporated herein by reference. The combination of olfactory nerve stimulation and delivery of therapeutic agents through the olfactory mucosa is the most important method of treatment for Alzheimer's, senile dementia and other CNS diseases.

Hundreds of studies have shown that the olfactory mucosa with olfactory nerves transports many therapeutic agents directly to the brain by passing the BBB. Hence, it is a useful anatomical site besides electrical impulses delivery to the CNS, and for the delivery therapeutic agents with or without producing Iontophoresis and electroporation described in U. S. Patent Application Publication Number: 2012/0323214. The device described herein can optionally incorporate Iontophoresis and electroporation stimulation applied to olfactory mucosa to cause the olfactory mucosa open up (leaky) to deliver large molecules to the CNS by bypassing BBB.

ANATOMY OF SPHENOPALATINE GANGLION AND ITS CONNECTION TO THE CNS CORTICAL, AND BRAIN STEM CENTERS FOR THE TREATMENT OF ALZHEIMER DISEASE USING THIS INVETIVE DEVICE (FIGS. 1-5, 13, 15)

The sphenopalatine ganglion (synonym: SPG, Meckler's ganglion, ganglion pterygopalatinum, nasal ganglion, pterygopalatine ganglion,) is the largest parasympathetic ganglion in the body found in the pterygopalatine fossa associated with the branches of the maxillary nerve (Fig. 2). The sphenopalatine ganglion supplies the lacrimal gland, paranasal sinuses, glands of the mucosa of the nasal cavity and pharynx, the gums, and the mucous membrane and glands of the hard palate and cerebral blood vessels, which form the Circle of Willis and its branches. It gets many nerve connections from CNS to ganglion and back, which transmit electrical impulses to the CNS. When we say the stimulation of sphenopalatine ganglion, it includes any and all of these communicating branches of the ganglion described herein. Sphenopalatine ganglion receives a sensory, a motor, parasympathetic, and sympathetic roots. Activation of the ganglion is believed to cause vasodilatation of these blood vessels as described in US 7,640,062 B2. Such stimulation opens the pores in the vessel walls of the cerebral BBB blood vessels due to the dilatory effect, causing plasma proteins and therapeutic agents to extravasate to neuropil. This effect allows easy transport of molecules from within these blood vessels to surrounding tissue and from the neuropile back to the circulation, thus facilitating the removal of neurotoxin compounds, which are involved in Alzheimer's disease.

The stimulation of olfactory mucosal nerves, sphenopalatine ganglion, trigeminal nerves, pituitary gland with hypothalamo hypophysial tract, cause an increased clearance of the substance from cerebrospinal fluid such cytokine, and RNA fragments, neurotoxins and others which act as marker of neuronal pathology resulting in Alzheimer's and other neurodegenerative diseases.

The main object of the present invention is to deliver the electrical impulses to activate the Alzheimer's afflicted brain and reset the function of the CNS at neuronal and synaptic level (by increasing the electrical conductivity and reducing the inflammation). The present invention also provides a method and apparatus for

delivery of electrical impulses by stimulation of the olfactory nerves, sphenopalatine ganglion, trigeminal nerves, pituitary gland with hypothalamo hypophysial tract, five cranial nerves on each side, and their outgoing parasympathetic connection to cerebral BV. Methods and devices as described can also be optionally used to deliver therapeutic agents directly to the CNS through the olfactory mucosa by passing the BBB.

Stimulation as described herein of one or more of olfactory mucosal nerves, sphenopalatine ganglion, trigeminal nerves, pituitary gland with hypothalamo hypophysial tract, may lead to increased clearance of the substance from cerebrospinal fluid for example amyloid, tau, cytokine, and RNA fragments, which act as a marker of neuronal death resulting in Alzheimer's and other neurodegenerative diseases.

The middle and anterior cerebral arteries provide the blood supply to the cerebral hemispheres, including the frontal and parietal lobes in their entirety, the insula, the limbic system, and most of the temporal lobes, internal capsule, basal ganglia, and thalamus. These structures are involved in many of the neurological and psychiatric diseases of the brain. Hence, certain embodiments of methods and devices as described herein can involve providing improved blood supply and drug delivery to these structures. There is a presence of parasympathetic innervations in the posterior cerebral and basilar arteries from the sphenopalatine ganglion resulting in the above described therapeutic agents' delivery and effects due to BV dilatation and leakage development in the BBB.

A function of the present invention is to deliver the electrical impulses to activate the silent Alzheimer's afflicted brain, their neurons, and synapses. According to certain embodiments described methods and apparatus also deliver therapeutic molecules bypassing the BBB. It is accomplished by this inventive device due to stimulation of the olfactory mucosal nerves, sphenopalatine ganglion, trigeminal nerves, pituitary gland with hypothalamo hypophysial tract, five cranial nerves on each side, and their outgoing parasympathetic connection to cerebral BV to make them more permeable to large molecules from within the cerebral BV.

The afferent fibers innervate from the cranial nerves that are stimulated by our method include several midbrain, pons and medullary structures; and their

nucleus including the tractus solitarius (NTS). They receive most of the afferents and bilateral inputs of all cranial afferents. The cranial nerve nuclei stimulated has widespread projections, including direct or multiple synaptic projections to the parabrachial nucleus, vermis, inferior cerebellar hemispheres, raphe nuclei, periaquaductal gray, locus coeruleus, thalamus, hypothalamus, amygdala, nucleus accumbens, anterior insula, infralimbic cortex, and lateral prefrontal and temporal cortex. Brain functional imaging studies show that stimulation of these cranial nerves bring about changes in several areas of the brain, including the thalamus, cerebellum, orbitofrontal cortex, limbic system, hypothalamus, basal ganglion and medulla.

The stimulation of particular areas of the brain has been suggested as a mechanism for the effects of vagus nerve stimulation, but such localized stimulation of the brain may depend upon the parameters of the stimulation (current, frequency, pulse width, duty cycle, etc.). These parameters may determine which neurotransmitters are modulated including norepinephrine, seratonin, and GABA (Mark S. George, Ziad Nahas, Daryl E. Bohning, Qiwen Mu, F. Andrew Kozel, Jeffrey Borckhardt, Stewart. Mechanisms of action of vagus nerve stimulation (VNS). Clinical Neuroscience Research 4 (2004) 71-79; Jeong-Ho Chae, ZiadNahas, Mikhail Lomarev, Stewart Denslow, Jeffrey P. Lorberbaum, Daryl E. Bohning, Mark S. George. A review of functional neuroimaging studies of vagus nerve stimulation (VNS). Journal of Psychiatric Research 37 (2003) 443-455; G. C.Albert, C. M. Cook, F. S. Prato, A. W. Thomas. Deep brain stimulation, vagal nerve stimulation and transcranial stimulation: An overview of stimulation parameters and neurotransmitter release. Neuroscience and Biobehavioral Reviews 33 (2009) 1042-1060; Groves D A, Brown V J. Vagal nerve stimulation: a review of its applications and potential mechanisms that mediate its clinical effects. Neurosci Biobehav Rev (2005) 29:493-500; Reese TERRY, Jr. Vagus nerve stimulation: a proven therapy for treatment of epilepsy strives to improve efficacy and expand applications. Conf Proc IEEE Eng Med Biol Soc. 2009; 2009:4631-4). The most important effects of electrical stimulation are to inhibit inflammation by inhibiting the cytokines, increase acetylcholine in the brain content and other neurotransmitters including epinephrine, facilitate the removal of the Aβ from the neuropile, prevent further

apoptosis of neurons, improve the mitochondrial, endoplasmic reticulum and nuclear function by increasing the production of proteins, and amino acids involved in memory and cognition.

This invention is used to deliver electrical impulses directly to the CNS through the ORE by passing the BBB by making the CNS blood vessels leaky.

Optional therapeutic agents that may be delivered in combination with the described electrical stimulation of nerve fibers, using an electrical stimulator-catheter system as described to treat Alzheimer's disease are numerous. Some of them are:

I. glutamate receptor antagonist, and
II. an NMDA-receptor blocker for example ketamine and others;
III. β- amyloid inhibitor,
IV. bexarotene which increases the production of a fat-protein complex, apolipoprotein E, that helps to clear excess β amyloid form the brain,
V. an Alzheimer's vaccine;
VI. anti-inflammatory drugs;
VII. a microglial activation modulator;
VIII. a cholinesterase inhibitor, acetylcholine enhancer;
IX. various nerve growth factor, brain-derived neurotrophic factor,
X. gangliosides,
XI. phosphatidylserine (PS),
XII. fibroblast growth factor,
XIII. insulin,
XIV. insulin like growth factors (IGF-1),
XV. ciliary neurotrophic factor and glial derived nexin;
XVI. antioxidant; hormones; Vitamin B_{12} and B Vitamins,
XVII. an inhibitor of protein tyrosine phosphatases;
XVIII. endogenous protein for instance albumin and memory enhancing nerve growth factors to protect the brain from neurodegenerative diseases,
XIX. anti tumor necrosis factors, (TNF), anti cytokines therapeutic agents-monoclonal antibodies, chemotherapeutic agents, and

XX. A range of known therapeutic agents, as well as other pharmaceutical, biochemical, nurticeuticals, and biological agents or compounds including stem cells which have curative or curtailing effect on Alzheimer's and other neurodegenerative CNS diseases.

THE ADVANTAGES OF OLFACTORY REGION, SPHENOID SINUS, POTUITARY GLAND, AND CRANIAL NERVES I, III, IV, V, AND VI, INTERNAL CAROTID ARTERY, SPHENOPALATINE GANGLION AND TRIGEMINAL NERVE DELIVERY OF ELECTRICAL IMPULSES AND ADJUVANT THERAPEUTIC AGENTS FOR THE TREATMENT OF ALZHEIMER'S AND RELATED DISEASES BY THIS INVENTION DESCRIBED BELOW.

This present invention describes a method of use of electrical impulses through the above described anatomical regions transmitted and transported to the CNS to curtail Alzheimer's disease and other related diseases. These regions can also be used for administration of insulin, IGF-1 (7.65kDa) protein neurotrophic factor, vitamin A related compound bexarotene, to remove B amyloid, acetylcholine esterase inhibitors, and various adjuvant pharmaceutical, biochemical, nurticeuticals, and biological agents or compounds developed or being developed to treat Alzheimer's and neurodegenerative diseases in conjunction. The advantages of this invention are as follows:

a) Due to the close proximity of the olfactory nerves, sphenopalatine ganglion and its branches, and trigeminal nerves, pituitary gland, hypothalamus, it is easy to stimulate the central nervous system by transmitting electrical impulses (Figs. 1-5, 11-15) through these neural pathways;

b) Ease and convenience: This method is easy to use, painless, does not require strict sterile technique, intravenous catheters or other invasive devices; methods can be performed without the use of general anesthetic on a patient, and on an outpatient basis;

c) It is immediately and readily available to all patients at all times;

d) High therapeutic efficacy: Due to the achievement of higher local concentration of electrical impulses in the CNS through the rich nerve plexus delivered to disease afflicted areas of the CNS;

e) Increased efficacy of its use along with optional adjuvant therapeutic agents: Due to the ability of the administered therapeutic molecule to reach the target tissue without degradation caused by digestive enzymes, hepatic or systemic circulation (first phase metabolism); and the ability of the insulin to augment and amplify the effects of other therapeutic agents used to treat CNS disease;

f) Fast onset of action: Due to their proximity to the CNS, the site where they are needed and most of the therapeutic modality reach the CNS within seconds to minutes;

g) The inventive devise can be used for long duration;

h) It has fewer side effects, if any;

i) Due to improved delivery of the therapeutic electrical pulses or signals to the CNS, the site of the disease, benefits are felt without delay; and has anti inflammatory effect thus reducing the subtle brain inflammation that contributes to the disease conditions.

j) The advantage of using this invention of electrical impulse delivery in the above-described regions is that it does not require any modification of the device or the use of therapeutic agents;

k) It is low cost, patient and healthcare provider friendly, hardly invasive, non injected, and is a safe method when used appropriately; and,

l) Electrical impulses can also act as iontophoresis, and electroporation of the olfactory mucosa, sphenopalatine ganglion and sphenoid sinus lining, thus augmenting the uptake of therapeutic agents from these regions to be delivered to the CNS by passing the BBB in the treatment of Alzheimer's and other neurological diseases.

Caution: Exercise cautions when using the device in epileptics, they should be under control to use this device. On the other hand, it can be of use to send counter pulses to treat status epilepticus, to counter the brain electrical activity. Its use may have effect on smell (anosmia). Nasal congestion due to cold or allergies, sinus pathology, tumors, and nasal septal diseases may interfere with the introduction of device, but are not contraindications to use this inventive device to treat Alzheimer's disease.

DETAILED DESCRIPTION OF THE DIGRAMS EXPLAINING THE INVENTON TO TREAT ALZHEIMER'S AND HOW THE THERAPEUTIC AGENTS REACH THE CNS TO CURTAIL THE DISEASE

With reference now to the various figures in which identical embodiments are numbered alike throughout the description of the preferred devices and techniques of the present invention presented below. These diagrams represent examples of the present invention and describe how electrical impulses are delivered to CNS to treat CNS diseases including Alzheimer's and deliver the impulses to reach the site of pathology in the CNS to curtail the affliction. While preferred embodiments of the present invention have been described, it should be understood that various changes, adaptations, and modifications may be made thereto. It should be understood, therefore, that the invention is not limited to details of the illustrated invention.

FIG. 1 is the diagram of the lateral and medial wall of the nasal cavity 100 reflected back at cribriform plate of the ethmoid bone 8. It shows ORE (olfactory nerves) with various nerve structures (shown in black surface with white lines) with which electrical impulses come in contact, then are conducted to the CNS to the brainstem, hippocampus, entorhinal cortex, thalamic, hypothalamic, cerebral cortical centers, cerebellum and other cortical neuropil (see FIG. 14). The olfactory tracts are connected to the entorhinal cortex (EC) located in the medial temporal lobe (area 28, and 34 of the brain). The entorhinal cortex is one of the first areas affected in Alzheimer's disease. It functions as a hub in a widespread network for memory and navigation-routing of impulses. The EC is the main interface between the hippocampus and neocortex. The EC-hippocampus system plays an important role in autobiographical/declarative/episodic memories and in particular spatial memories including memory formation, memory consolidation, and memory optimization. Electrical impulses transmitted to this area from an inventive device as described have a remarkable therapeutic effect on Alzheimer's patients and senile brain atrophy, as well as other neurodegenerative diseases.

Note the olfactory mucosa (OM) with olfactory receptor and its nerve fasciculi 2, 5, cover extensive areas of the medial 3 and lateral 4 wall of the upper part of the nasal cavity, which is separate from the respiratory part of the nose, and

pass through the cribriform plate of the ethmoid bone 8 to the olfactory bulb. This region also contains the sphenopalatine ganglion (Pterygopalatine) 6 with its extensive central and peripheral connecting branches (see Fig. 2 below). This ORE 2, 5 is also surrounded by anterior ethmoidal nerves 7 connected to the ophthalmic branch of the trigeminal nerves. The therapeutic agents and electrical impulses delivered through this invention pass on to the CNS through the olfactory nerves, trigeminal nerve branches 7 (CN V), III, IV, V (V1-2), VI th Cranial nerves 359, and sphenopalatine ganglion 6 that supply the upper third of the nasal cavity close to the olfactory mucosa, pituitary gland 362 and sphenoid sinus 361 with 10 cranial nerves in its wall located in the cavernous sinus. The therapeutic delivery of electrical impulses delivered through this invention is passed on to the CNS through the olfactory nerves, trigeminal nerve branches, III, IV, V, VIth Cranial nerves, and sphenopalatine ganglion that supply the upper third of nasal cavity close to the olfactory mucosa. The CSF (cerebrospinal fluid) in the SAS (subarachnoid space) surrounding the olfactory bulb also conduct the electrical impulses and therapeutic agents to the brain surface from short olfactory nerves in the treatment of Alzheimer's and other neurodegenerative diseases.

FIG. 1a is the diagrammatic presentation 100a showing vestibule 375, respiratory nasal mucosa 376 with olfactory nerve and olfactory mucosa 377 of the lateral and medial walls of the olfactory mucosal nerve area of the nose (ORE). The arrows point to the spread of electrical impulses and therapeutic agents from the ORE 377 to the CNS. Note to get the maximum delivery of therapeutic agents to the ORE, the head should be extended as shown in the diagram and electrical impulses delivered to the ORE 377 using the special delivery catheter described herein. Just passing electrical impulses through the vestibule 375 and the respiratory mucosa 376 is not effective for the treatment of Alzheimer's disease. The therapeutic dose of electrical impulses and therapeutic agents' delivery catheter and Iontophoresis device are placed on the ORE 377 to treat Alzheimer's disease.

FIG. 2 is the diagram of the lateral wall of the nasal cavity 200 showing how various nerve structures that the therapeutic electrical current (and optional therapeutic agents) delivered by a device as described come in contact with and are transported to the CNS through nerve fasciculi of the nerve structures located in the

ORE, and sphenoid sinus (525) through the sphenoid ostium 524. The subarachnoid space (SAS) and the cerebrospinal fluid (CSF) surrounding the nerve fasciculi and olfactory bulb also conduct the electrical impulses to the surface of the brain. The therapeutic delivery of electrical impulses passes through the olfactory bulb 35 transported by the olfactory mucosa and olfactory nerves 105 passing through the cribriform plate of the ethmoid bone 8. The electrical pulse and stimulus are passed on to the CNS through the trigeminal nerve 118, external nasal nerve 116, the anterior ethmoidal nerve 117; and from the sphenopalatine ganglion 110 to the greater petrosal nerve 119, nerve of the pterygoid canal 111, pterygopalatine and pharyngeal nerve 112, lesser palatine nerve 114, greater palatine nerve 115, nasopalatine nerves 109, parasympathetics to the internal carotid artery 510 many cranial nerves immediately adjacent to the lateral wall of the sphenoid sinus 525. The sphenopalatine ganglion 112 neuronal center is located in the brain behind the nose (see Fig. 13). Besides the above branches, it consists of parasympathetic neurons innervating the Circle of Willis (middle cerebral, anterior cerebral, vertebral, basilar, posterior cerebral arteries and their lumen). Activation of this ganglion causes the vasodilatation of these vessels in the Circle of Willis including the basilar and posterior cerebral arteries. A second effect of such stimulation is the opening of pores in the vessel walls, breaking of the BBB causing plasma proteins and therapeutic agent's extravasations to neuropil. This effect allows better transport of molecules from within these blood vessels to surrounding nerve structures in the treatment of Alzheimer's.

The olfactory mucosa and olfactory nerves 105 and 10 cranial nerves adjacent to the sphenoid sinus (see Fig. 13) play a major role in delivering electrical impulses and therapeutic agents in the treatment of Alzheimer's in this invention by bypassing or overcoming the BBB (diagram modified after Grays Anatomy).

FIG. 3 is the diagram of the medial wall of the nasal cavity 300 and nerve structures located in the olfactory anatomical region. Various nerve structures on the medial wall of the nose conduct the electrical impulses to treat Alzheimer's as this invention comes in contact, and are transmitted to the CNS from the upper part of the nose from the ORE 106 and the 10 cranial nerves adjacent to the two outer walls of the sphenoid sinus 524. The electrical impulses of this invention are

conducted through the olfactory nerves, through the cribriform plate of the ethmoid bone 8 to the olfactory bulb 35. The nerve impulses pass from the olfactory mucosa 106 and the 10 cranial nerves adjacent to the wall of the sphenoid sinus 525 to the various centers of the brain and cortex, especially the temporal and prefrontal and orbital cortex, the front part of the brain stem through the olfactory tracts 36, 38 as well as to the cerebellum (see FIG. 14). Olfactory nerves are the shortest of the cranial nerves, hence it is easy for them to carry the electrical impulses to the olfactory bulb, and the impulses connect to the CNS without decay.

The axons and dendrites of the olfactory tract transport the therapeutic delivery of electrical impulses to the brain centers involved in Alzheimer's disease. The electrical impulses also pass through the trigeminal nerve branches and sphenopalatine ganglion 110 that supply the nasal cavity through the anterior ethmoidal nerve 107, nasoplatine nerve 109, medial, posterior and superior nasal branches 108 and the sphenopalatine ganglion 110 and its branches to reach the circle of Willis to reach the brain stem cranial nerve nuclei. The electrical impulses also pass from the sphenoid sinus to pituitary gland 509, a rich vascular network surrounding the gland 511and pituitary stalk 512; pituitary hypothalamo-hypophysal tract 512, hypothalamic nuclei 513, and thalamic centers 514 and then to the cortical radiation of the entire brain. Note how easy it is to get into the sphenoid sinus 525 through sphenoid ostium 524 located behind the olfactory mucosa (diagram modified from Grays Anatomy).

FIG. 4 is the drawing of the nasal cavity diagram 400 showing the nerve structure locations involved in the transmission of electrical impulses to the brain using this invention. The electrical impulses are conducted to the CNS from the olfactory mucosa 45, olfactory mucosal nerves 44, olfactory nerve fasciculi 105, olfactory bulb 35, and medial and lateral olfactory tracts 516. The electrical impulses transmitted through the trigeminal nerve branches including anterior ethmoidal nerve 107, from the sphenopalatine ganglion and its branches 110, parasympathetic supply from the sphenopalatine ganglion to Circle of Willis 510, pituitary gland 509, rich portal blood system of the pituitary gland 511, hypothalamo-hypophysal tract 512, hypothalamic nuclei 513, and thalamic radiation 514 (insert 4A). Note the presence of five cranial nerves 515 (CN III, IV, V, and

VI) on each side of the sphenoid sinus that conduct the electrical impulses to the CNS in the treatment of Alzheimer's and other neurodegenerative diseases.

FIG. 5 is the diagrammatic presentation 500 of the ORE with similar explanation of the regions as FIG. 4. It is showing the pituitary gland 509 (see insert 5A), sphenopalatine ganglion 110, olfactory mucosa with olfactory nerves, olfactory mucosal nerves 44, olfactory bulb 35 being electrically stimulated by electrical output manipulator control box 517. The power source is contained within this pulse generator box, and generates a battery powered current delivered through the conducting wires 518 which will send electrical impulses to the CNS for the treatment of Alzheimer's and other neurodegenerative diseases.

According to methods as described, electrical impulses are transmitted to the CNS from the trigeminal nerve branches including anterior ethmoidal nerve107 sphenopalatine ganglion and its branches 110, parasympathetic supply from the sphenopalatine ganglion to Circle of Willis 510, pituitary gland 509, rich portal blood system of the pituitary gland 511, hypothalamo-hypophysal tract 512, hypothalamic nuclei 513, and thalamic radiation 514 (insert 4A). Note the presence of five cranial nerves 515 (CN III, IV, V, and VI) on each side of the sphenoid sinus that conduct the electrical impulses to the CNS in the treatment of Alzheimer's and other neurodegenerative diseases.

FIG. 6 is the diagrammatic presentation 600 of this inventive device 220 designed to stimulate the ORE and deliver therapeutic agents. It has electrical output manipulator 517 attached to the olfactory stimulator part 520 passing the conductive wires through the main body of the device 518. It has balloon 519, capable of being inflated while the device is positioned in the ORE with the insertion end at a trans-nasal location. This balloon will prevent the trauma to the delicate nasal mucosa as the device is advanced to the ORE through the external nasal opening. The balloon is connected to the inflating syringe 522. The balloon is inflated with air or sterile liquid or gel and the size of the balloon can be adjusted according to the size of the patient's nose. The device connected to the therapeutic agents delivery syringe 521 which delivers them through the electrical current delivery part of the device 520 pores if needed in the treatment of Alzheimer's and other diseases. This catheter acts as iontophoresis and electroporation with simple

modification to facilitate the delivery of therapeutic agents to the CNS by passing the BBB. The tip of the inventive device is provided with radio opaque marker 540 to identify the position of the catheter in the sphenoid sinus and/or on the olfactory mucosa after insertion and during insertion with radiographic examination. The device embodiment of figure 6 does not include a opening or injection orifice at the insertion end of the device that would allow for a fluid such as a fluid containing a therapeutic agent, to be dispensed from the device at the insertion end, such as to tissue of the olfactory mucosa, sphenoid sinus, or both.

FIG. 7 is the drawing of the medial wall of the nose 700, showing various structures of the described device (e.g., catheter) 220, that may be stimulated by the nasal stimulator device to transmit electrical pulses to the CNS. The insertion end of the device is placed at a trans-nasal location. The tip of the electrical impulses delivery device is positioned in the sphenoid sinus through the ostium of the sphenoid sinus 524. This positioning between the sphenoid sinus and the nasal balloon 519 will keep the proximal stimulating part of the device 520 located firmly in the desired location i.e. on the olfactory mucosa close to the cribriform plate of the ethmoid bone immediately below the olfactory bulb 35. The electrical impulses also pass (spillover effect) from this device to sphenopalatine ganglion 110 and to the anterior ethmoidal nerve 107. Optional injection port 522 is used to pass guide wire 523 to facilitate placement of this device with ease. Syringe with three way stop cock 521 can be used to deliver therapeutic agents to the olfactory mucosa through the catheter. The device insertion is facilitated by the use of flexible fiber optic nasal scope and guide wire 523. The desired current is delivered through the electrical output manipulator 517. The power source is contained within this pulse generator box and generates a battery powered current delivered through conducting wires 518, which send electrical impulses to the CNS for the treatment of Alzheimer's and other neurodegenerative diseases. The electrical current passes to the CNS through the pituitary gland 509.

FIG. 8 is the view of diagram 800 showing catheter 220 with two balloons holding the electrical impulses delivering part of the device 520 in position between the sphenoid sinus with a balloon 525 and nasal balloon 519 without movement at the olfactory region, i.e., in the insertion end is in a trans-nasal location. The syringe

526 inflates the balloon in the sphenoid sinus 525 and the balloon in the nose 519 is inflated by the inflator 522 to hold the electrical impulses delivery on the olfactory mucosa (ORE) to the CNS in position especially in patients who are difficult to control. It is also provided with a guide wire port with a guide wire 523 to facilitate the insertion of this device and place it in the desired position. The device is connected to optional therapeutic agents delivery syringe 521, which is capable of delivering therapeutic agent to the interior of the nasal cavity through one or more external openings or apertures present along the shaft at the electrical current delivery part of the device 520 in the treatment of Alzheimer's and other diseases. The diagram also shows the proximity of portions of device 520 to the anterior ethmoidal nerve 107, olfactory mucosa 44, olfactory bulb 35, pituitary gland 509, and the sphenopalatine ganglion 110. The electrical impulses' spillover stimulates these structures. The rest of the explanation is the same as FIGS. 5 and 6. The olfactory mucosa is being electrically stimulated by electrical output manipulator control box 517. The power source is contained within this pulse generator box and generates a battery powered current delivered through the conducting wires 518 which will send electrical impulses to the CNS for the treatment of Alzheimer's and other neurodegenerative diseases.

FIG. 9 is the diagrammatic presentation 900 of the electrical impulse delivery device (catheter) 220. This diagram shows three separate electrical impulses delivery methods to the nerve structure as described here. This device incorporates olfactory nerve stimulator 520, and sphenoid sinus stimulator 527 which can be placed in a patient to stimulate the five cranial nerves and the internal carotid artery (part of the Circle of Willis) in the wall of the cavernous plexus located on the lateral wall of the sphenoid sinus. Sphenoid sinus stimulator 527 also sends electrical impulses to the pituitary gland to distribute the electric signals to the thalamic radiation and wake up the brain in those suffering from the Alzheimer's and other CNS diseases. Sphenoid sinus stimulator 527 can also be provided with a sphenopalatine ganglion stimulator in the form of an extension electrode that extends or that can be extended at the distal part of the catheter to be placed adjacent to and deliver electrical impulses to stimulate this ganglion in the treatment of Alzheimer's and other neurological diseases. Including an extension electrode, three

separate electrical impulses delivery terminals can be activated through the electrical output manipulator 517 and connecting wires 518, at the same time, one at a time or two at a time as needed and depending on the tolerability and need of the patients. The balloons 519 and 520 can be expanded by using air or liquid by a tube in the interior connected through inflation stopcocks 521, 522 and 526 connected by a tube to the inflation syringe located outside the nose. The tip of the inventive device may be provided with radio opaque marker 540 to identify the position of the catheter in the sphenoid sinus and/or on olfactory mucosa after insertion and during insertion with radiographic examination. Injection port 522 is used to pass the guide wire 523 to facilitate placement of this device with ease.

FIG. 10 is the diagrammatic presentation 1000 of and embodiment of catheter device 220, which incorporates many features in the device. It has many of the features already described in FIGS. 7, 8, and 9. It shows the complete assembly of this inventive device to treat Alzheimer's disease. It has two balloons 519 and 527. The balloon 527 part has the insertion body or insertion end that may be is inserted in the human nose through the sphenoid foramina and then into the hollow sphenoid sinus optionally with the aid of a fiber optic nasal scope. The insertion body consists of two parts. One part is an inflatable outer membrane or balloon 527, which is adapted in size and flexibility to fit inside the sphenoid sinus cavity as illustrated in FIGS. 12, 3, and 15. The interior of this balloon 527 is connected to an inflation tube or inflation lumen, which in turn is connected through an inflation stopcock and a tube to the inflation syringe 521, 522, and 526. The inflation syringe 522 is used to pump air or fluid through the inflation tube to the interior of the balloon 527 so the balloon inflates to at least partially fill the sphenoid sinus cavity during the use of the apparatus. This embodiment includes additional syringe 529 (which is optional) with stopcock to deliver additional therapeutic agents. An infusion tube may also be connected to the interior of the balloon 527 and used to pump fluid at ambient, elevated, or low temperatures through the infusion tube and to the interior of the balloon during the operation of the apparatus. A device for heating or cooling the fluid to be pumped into the interior of the balloon 527 may also be included in the apparatus 530. The balloon 527 is provided with multiple electrical leads on the expandable exterior of the balloon as shown. The leads may

be attached to or part of an expandable structure that is for example in the form of a polymeric mesh or fabric or a wire mesh that is placed at a surface of balloon 527, and that is capable of expanding as the surface of balloon 527 is expanded, e.g., within a sphenoid sinus. These leads are connected by electrical connectors 517 to an electrical output manipulator 517. This electrical output device 517 is connected to a source of electricity. Electrical stimulus is provided through the electrical leads to stimulate the pituitary gland, pituitary hypophysal track and surrounding five cranial nerve structures and the internal carotid artery encased in autonomic nerves. It is accomplished by stimulating the interior surface of the sphenoid sinus cavity and its walls through the balloon surrounded by electrical conductor wires, including electrodes, which will in turn transmit electrical impulses to the above mentioned tissue structures for treatment of Alzheimer's and other diseases of the nervous system including pain. It also has electrodes 531 which come in contact with the sphenopalatine ganglion and transmit electrical impulses to it for treatment of Alzheimer's.

An optional catheter and liquid dispensing port or aperture can be located at on the surface or the center of the balloon (527) with a suitable tube to allow a administer drugs or other therapeutic agent or other fluid to be directly dispensed to the sphenoid sinus cavity, besides delivering the electrical impulses. The therapeutic agents are infused so that they are absorbed by the central nervous system directly across the sphenoid sinus walls into the perforating vessels, which empty into the cavernous sinus plexus and circulate in the BV of the CNS. This method allows us to use a small dosage of drugs instead of using large dosages systematically. The antibiotics and anticoagulants may be impregnated onto the surface of the balloon of the sphenoid sinus cavity to prevent clotting and infection. The tip of the inventive device is provided with radio opaque marker 540 to identify the position of the catheter in the sphenoid sinus after insertion and during use with radiographic examination. Injection port 522 is utilized to pass the guide wire 523 to facilitate placement of this device with ease.

All of the tubes and connectors to the balloon 527 can be assembled together in a connector assembly. The inner portion of this connector assembly constitutes

part of the insertion body. This assembly needs to be small in diameter and flexible for easy insertion through the nose and into the sphenoid sinus cavity ostium.

An optional temperature sensor wire can be connected to a temperature sensor and indicator. The temperature sensor wire is connected to sensors (not shown) in the balloon 527 to determine the temperature of the balloon surface and the structures in the immediate vicinity of it. This fluid within the balloon may be heated around 42°-44° C. or higher or cooled if so desired to stimulate or decrease the output of pituitary hormones, including growth hormone from the pituitary gland. Other means, for instance, a device embodying the Peltier 530 effect, can be used to heat or cool the outer surface of the balloon. Heating will enhance the conduction of electrical impulse and facilitate the stimulation of pituitary gland and other surrounding nerve structure.

FIG. 11 is the diagrammatic presentation 1100 of the longitudinal section of the olfactory bulb 1100 and the olfactory mucosa showing the route of electrical impulses transmission (and of transport of the insulin and other therapeutic agents) by the direct stimulation (application) of the olfactory mucosa in the treatment of Alzheimer's and other neurological diseases including autism. Electrical impulses and optional therapeutic agents pass through the olfactory nerves from the olfactory mucosa 45 transported through the subperineural epithelial space and olfactory axons to the olfactory bulb 35. The electrical impulses are also transmitted to the CNS to subarachnoid space (SAS) 36 after passing through the olfactory nerve fasciculi surrounded by perineural epithelium with CSF surrounding them. The SAS surrounding the olfactory bulb with its CSF is directly connected to the sub perineural epithelial space surrounding the olfactory nerve fasciculi 25 and other cranial nerves on the lateral wall of the sphenoid sinus which transmits the electrical impulses [Shantha et al: Z. Zellforsch. 103, 291—319 (1970). J National Cancer Inst 35(1):153-165 (1965). Expt Cell Res 40:292-300 (1965). Science 154:1464-1467 (1966). Nature 199, 4893:577-579 (1963). Nature, 209:1260 (1966). Histochemie 10:224-229 (1967).Structure and Function of Nervous Tissues. Volume I. pp 379-458]. The electrical impulses pass from receptor cells 44 and are transported through the axons, olfactory nerve fasciculi, retrograde through the cribriform plate of the ethmoid bone 43 to stimulate the olfactory bulb 35. From the

olfactory receptor cell axons 45, the electrical impulses travel through the olfactory glomeruli 40 to periglomerular cells 39, mitral cells 41, and granule cells 42, to olfactory tract 37, and reach the CNS 38 then to the entorihinal cortex. The electrical impulses then exert their effect on the entorhinal cortical neurons, synapses between the neurons; oligodendroglia, astroglia and microglia in the neuropil involved in the disease process of Alzheimer's and other neurodegenerative diseases.

This diagram shows that the inventive device 220 may be placed on the olfactory mucosa to stimulate the olfactory nerves to allow the stimulation to be transmitted to the central nervous system. The entorhinal part of the olfactory system is very much involved in the genesis of Alzheimer's and other neurodegenerative diseases and the electrical impulses from this inventive device reach this area through the olfactory bulb with ease.

The above described nerve structures can be electrically stimulated by electrical output manipulator control 517. The power source is contained within this pulse generator box, and generates a battery powered current delivered through the conducting wires which will send electrical impulses to the CNS for the treatment of Alzheimer's and other neurodegenerative diseases.

FIG. 12 is the view of diagram 1200 showing the anatomy of the sphenoid sinus 525 and its relation to the surrounding structures in the cavernous sinus 541, and possible route of electrical impulses passing to the CNS. The inventive device is passed through the sphenoid ostium 524 into the sphenoid sinus 525 and the balloon 527 is inflated. Note that the balloon has fine electrical conducting wires (including electrodes) surrounding that are capable stimulating the pituitary gland, five cranial nerves, autonomic nerves and internal carotid artery. In the illustrated embodiment there is Peltier device 530 within the balloon to heat or cool the fluid within the balloon if desired. It also has a temperature sensor connected to the monitor outside the nose (not shown). The electrical impulses are transmitted to cranial nerves III, IV, V, VI and nerves 503, 504, 505, 506, 507 in the cavernous sinus that carry the electrical impulses to the brain stem and basal ganglion. The parasympathetic (autonomic) nerves supplying the internal carotid arteries 510 (and the Circle of Willis) within the wall of the cavernous sinus are stimulated by this

inventive device, which makes them dilate within the BBB of the brain. This effect facilitates the transport of therapeutic agents within the BBB capillary plexus of the CNS and helps to remove the accumulated toxic substances within the neuropile. The tip of the inventive device is provided with radio opaque marker 540 to identify the position of the catheter in the sphenoid sinus after insertion and during use with radiographic examination.

The pituitary gland in the sella turcica also are exposed to electrical impulses transmitted to the pituitary gland 509, which also transmits impulses to arterio venous plexus 511, pituitary stalk 512, and hypothalamic nuclei 513 and to thalamic radiation 514 to the rest of the brain. The stimulation of the pituitary gland will have a profound effect on transmitting the electrical impulses and release of many trophic hormones from this master endocrine gland and hypothalamic nuclei. The pituitary gland is heated or cooled with the Peltier device within the balloon 530 to the desired temperature for the treatment of CNS disease.

FIG. 13 is the diagrammatic presentation 1300 of the coronal section of the sphenoid sinus with inflated balloon 527 inside the sinus and its anatomical relationship to five cranial nerves within the cavernous sinus 541 on both sides, pituitary gland in the sella turcica, hypothalamus, thalamic radiation, and internal carotid artery. In the diagram, the inventive device is positioned in one of the sphenoid sinus 525 passed through sphenoid sinus ostium 524, and the balloon 527 is inflated. The electrical impulses from the balloon are transmitted to cranial nerve III 503, CN VI 504, CN V_1 and V_2- 505, 507, and CN VI 506 and internal carotid artery 510, pituitary gland 509 with its portal system 511, pituitary stalk 512, with its connection to hypothalamus 513, and thalamus 514 (Insert 13A-511, 512, 513, 514). The insert 13A shows the detail of the structure, which gets stimulation from the electrical impulses from the sphenoid sinus. This inventive device delivers electrical stimulating impulses to these structures in the treatment of Alzheimer's and other neurological disease. Further, saline can optionally be infused from the catheter from pores at the end of the device, e.g., at or adjacent to balloon 527, and into the interior space of the sphenoid sinus; the saline can improve the strength of the electrical current, allowing improved transmission to the pituitary gland and its connection to cranial nerves and CNS.

It is important to note that when the hypertonic saline fills the sphenoid sinus; the process must wait for 30-60 minutes so that the saline saturates the mucosal and boney wall of the sphenoid sinus absorbing the salt solutions. By this method, the walls of the sphenoid sinus become more conductive to electrical pulses conducted to the surrounding structures including the cranial nerves in the cavernous sinus 541 pituitary gland 509. The tip of the inventive device can be provided with radio opaque marker to identify the position of the catheter in the sphenoid sinus or on the olfactory mucosa after insertion and during use with radiographic examination. It is important to note that the sphenopalatine ganglion 508 is located immediately close to the sphenoid sinus ostium which can also be directly stimulated with additional electrical circuitry as shown in the diagram.

FIG. 14 is the diagrammatic presentation 1400 and the catheter device 220 whose tip is placed at the olfactory mucosa 45 lining of the nose close to the cribriform plate of the ethmoid bone and the olfactory bulb 35 within the cranium situated immediately above cribriform plate of the ethmoid bone. The diagram shows the transmission of electrical impulses and route taken by the therapeutic agents deposited at the olfactory region of the nose (ORE) in this invention to treat Alzheimer's and other neurological ailments. The electrical signals (therapeutic agents as well) from the olfactory mucosa 45 are transmitted to the olfactory bulb 35 to subarachnoid space (SAS) to the cerebrospinal fluid (CSF) then to various centers of the CNS. The electrical impulses spread to the olfactory tract 46, to prefrontal cortex 47, medial olfactory area 48, to temporal lobes 50 (Entorhinal cortex), to lateral olfactory area 51 and its associated adjacent nuclei 49, hippocampus 52, hypothalamus 53, brain stem nuclei 54, to cerebellum 55. The arrows show the extensive area where the electrical impulses and adjuvant therapeutic agents spread from the ORE to the CNS. From the subarachnoid space, the therapeutic agents can be transported to the eyes 56 through the optic nerve subarachnoid space, and the electrical impulses can also be transmitted to the eyes' optic nerve and cranial nerve III, IV, V, and VI nerves.

FIG. 15 is the diagrammatic presentation of the medial wall 1500 of the sagittal section of the nose with this inventive device in place. The electrical impulse transmitter comes in contact with the olfactory mucosa 44, olfactory bulb

35, sphenopalatine ganglion 110, anterior ethmoidal nerve 107, pituitary gland 509 with its connection to the hypothalamus and thalamus, and its surrounding structures in the cavernous sinus with five cranial nerves 515 on each side and internal carotid artery 510.

The electrical impulses from the balloon are transmitted to cranial nerve on the adjacent wall of the sphenoid sinus and internal carotid artery 510, pituitary gland 509 with its portal system 511, pituitary stalk 512, with its connection to hypothalamus 513, and thalamus 514 (Insert 13A-511, 512, 513, 514). The insert 15B shows the detail of the structure, which gets stimulation from the electrical impulses from the sphenoid sinus. This inventive device delivers electrical stimulating impulses to these structures in the treatment of Alzheimer's and other neurological disease. Further, saline is infused from the catheter within the balloon 527 device and makes the electrical current more conductive and easier to be transmitted to the pituitary gland, and its connection to cranial nerves and CNS. The tip of the inventive device is provided with radio opaque marker 540 to identify the position of the catheter in the sphenoid sinus and /or on the olfactory mucosa after insertion and during insertion with radiographic examination. It has balloon 519, inflated while inserting and positioning the device in the ORE. A device for heating or cooling the fluid to be pumped into the interior of the balloon 527 may also be included in the apparatus 530.

Figure 16 shows the catheter (device) in sinus and the nose with the insertion end located in a trans-nasal location. Explanations of the dimension of the number given are as follows:

1. It indicates the dimension of the sphenoid sinus, which varies per patient and becomes bigger with advancing age. The height, breadth, and length of the sinus are around 2.2cm. That means it is about 1¼ to 1½ inches in all directions. So the catheter that enters the sphenoid sinus should be shorter, and may be a inch long (e.g., from 0.75 to 1.25 inch).
2. The ostium or the opening for the sphenoid sinus and diameter is not found in the literature. I do believe it is bout 2 to 4millimeter in diameter. It may be enlarged with a boogie or angocath dilator like catheter. It is mostly made of thin sphenoid bone. Even if it cracks, while dilating, had no consequence.

So the diameter of the catheter distal end with the balloon should be no more than 3 to 5 mm, e.g., from 2 to 6 millimeters.

3. This part of the catheter represents the distance of the roof of the nose which forms the olfactory mucosa and olfactory nerve. It is about 2.5 (e.g., 2.2 to 2.7) inches long and the catheter lodged at this part can be bit bigger in diameter than the part that enters the sphenoid sinus.
4. This part represents the anterior descending part of the nose. It is about ½ -¾ inches' long. No special features are needed.
5. This represents the length of the catheter that occupies the external nose as it emerges from the roof of the nose. The size of the nose varies. This portion of the device may be from about 2-3 inches long. Note there is a balloon at the junction of the # 4 and #5. It holds the catheter in place without moving downwards. It abuts against the middle concha of the nose.
6. Represents as the catheter emerges through the external nasal opening.
7. This is external part of the catheter. It can be any length. It can be between ± 9-12 inches to be placed in the pocket and connected to electrical output monitor.

Preferred devices may include a nasal fiber optic scope to position the insertion end of the catheter device.

Figure 17 shows the electrical stimulator catheter device in place with the insertion end located at a trans-nasal location, connected to expanding balloon and/or injections port. The device includes only a single injection port at the proximal (external) end, and no fluid delivery port at a location to deliver therapeutic fluid to olfactory mucosa.

Figure 18 shows an example of an assembled catheter in position with an insertion end located at a trans-nasal location. It has three syringes. One each to expand the balloon and third one (which is optional) to instill therapeutic agents into sphenoid sinus or olfactory mucosa surface. It can be used to inject antibiotics to prevent any sphenoid sinus infection also or other anti Alzheimer's disease therapeutic agents.

Figure 19 shows various embodiments of the electrical stimulation catheter that can be incorporated. As an optional feature, the electrodes of the distal end are

located on the expandable surface (e.g., balloon) and may be placed on an expandable mesh, such as an expandable wire, polymeric, or other type of natural or synthetic fabric or expandable sheet.

Figure 20 shows another embodiment of the electrical stimulation catheter placed in a trans-nasal location.

Figure 21 shows another embodiment of electrical stimulation with two balloon expanding syringes and electrical cell output monitor. The device does not include any port at the insertion end that will allow for delivery of a fluid, e.g., a therapeutic fluid, to the nasal cavity such as to the olfactory mucosa or sphenoid sinus; methods of using this device also do require delivery of therapeutic fluid to the nasal cavity.

The device (catheter) system described herein can be miniaturized and designed with a small diameter for insertion in the nose of children and teens to treat autism, cerebral palsy, Down syndrome and such related central nervous system diseases other than Alzheimer's disease.

It is a purpose and an intention of this invention to use the electrode stimulator system that is capable of conducting electricity with the least resistance and that the electrodes be made up of suitable conductive physiologically acceptable material, for example, silver, iridium, platinum, iridium alloy, titanium, nickel-chrome alloy or other suitable combination of conducting metal alloys. Each electrode can be insulated with a physiologically acceptable material such as polyethylene, polyurethane, or a co-polymer, which is a non-conductive, non-allergic, non-reacting synthetic or semi synthetic material. Each one of the electrodes can exhibit a smooth surface, except for the distal end of each such electrode. The ends can be optionally constructed to have a large surface area #110 to encounter the largest surface area of the olfactory mucosal nerves, sphenopalatine ganglion (SPG), trigeminal nerves, sphenoid sinus, and pituitary gland with hypothalamo hypophysial area. The amount of electrical current used for stimulation of the neurological structures described herein is conducted through these electrodes is controlled by a control pane in electrical output manipulator 517 as shown in other figure11 in order to keep the procedure within the desired parameters.

In addition, embodiments of described methods can also result in improving the oxygen supply to neurons and surrounding nerve structures due to parasympathetically mediated Circle of Willis blood vessels stimulation, which results in dilatation of the BBB BV of the brain and their supply to the neuropil. This will be a therapeutic agent in the treatment of Alzheimer's and other CNS diseases. The dilatation of BV also results in the breaking of the BBB and allows the therapeutic agents to enter the brain substance. This method facilitates the drug delivery to the neuropil without the sacrifice of change in the molecular weight and its configuration. It is important to note that the permeability does not remain for a long time and closes very rapidly after the electroporation and Iontophoresis effects, indicating that this method of therapeutic window is open for a short time to deliver therapeutic agents circulating in the blood after intravascular administration. Hence, the longer we continue electrical stimulation, the longer the leaking of the therapeutic agents to the brain substance and the better the therapeutic effect. Before the electrical impulses stimulation, it is best to administer parenteral, oral or ORE therapeutic agents in advance, so that they will reach the effective therapeutic dose circulating in the BV and delivered by the BBB broken BV within the brain.

As appropriate, an optional therapeutic agent such as a pharmaceutical agent or other biologically active agent may be delivered to a patient in combination with electrical impulses stimulation as described. One or more of the following therapeutic active agents may be given systemically or if available through the olfactory mucosa. Examples of therapeutic agents that may be delivered to a patient for treating Alzheimer's and other CNS degenerative diseases delivered directly to ORE include:

I. Intranasal Insulin, and IGF-1

II. a glutamate receptor antagonist; and NMDA-receptor blockers and antagonists, including ketamine, memantine

III. a β amyloid inhibitor; and a microglial activation modulator for example bexarotene

IV. a combination of an Alzheimer's vaccine

V. anti-inflammatory non-steroidal anti-inflammatory drugs, COX-2 inhibitor (NSAIDS), glutathione antioxidant

VI. monoclonal antibodies (mAB) for instance Etanercept

VII. a cholinesterase inhibitor which is already in use in the treatment of Alzheimer's such as tacrine, donepezil (Aricept®) Rivastigmine (Exelon®), Galantamine, and similar therapeutic agents

VIII. a stimulant of nerve regeneration and nerve growth factor using this method and adding neuro generative therapeutic agents

IX. Acetylcholine esterase inhibitor so as to enhance the acetylcholine in CNS

X. L-DOPA (L-3,4-dihydroxyphenylalanine), monoamine oxidase-B (MAO-B) inhibitors, apomorhine, and dopamine agonists (include bromocriptine, pergolide, pramipexole, ropinirole, piribedil, cabergoline, apomorphine and lisuride) to increase dopamine levels in basal ganglia of the CNS for treating Parkinson's

XI. an antioxidant; vitamins for example vitamin A, B_{12} B complex, D_3 and others

XII. hormone such as progesterone; an inhibitor of protein tyrosine phosphatases; an endogenous protein

XIII. Neurotrophic factors for example Nerve growth factors (NGF), fibroblast growth factor (bFGF), glial-derived neurotrophic factor (CNTF), pigment epithelium-derived factor (PEDF), glial-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), erythropoietin's, insulin, IGF-1, platelet derived growth factor (PDGF) and as such

XIV. Gene and stem cell therapy; and therapeutic agents therapy through the ORE after electrical impulses stimulation, or after electroporation or Iontophoresis.

METHOD OF USE OF INTRANASAL INSERTION OF THE ELECTRICAL IMPULSES DELIVERY DEVICE

Before insertion of the electrical impulses stimulator through the nasal cavity, a thorough examination of the nasal cavity by an ENT specialist is in order. The patient should not be taking any blood thinning medications, free of nasal tumors, and without the history of epilepsy. It is also important for the attending physician to examine both sides of the nose with a fiber optic nasal scope and inspect the nasal passage, turbinates, roof of the nose, and ostium of the sphenoid sinus as well as the olfactory region (ORE). These scopes are flexible, easy to use and to clean. If the patient is sensitive for instrumentation, local anesthetic spray and KY jelly or similar lubricant will facilitate the examination and insertion of this device. It is important to have an intravenous infusion line open during the first

insertion -stimulation, and it is not needed afterwards when one experiences the safety and simplicity of its use. For experimental reasons, the patient may also be connected to an EEG or EKG and record before, during, and after the insertion and turning on the electrical impulses delivery system of invention. If the EEG shows the epileptic type of brain waves, the amperes of electrical impulses delivered is reduced, so that no epileptic episode will occur during use of this inventive device. It may be important to have a brain scan and anterior-lateral view of X rays of the nose with sphenoid sinus and nasal sinuses. Have emergency first aid supplies available in case they are needed.

Once the diagnosis of Alzheimer's is established, and if there are no contraindication for the procedure, start the electrical impulses delivery procedure after carefully positioning the device in the sphenoid sinus, on the olfactory mucosa, and sphenopalatine ganglion. Use the nasal fiber optic scope to place the device anatomically in the correct position to deliver the electrical impulses to the desired anatomical site to stimulate the appropriate neurological structures.

Once the device is positioned at the desired anatomical position in the nose, with the insertion end at a trans-nasal location, start switching on the electoral output manipulator (Figs. 6-11, #517) slowly rising the mAP output. Only deliver the milliamps of electrical current the patient tolerates. The threshold amplitude for neuronal and neuropil activation will vary from one patient to the next. To ensure an adequate response, the stimulation parameters may be adjusted to stimulate at amplitude of about 5-10% below the patient's neuronal activation threshold to about 15-20% over the patient's neuronal activation threshold. The amplitude of the electrical stimulation typically is about 200 micro amps (uA) to about 400-500 milliamps (mA). Other suitable combinations of stimulation amplitude and frequency are provided on a per patient dependent basis. For example, the electrical stimulation can be provided by pulse trains of an intermittent duration or continuously, at a frequency of about 10 Hertz (Hz) to about 30 Hertz (Hz), with a pulse width of about 50 microseconds (μs). Put together an EEG recording during the procedure and set the desire milliamps of electrical current delivered to get the desired therapeutic effect.

During the insertion, hold the device directed towards the external canthus of the eye abutting against the outer edge of the nose, directing it upwards and backwards. Do not pass the device horizontally where the tip will end at the respiratory mucosa. The device is inserted with the patient lying down with the neck extended and a small support under the patient's shoulders. The nose is sprayed with a local anesthetic and neosynephrine or Afrin to shrink the mucus membranes. A cotton wad soaked in local anesthetics and vaso-constrictors is packed with angled nasal forceps. Antiseptic solutions are sprayed inside the nasal cavity. As the local anesthetic takes effect, a fiber optic naso scope is introduced through the external naris, all the way up to the sphenoethmoidal recesses located at the posterior upper angle of the nose. Then the body of the device is guided gently into the sphenoid sinus through the sphenoid foramina. If the opening (ostium) of the sphenoid sinus is narrow, it can be enlarged by dilators or inflatable balloons. The balloon is inflated with a liquid and the stimulation started. It may be necessary in some cases to insert the apparatus into both right and left sphenoid sinuses to achieve the desired therapeutic effect. Make sure the patients and caregivers participate during the treatment so that they may carry out the treatment at home.

Position the electrical impulses delivering system as shown in the diagrams 5-15. Pull the electrical impulses delivery device out, slowly at the end of the procedure.

This invention is based on electrical impulses delivery to the afflicted area, as the memory recall is related to electrical activity. The device also give positive results during the stimulation processes by increasing the memory, recall of the past and remembrance of the events as they are happening due to the enhancing of the memory protein generation and activation of the ones that are already inside the neurons and providing electrical impulses needed to transmit the messages.

The electrical impulses are delivered continuously or intermittently depending upon the comfort of the patient and diagnosis of the condition. It may need to switched off as needed and the improvement in the signs and symptoms. The device can be left in place for hours and days or more at a time. The device can be removed to clean, treat with antiseptics, sterilize, reuse or replace. The patient can be put on antibiotics if the infection of the nose and sinus are suspected. The

catheter and the balloon can be impregnated with antibiotics, antiseptics such as silver nitrate, antifungal agents to prevent the growth of the microbes on the device.

Therapeutic agents are administered orally, intravenously or intra nasally to olfactory mucosa depending on their formulation to the patient once it is determined the electrical impulse have caused dilatation CNS BV and broken the BBB to a certain extent. The drugs administered are specific to the disease. They are selected from described list herein for Alzheimer's disease.

EXAMPLES OF OLFACTORY MUCOSAL DELIVERY OF THERAPEUTIC AGENTS TO TREAT ALZHEIMER'S DISEASE

Once the nerve stimulation has been established using the inventive device described herein which incorporates Iontophoresis, any one or more of the following therapeutic agents may optionally be administered to the site of the olfactory mucosa to treat Alzheimer's disease through the delivery syringe attached to the catheter as shown in the diagrams Figs. 6-10 as an example. Optionally, a device and method may be used that do not involve delivery of therapeutic agent.

Preparation of stock solutions and method of olfactory mucosal administration:

a) Take 300 mg of bexarotene; dissolve it in a solvent alcohol, or dimethyl sulfoxide (DMSO), with suitable carriers, which include physiological saline or phosphate buffered saline (PBS). This solution can contain thickening and solubilizing agents, for example glucose, polyethylene glycol, and polypropylene glycol and mixtures thereof. The final formulation contains 30 mg of bexarotene per ml of solution.

b) Then take 100 IU of rapid acting insulin and dilute it in 5ml of normal saline, in which each ml contains 20 units of insulin.

c) Take 2.5 mg of Ketamine, and dilute it in 5ml of saline, resulting in 0.5 mg per ml or 500 mcg of active ingredient per ml.

d) Place the patient in a supine position with head extended, and the inventive device inserted and operating,

e) Instill through the syringe 0.5ml of bexarotene into delivery catheter to each olfactory mucosal surface as shown in figures 5-7. Wait for 10 minutes, then instill 0.25 to 0.5 ml insulin to each olfactory mucosal surface, wait for 10 minutes, then follow with olfactory mucosal delivery of ketamin, 0.5 ml to each

side. During this procedure, olfactory mucosal stimulation is discontinued and resumed after the delivery of therapeutic agents to the olfactory mucosa. Electrical stimulation is continuing which will facilitate the uptake of these therapeutic agents. This procedure is repeated twice a day for the first week and then three times a week and then once a week depending on the response. The concentration of therapeutic agents is increased or decreased depending upon of the reaction and response of the patient.

It is important to note also that there are no adverse reactions due to use of bexarotene, which is entirely dose dependent. High dose usage in the treatment of cutaneous T-cell lymphoma can be associated with hypertriglyceridemia, hypercholesterolemia and decreased high-density lipoprotein levels, as well as hypothyroidism (SI Sherman, Gopal J, Haugen BR, et al et al, Central hypothyroidism with retinoid X receptors -selective ligands. N Engl J Med, 1999, 340:1075-1079.7), headache, asthenia, leucopenia, anemia, infection, rash, alopecia and photosensitivity. This is due to use of mega doses of bexarotene for weeks. The dose we use to treat Alzheimer's through the olfactory mucosal delivery is infinitesimally small compared to those seen to treat cancer, hence no such reaction is seen with this mode of delivery of bexarotene.

The manufacturer cautions that bexarotene given to diabetic patients concurrently with insulin, sulfonylureas, metformin (Glucophage), repaglinide (Prandin) or the thiazolidinediones ("glitazones") might cause hypoglycemia. Hence, in diabetics with Alzheimer's, the insulin should be used with caution. One should be prepared with glucose tablets and should be familiar with episodes of hypoglycemia, and how to treat if the complication develops. It is important to note that if it is deposited on the olfactory mucosa, chances of developing hypoglycemia will be avoided. It can occur if the insulin is deposited in the respiratory part of nasal mucosa instead of olfactory mucosa; which will be absorbed systemically which may contribute to the hypoglycemic effect. Since bexarotene is a vitamin A derivative, co administration with vitamin A may add to the drug's toxicity. The dose we use is so small; we do not believe that one need to be concerned with such toxic effects including hypoglycemia.

We have used insulin delivered to the olfactory mucosa for the treatment of many neurodegenerative diseases including the cases of reduced mental cognition with declining memory in the aged, Parkinson's with glutathione, as well as for depression due to any number of reasons including Posttraumatic Stress Disorder (PTSD) which is a mental health problem that can occur after someone goes through a traumatic event like war, assault, or disaster. The treatment reduced the depression, improved the memory, and increased cognition. Further, the insulin augments and amplifies the effect of many therapeutic agents such as bexarotene and ketamine many fold as described in the ingenious experiments by Alabastor et al (Oliver Alabaster' et al. Metabolic Modification by Insulin Enhances Methotrexate Cytotoxicity in MCF-7 Human Breast Cancer Cells, Eur J Cancer Clinic; 1981, Vol 17, pp 1223-1228). It has a trophic effect on the neurons, and it is a mitogenic, thus it prevents or delays further decay of the neurons afflicted by this disease and reduces the ROS damage to the nerve tissue. Besides its effect on cognition, and improving the psychological status of the Alzheimer's patients, it is used in conjunction with the bexarotene to enhance its uptake and delivery to the CNS, as well as to augment and amplify the effects (paracrine and intracrine effect) on the neuropil to reduce the β amyloid, and its soluble precursors so as to curtail the disease.

Ketamine is a GABA receptors antagonist. It acts by blocking the N-methyl-D-aspartic acid (NMDA) receptor, which receives signals from glutamate. There are many examples of antagonists of the NMDA receptor, but ketamine is most suitable in the treatment of Alzheimer's. Besides protecting the neurons from the excitotoxicity of Glutamate, Ketamine is also a dissociative anesthetic (no such effect due to the very small doses we use here), an excellent sedative, it is an anti arrhythmic, and reduces the pain perception due to its local anesthetic like effects. We have used ketamine for wound dressing changing in burn patients since 1969 and postpartum after delivery to ally the anxiety under regional anesthesia. The micro doses of ketamine we use in the olfactory mucosal instillation in this invention have no hallucinogenic or other ill effects. The present inventor has used these therapeutic agents in hundreds of cases such as dissociative anesthesia, neuropathic pain, depression, hiccup (Shantha, T. R. Ketamine For the Treatment of

Hiccups During and Following Anesthesia: A Preliminary Report in Anesthesia And Analgesia. Current Researches VOL. 52, No.5, September-October, 1973), ALS with Insulin -like growth factor-I (IGF-1), insulin, and experiment show that it inhibits the rabies virus multiplication (U. S. Patent Application Publication Number: 201110020279 AD-Rabies cure)

The invention described herein can incorporate ketamine delivered to olfactory mucosa with bexarotene and insulin. The intranasal use of ketamine delivery to the olfactory mucosa reduced or relieved the depression associated with many neurodegenerative diseases. In the early cases, it completely ameliorated the depressive condition especially in dementia. These patients felt a sense of well being. Because of the small dose used to treat the above described neurodegenerative diseases, it has no hallucinogenic effect. Along with the bexarotene, insulin, and ketamine, the adjuvant therapeutic agent such as acetyl cholinesterase inhibitors are added to increase the CNS levels of acetylcholine to enhance the memory and cognition in Alzheimer's disease patients.

The electrical stimulation of the brain described in this invention through the peripheral nervous system projections, and pituitary gland; which in turn stimulates the malfunctioning nerve tissue (neuropil) of the CNS holds significant promise for the treatment of Alzheimer's, and other neurodegenerative diseases. Such stimulation is reversible, non-destructive, easy to use, non invasive, and least expensive. Nerve stimulation is accomplished directly or indirectly by depolarizing a nerve membrane, causing the discharge of an action potential; or by hyperpolarization of a nerve membrane, preventing the discharge of an action potential. Such stimulation occur after electrical energy, transmitted to the vicinity of a nerve or directly in contact with the nerve itself as it happens in olfactory region stimulation to be transmitted to the afflicted brain of Alzheimer's disease. The nerve stimulation is also anti-neuroinflammatory. Neuroinflammation is the primary denominator in all these conditions including Alzheimer's disease.

Numerous modifications; adjuvants, alternative arrangements of steps explained and examples given herein may be devised by those skilled in the art without departing from the spirit and scope of the present invention and the appended claims are intended to cover such modifications and arrangements. Thus,

the present invention has been described above in detail in connection with what is presently deemed to be the most practical and preferred embodiments of the invention. It will be apparent to those of ordinary skill in the art that numerous modifications, including, but not limited to, variations in size, materials, shape, form, function and manner of procedure, assembly, and use may be made. While the preferred embodiment of the present invention has been described, it should be understood that various changes, adaptations, and modifications may be made thereto. It should be understood, therefore, that the invention is not limited to details of the illustrated invention. Therefore, the present invention shall include embodiments falling within the scope of the appended claims. Different embodiments of the described methods and devices can include one or a combination of features as indicated by the following examples.

Example 1. A method for treating Alzheimer's diseases, with this said device and method applying to a subject a specific low frequency pulsed electrical impulses (signals, pulses) through this inventive device located at adjacent nerves whose stimulation is transmitted to the central nervous system to excite the central nervous system through the olfactory nerves, sphenopalatine ganglion, sphenoid sinus, cranial nerves III, IV,V, and VI, pituitary gland, hypothalamic - hypophysis tract, thalamic radiation, brainstem, cerebellum, parasympathetic nerves of the human body. This method and device is comprising of:

a. an insertion body having a balloon with a flexible outer surface adapted to contact and conform to the interior surface of the sphenoid sinus, the balloon having an interior;
b. means connected to the interior of the balloon for inflating the balloon while in the sphenoid sinus;
c. a (optional) thermocouple connected to and residing within the interior of the balloon for locally heating and cooling fluid present within the balloon and for locally heating and cooling the interior surface of the sphenoid sinus immediately adjacent to the outer surface of the balloon;

d. a (optional) temperature sensor being connected to the interior of the balloon and to a temperature indicator external to the balloon for monitoring the temperature of the outer surface of the balloon;

e. multiple electrical stimulator electrodes incorporated onto the outer surface of the balloon which come in direct contact with the interior lining of the sphenoid sinus;

f. connection means for connecting the electrical stimulators electrodes to a power source and control device outside of the sphenoid sinus for stimulating the sphenoid sinus and proximate structures with controlled electric current output;

g. an open catheter at the end of the balloon to deliver saline to increase the electrical conductivity and for delivering adjuvant therapeutic agents.

Ex. 2. A method for delivering the electrical impulses according to example 1, for stimulating the brain of a Alzheimer's disease patients through olfactory nerves via olfactory mucosa comprising of:

a. Electrodes, applied to the olfactory nerves through olfactory mucosal area which conducts the electrical pulses to the neural tracts connecting these structures to the CNS through the olfactory bulb, and

b. a control unit, located outside the nasal cavity adapted to drive the one or more electrodes to apply a electrical current to the site capable of stimulating olfactory nerves, which will transmit the electrical impulses to the regions of the brain through their connection in the CNS conducted to the CNS affected by the Alzheimer's, and

c. the olfactory region (ORE) part of the inventive device is provided with therapeutic agents' delivery pores to deliver adjuvant therapeutic agents specific to Alzheimer's and neurodegenerative diseases to the olfactory epithelium to be transported to the CNS bypassing the blood brain barrier through the olfactory bulb.

d. The stimulator device for the olfactory mucosa is provided with Iontophoresis electrodes to enhance the uptake of therapeutic agents by the receptor cells to be transported to the CNS by passing the BBB.

Ex. 3. A method for applying the electrical impulses according to example 1, for stimulating the brain of Alzheimer's patients using electrical impulses through sphenopalatine ganglion nerves, comprising of:

a. Electrodes, applied to the sphenopalatine ganglion area on the medial wall of the nasal cavity located immediately below the sphenoid sinus and to the neural tracts connecting these structures to the CNS through sphenopalatine ganglion, and

b. a control unit, located outside the nasal cavity adapted to drive the one or more electrodes to apply a electrical current to the site capable of stimulating sphenopalatine ganglion nerves, which will transmit the electrical impulses to the regions of the brain through their extensive connection in the CNS and to the blood vessels (BV) affected by the Alzheimer's.

Ex. 4 The method according to example 1, in which a tube is connected to the balloon for infusing fluid into the interior of the balloon which heats or cools the balloon. The apparatus is further comprising of a device external to the balloon and connected to the balloon for heating and cooling fluid prior to infusion into the interior of the balloon while the balloon is in the sphenoid sinus.

Ex. 5. The method according to example 1, in which the means for inflating the balloon is at least one tube connected to an inflator syringe.

Ex. 6. The method according to example 1 is comprised to configure the electrical impulses to cause an increase in the electrical activity in these diseases afflicted neurons and synapses of the brain and brain stem.

Example 7. According to the method of treating Alzheimer's and other neurodegenerative diseases using this device involves applying the electrical stimulation continuously or intermittently to olfactory nerves, sphenopalatine ganglion, trigeminal nerves, five cranial nerves, pituitary gland with hypothalamo hypophysial region, entorihinal and other cortical cognition centers.

Ex. 8. This present inventive method of treating Alzheimer's disease involves applying the electrical impulses through the transmitting device connected to the generator housing stimulator outside the nose by connecting electricity conduction wires.

Ex. 9. This present inventive method of treating Alzheimer's disease involves applying the electrical impulses through fine electrical wires made of suitable conductive physiologically acceptable material such as silver, iridium, platinum, iridium alloy, titanium, nickel-chrome alloy and other suitable combination of conducting metal alloys. Each electrode is insulated with a physiologically

acceptable material such as polyethylene, polyurethane, or a co-polymer, which is non-conductive, non-allergic, non-reacting synthetic or semi synthetic materiel.

Ex. 10. The apparatus according to example 1 is comprised of flexible insulated electrodes adapted for insertion through a nostril of the patient to the desired anatomical and histological areas.

Ex. 11. The apparatus according to example 1 is comprised of three wires, connected to the control unit separately so that they may be individually turned on and off to stimulate olfactory nerve, sphenopalatine ganglion, or structures around the sphenoid sinus individually or combination, as needed from the electrical output manipulator, from the external position to get the maximum therapeutic effect.

Ex. 12. The apparatus according to example 1 is configured such that each one of the wires connected to these individual anatomical sites has an Ampere (mAP) adjuster and a time setter to deliver the desired amperage of stimulating electricity at a set time, located outside the nose from the electrical output manipulator.

Ex. 13. The apparatus according to example 1 is configured such that the electrical control delivery unit is introduced to both sides of the nose.

Ex. 14. The apparatus according to example 1 is configured such that the catheter with electrical wired embodiment is provided with the temperature and location sensor located at the tip of the stimulator device.

Ex. 15. The apparatus according to example 1 is configured such that one or more electrodes are adapted for use for hours, weeks, and months at a time, based on the patient's compliance and the stage of the disease afflicting the patient.

Ex. 16. The apparatus according to example 1 is configured such that the electrical amplitude and milliamps delivered are adapted to set the amplitude of the current, to induce the increase therapeutic effect and induce permeability in the BBB blood vessels.

Ex. 17. The apparatus according to example 1 is configured such that the shape of the electrical impulse waveform is selected and delivered from the catalog, consisting of an exponential decay, a ramp up and down, square wave, a monophasic shape, a biphasic shape, a sinusoid, a saw tooth, and with a direct current (DC) component. The control unit is set to deliver the selected waveform of the current,

so as induce the desired therapeutic effect on the brain in the treatment of Alzheimer's, and other neurodegenerative diseases.

Ex. 18. The apparatus according to example 1 is configured such that the electrical amplitude and milliamps delivered are adapted to set the amplitude of the current, to induce the desired therapeutic effects. At the same time, it enhances the permeability (Iontophoresis), for the uptake and transport of therapeutic agents from the olfactory mucosa, and sphenoid sinus sites, bypassing the BBB, by creating elecroporation and iontophoresis effects of olfactory mucosa and sphenoid sinus lining, which allows large molecules of therapeutic agents' transportation to the CNS, the site of pathology bypassing blood-brain barrier.

Claims:

1. An apparatus for electrically stimulating nerves in a region of olfactory mucosa of the nasal cavity, the apparatus comprising

an elongate shaft having a proximal end and an insertion end, the insertion end adapted for placement at a trans-nasal location within the nasal cavity extending from an exterior nasal opening, along the nasal cavity adjacent to olfactory mucosa, and to an interior of a sphenoid sinus,

the insertion end comprising

a distal electrode adapted to be located within the sphenoid sinus with the insertion end located at the trans-nasal location, and

a proximal electrode adapted to be located adjacent olfactory mucosa with the insertion end located at the trans-nasal location,

wherein the apparatus exhibits one or more of:

the distal electrode is located on expendable mesh, or

the apparatus does not include an ejection port at the insertion end in fluid communication with the proximal end through which fluid can be delivered to the olfactory mucosa with the insertion end located at the trans-nasal location, or

the apparatus does not include an ejection port at the insertion end in fluid communication with the proximal end through which fluid can be delivered to the sphenoid sinus with the insertion end located at the trans-nasal location.

2. An apparatus as recited at claim 1 comprising

an expandable surface at the insertion end adapted for placement and expansion within a sphenoid sinus with the insertion end located at the trans-nasal olfactory region location,

wherein

the distal electrode is located at the expandable surface and is adapted to contact an interior surface of the sphenoid sinus with the expandable surface expanded within the sphenoid sinus, and

the proximal electrode is located on a proximal side of the expandable surface to be located adjacent olfactory mucosa with the insertion end located at the trans-nasal location.

3. An apparatus as recited at Claims 1 or 2 wherein the distal electrode is an electrode of a set or array of bipolar distal electrodes located at the expandable surface.

4. An apparatus as recited at Claim 3 wherein the bipolar distal electrodes are at the expandable surface and adapted to contact an interior lining of the sphenoid sinus with the expandable surface expanded within the sphenoid sinus.

5. An apparatus as recited at any of Claims 1 through 4 wherein the distal electrode or electrodes are capable of being activated to stimulate a nerve selected from cranial nerve I (also known as the Olfactory nerve), cranial nerve III, cranial nerve IV, cranial nerve V, cranial nerve VI, a pituitary gland, hypothalamic-hypophysis tract, thalamic radiation, brainstem, cerebellum, parasympathetic nerves on the internal carotid artery and circle of Willis in the brain, and combinations thereof, with the distal electrode or electrodes placed within the sphenoid sinus.

6. An apparatus as recited at any of Claims 1 through 5 wherein the proximal electrode is an electrode of a set or array of bipolar proximal electrodes located along a length of the insertion end on a proximal side of the expandable surface.

7. An apparatus as recited at any of Claims 1 through 6 wherein, with placement of the proximal electrode or electrodes adjacent olfactory mucosa with the insertion end located at the trans-nasal location, the proximal electrodes can be activated to stimulate olfactory nerves (also known as Cranial nerve I).

8. An apparatus as recited at any of Claims 1 through 7 wherein with the insertion end located at the trans-nasal location, the proximal and distal electrodes are adapted to stimulate one or more nerve capable of exciting the central nervous system and selected from the group consisting of an olfactory nerve, sphenopalatine ganglion, sphenoid sinus, cranial nerves III, IV,V, and VI, a pituitary gland, hypothalamic-hypophysis tract, thalamic radiation, brainstem, cerebellum, parasympathetic nerves on the internal carotid artery and circle of Willis in the brain, and combinations thereof.

9. An apparatus as recited at any of Claims 1 through 8 comprising a second expandable surface on a proximal side of the proximal electrode, wherein the expandable surface adapted for placement within a sphenoid sinus can be expanded to secure the insertion end at the trans-nasal location.

10. An apparatus as recited at any of Claims 1 through 9 wherein the expandable surface adapted for placement within a sphenoid sinus can be alternately expanded and retracted, and in the retracted state can be passed through the sphenoid ostium to place the expandable surface within the sphenoid sinus.

11. An apparatus as recited at any of Claims 1 through 10 wherein the proximal end comprises:

a proximal electrode connector in electrical communication with the proximal electrode, and

a distal electrode connector in electrical communication with the distal electrode.

12. An apparatus as recited at Claim 11 in combination with an electric stimulator adapted to be located exterior to the exterior nasal opening with the insertion end located at the trans-nasal location, the stimulator comprising a power source, a control device, a first connector adapted to electronically engage the proximal electrode connector to deliver an electronic stimulation signal to the proximal electrode or electrodes, and a second connector adapted to electronically engage the distal electrode connector to deliver an electronic stimulation signal to the distal electrode or electrodes.

13. An apparatus as recited at any of Claims 1 through 12 wherein the shaft comprises a fluid delivery lumen extending between the proximal end and the insertion end, wherein the fluid delivery lumen allows delivery of a liquid fluid to the sphenoid sinus, olfactory mucosa, or both, with the insertion end located at the trans-nasal location.

14. An apparatus as recited at any of Claims 1 through 13 wherein the expandable surface adapted for placement within a sphenoid sinus comprises an inflatable balloon.

15. An apparatus as recited at Claim 9 or 12 wherein the second expandable surface comprises an inflatable balloon.

16. An apparatus as recited at any of Claims 1 through 15 comprising a thermocouple useful to measure temperature at the expandable surface.

17. A method of nerve stimulation, the method comprising

providing an apparatus comprising an elongate shaft having a proximal end and an insertion end, the insertion end adapted for placement at a trans-nasal location within the nasal cavity extending from an exterior nasal opening, along the nasal cavity adjacent to olfactory mucosa located in the roof of the nose, and to an interior of a sphenoid sinus, the insertion end comprising

a distal electrode adapted to be located within the sphenoid sinus with the insertion end located at the trans-nasal location, and

a proximal electrode adapted to be located adjacent olfactory mucosa at the upper part of the nose with the insertion end located at the trans-nasal location,

inserting the insertion end into the exterior nasal opening and nasal cavity to place the insertion end at the trans-nasal location with the distal electrode at an interior of the sphenoid sinus and the proximal electrode adjacent to olfactory mucosa,

delivering an distal electrical signal to the distal electrode, and

delivering a proximal electrical signal to the proximal electrode, wherein the method does not include delivery of therapeutic fluid to the nasal region.

18. A method as recited at Claim 17 wherein the distal electrical signal is different from the proximal electrical signal.

19. A method as recited at Claim 16 or 17 wherein the distal electrical signal stimulates a nerve selected from cranial nerve III, cranial nerve IV, cranial nerve V, cranial nerve VI, and combinations thereof.

20. A method as recited at any of Claims 17 through 19 wherein the proximal electrical signal stimulates an olfactory nerve.

21. A method as recited at any of Claims 17 through 20 wherein the insertion end comprises an expandable surface capable of being placed within a sphenoid sinus and expanded within the sphenoid sinus to contact an interior surface of the sphenoid sinus, and the distal electrode is located on the expandable surface, the method comprising

passing the expandable surface through the sphenoid ostium to locate the distal electrode at an interior of the sphenoid sinus and expanding the expandable

surface within the sphenoid sinus to place the electrode in contact with an inner surface of the sphenoid sinus.

22. A method as recited at Claim 21 wherein the distal electrode is an electrode of a set or array of bipolar distal electrodes located on the expandable surface, and the electrical signal is delivered to the distal electrodes with the distal electrodes in contact with an interior surface of the sphenoid sinus.

23. A method as recited at any of Claims 17 through 22 wherein the proximal electrode is an electrode of a set or array of bipolar proximal electrodes located along a length of the insertion end on a proximal side of the expandable surface and the electrical signal is delivered to the proximal electrodes with the proximal electrodes being located adjacent to or in contact with the olfactory mucosa on medial and lateral walls of the olfactory mucosal surface.

24. A method as recited at any of Claims 17 through 23 wherein the insertion end comprises a second expandable surface on a proximal side of the proximal electrode, and the method comprises

passing the second expandable surface through at least a portion of the nasal cavity with the second expandable surface in an expanded state.

25. A method as recited at any of Claims 17 through 24 wherein the shaft comprises a fluid delivery lumen extending between the proximal end and insertion end, and the method comprises delivering a liquid fluid to the sphenoid sinus, olfactory mucosa, or both.

26. A method as recited at any of Claims 17 through 25 comprising delivering a liquid fluid with or without therapeutic agent to the olfactory mucosa to be delivered to the brain by passing the blood brain barrier.

27. A method as recited at Claims 25 or 26 wherein the fluid is selected from saline and a fluid comprising a therapeutic agent.

28. A method as recited at Claim 25, 26, or 27 wherein the fluid comprises a neurostimulator.

29. A method as recited at any of Claims 25 through 28 wherein the fluid comprises acetylcholine, insulin, or a combination of these.

30. A method as recited at any of Claims 17 through 29 comprising removing the insertion end from the nasal cavity after delivery of the electrical signals.

31. A method as recited at any of Claims 17 through 30 performed on an out-patient basis.

32. A method as recited at Claim 30 or 31 wherein the method, from the step of inserting the insertion end into the exterior nasal opening, to the step of removing the insertion end from the nasal cavity, takes not more than 30 minutes, not more than 60 minutes, or not more than 120 minutes.

33. A method as recited at any of Claims 17 through 32 performed without administering general anesthesia to the patient.

34. A method as recited at any of Claims 17 through 33 comprising administering the method to a patient diagnosed with a condition selected from the group consisting of: Alzheimer's Disease, Parkinson's Disease, Post-Traumatic Stress Syndrome, Senile brain atrophy, Cerebral Palsy, and stroke.

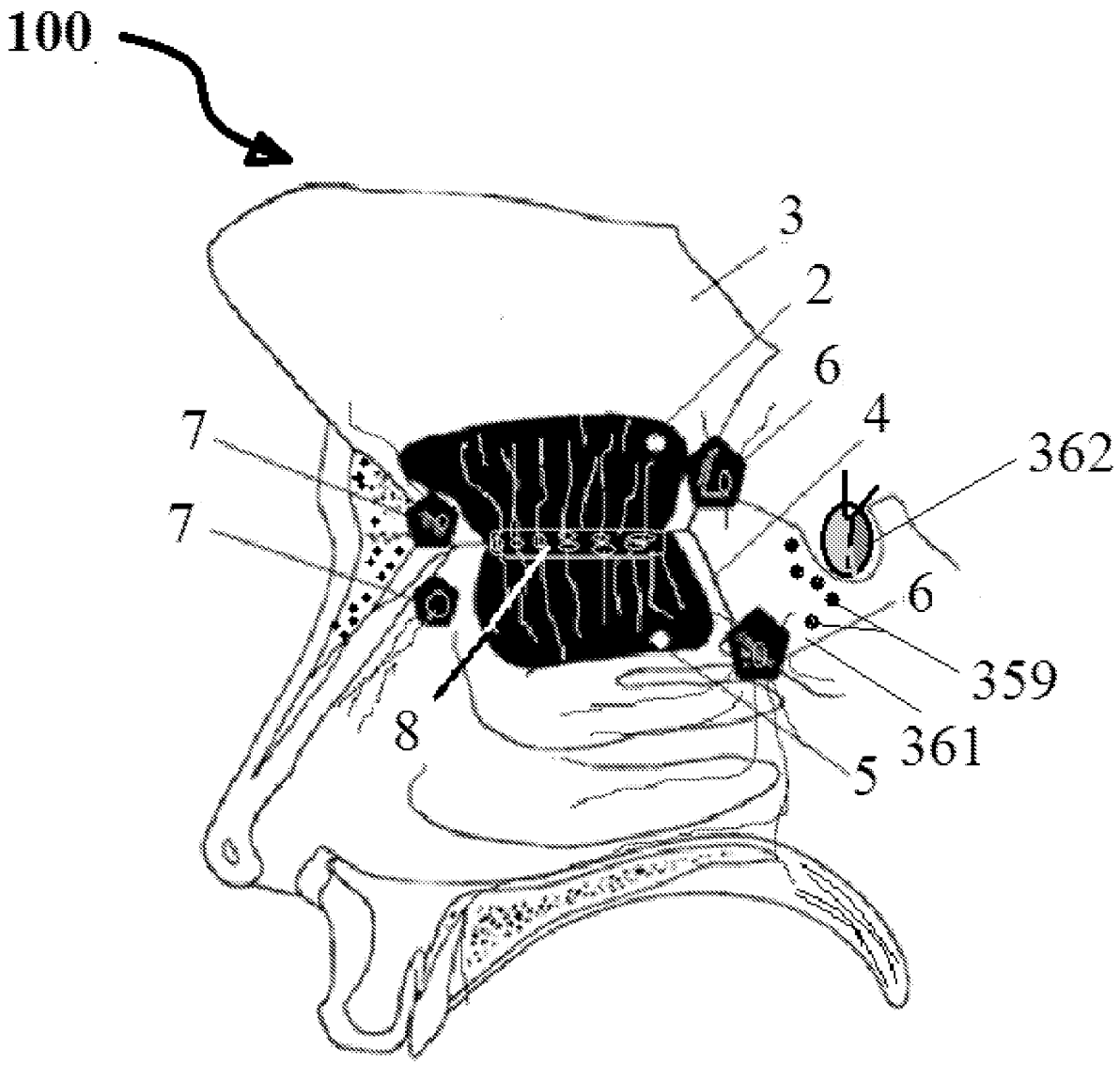

FIG. 1

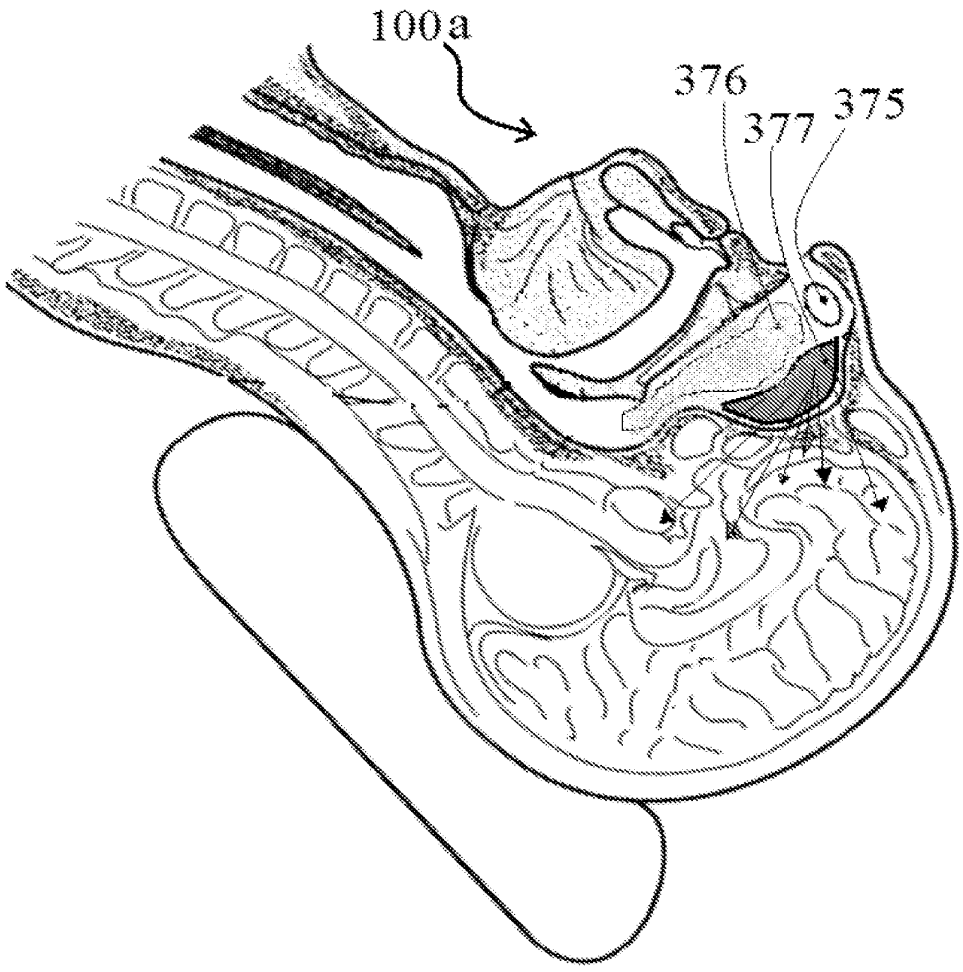

FIG. 1a

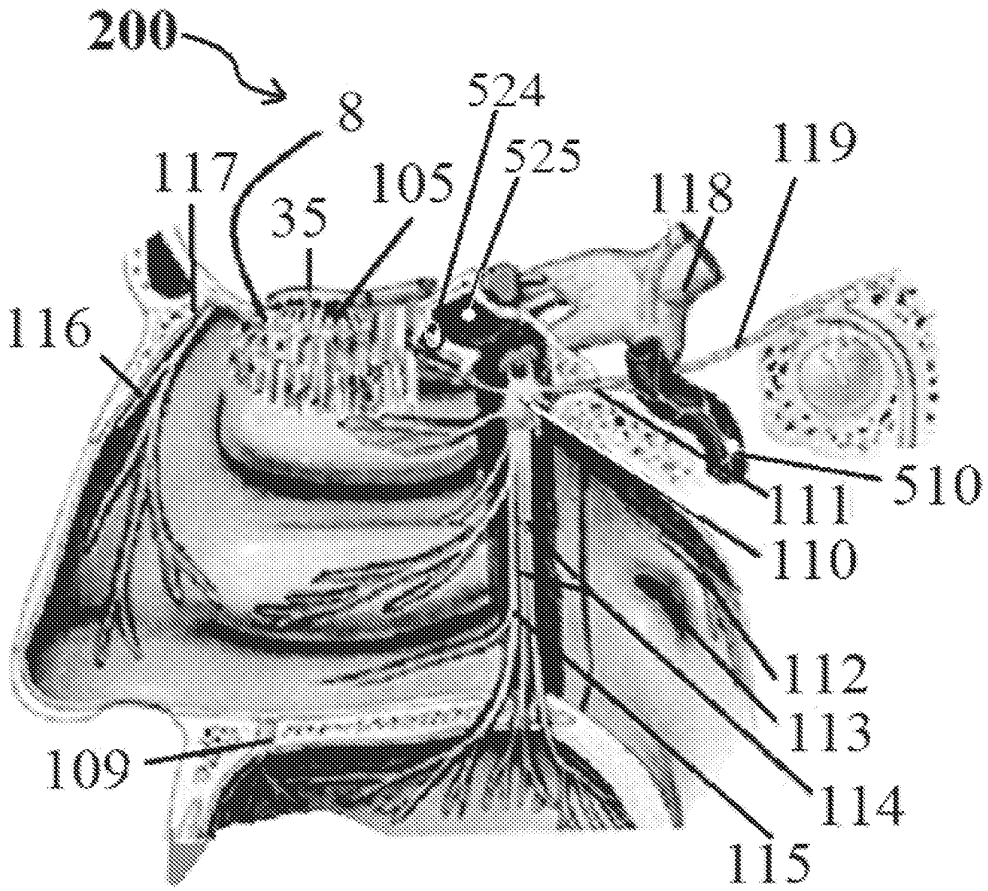

FIG. 2

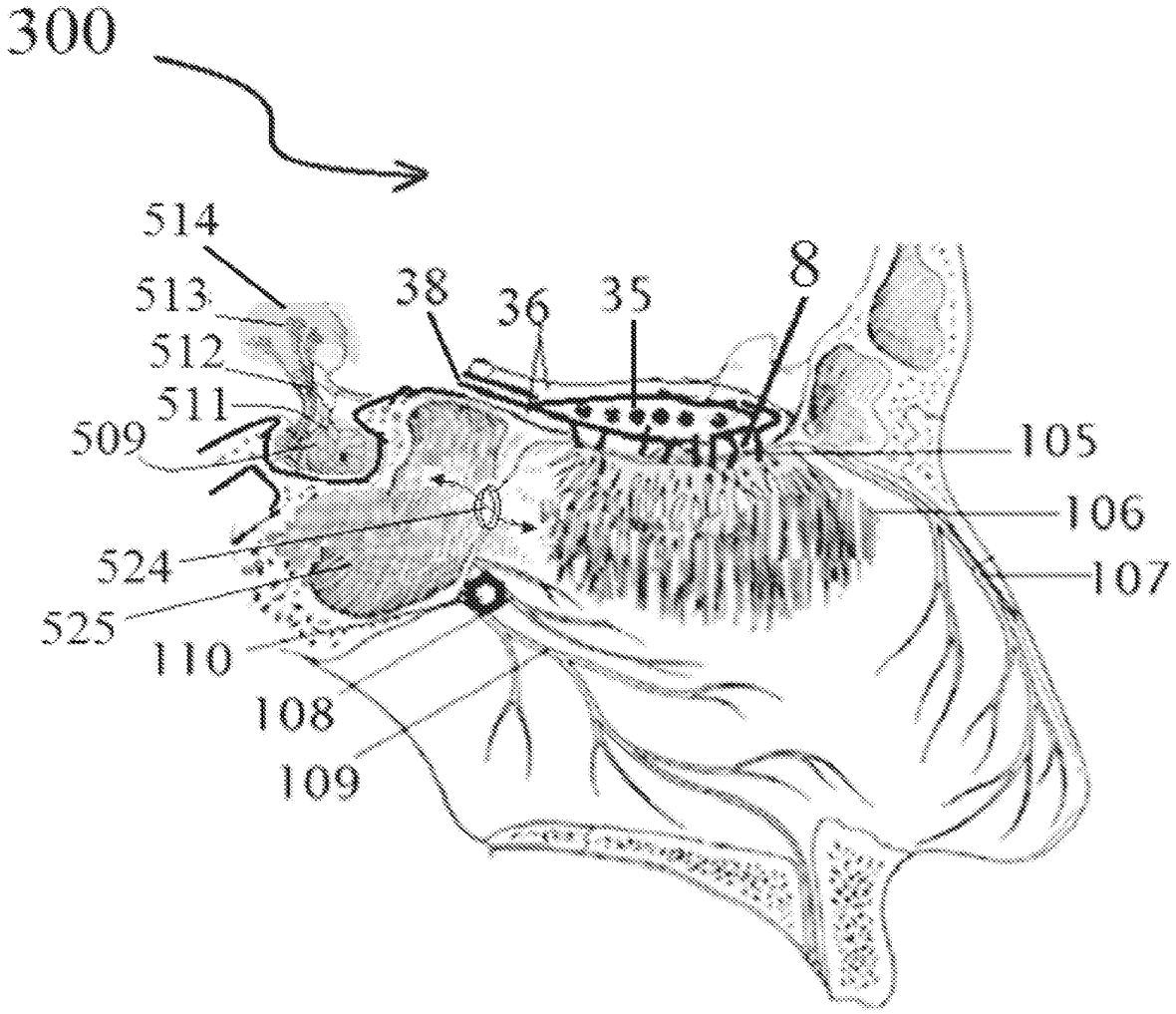

FIG. 3

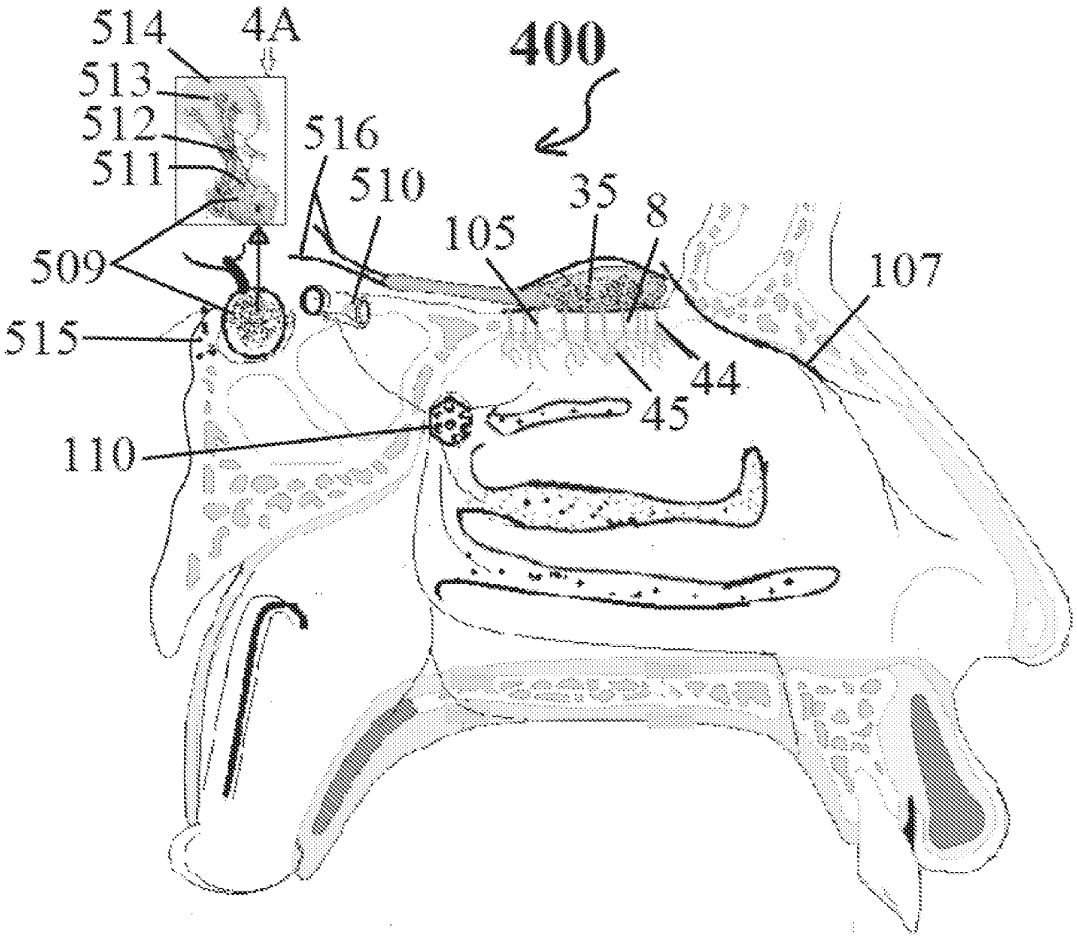

FIG. 4

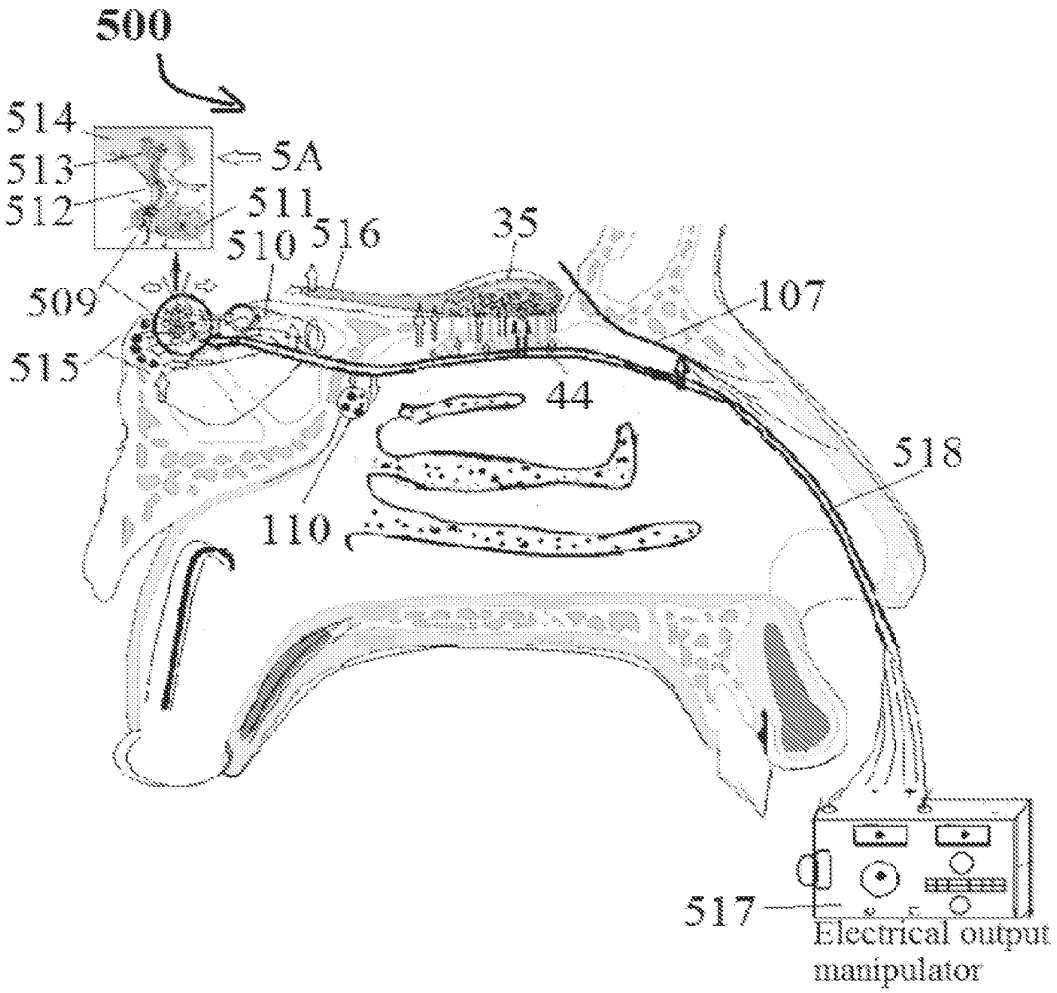

FIG. 5

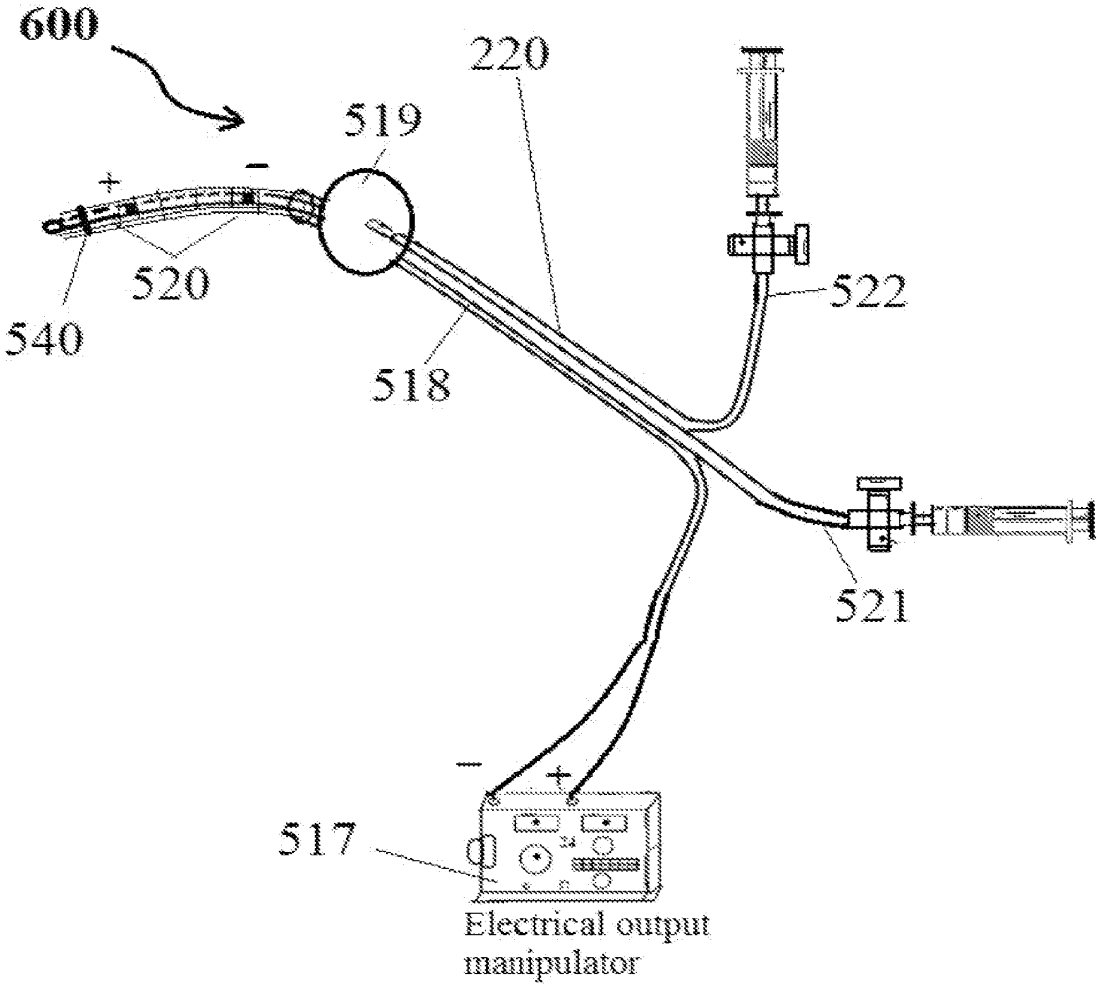

FIG.6

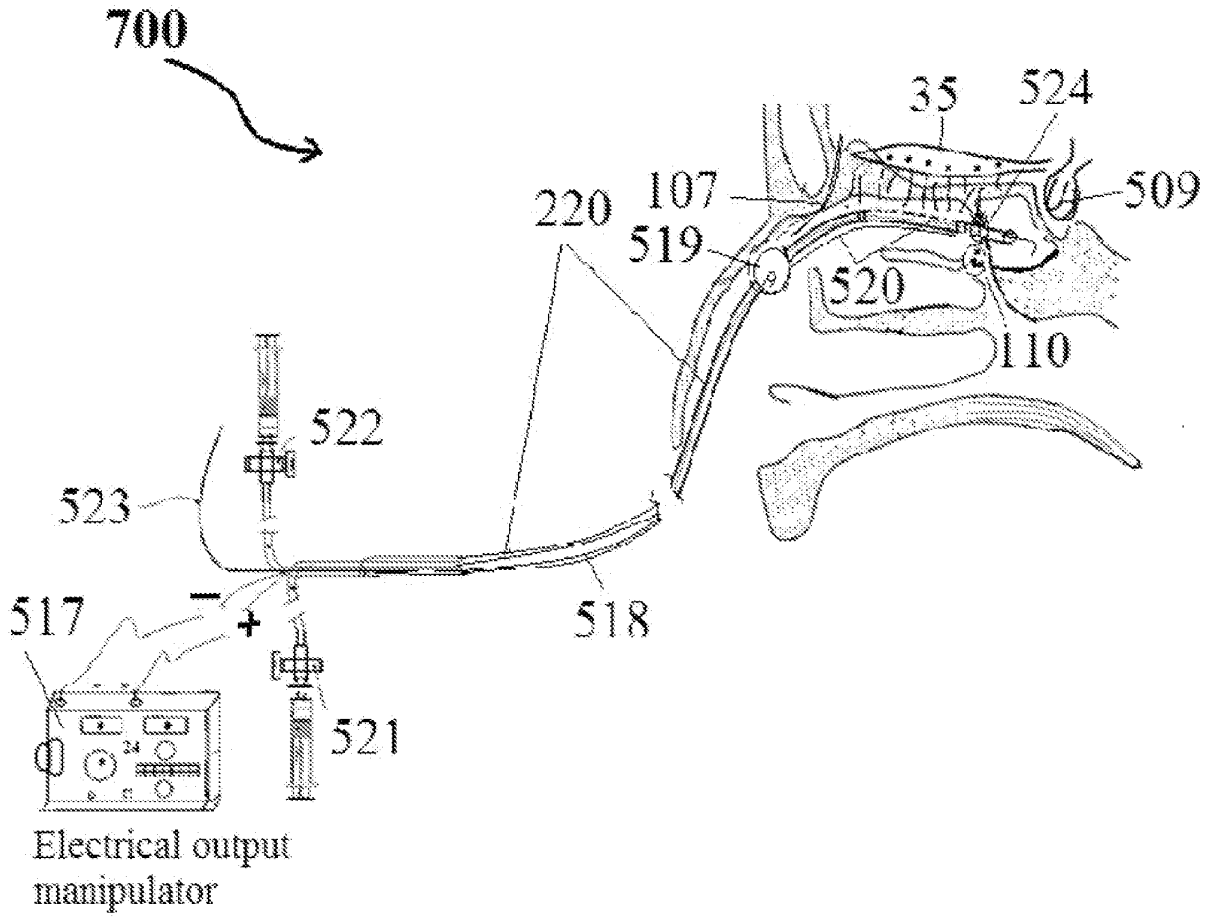

FIG.7

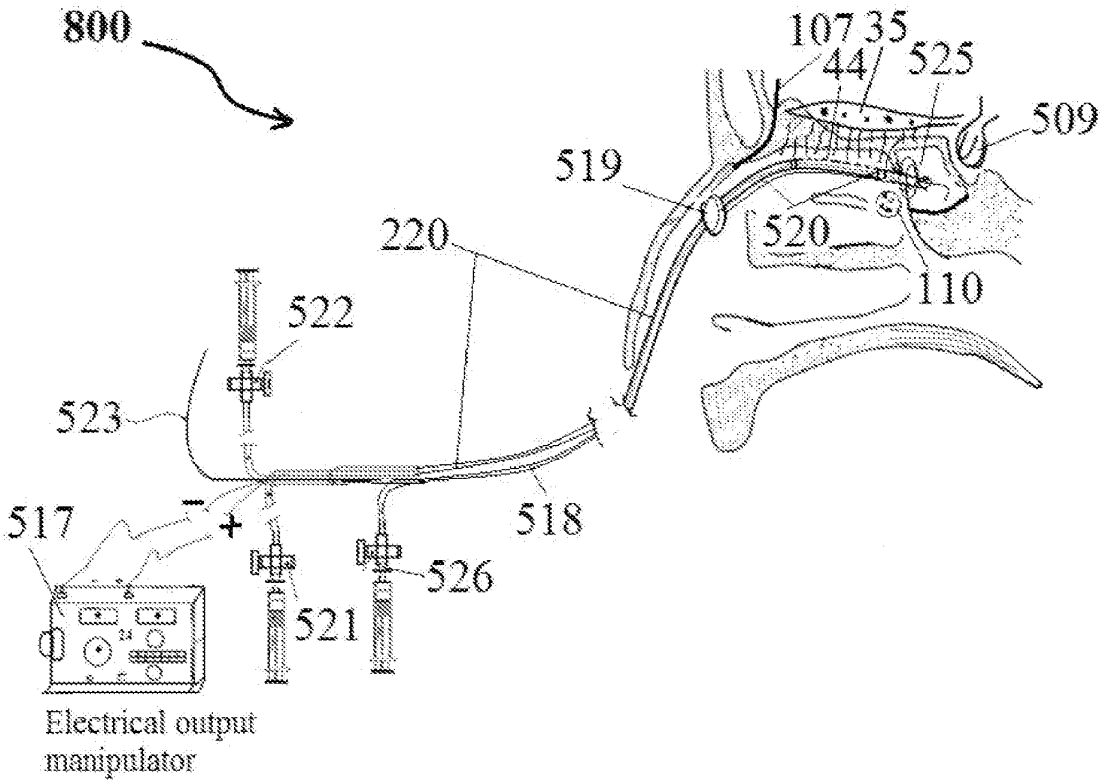

FIG. 8

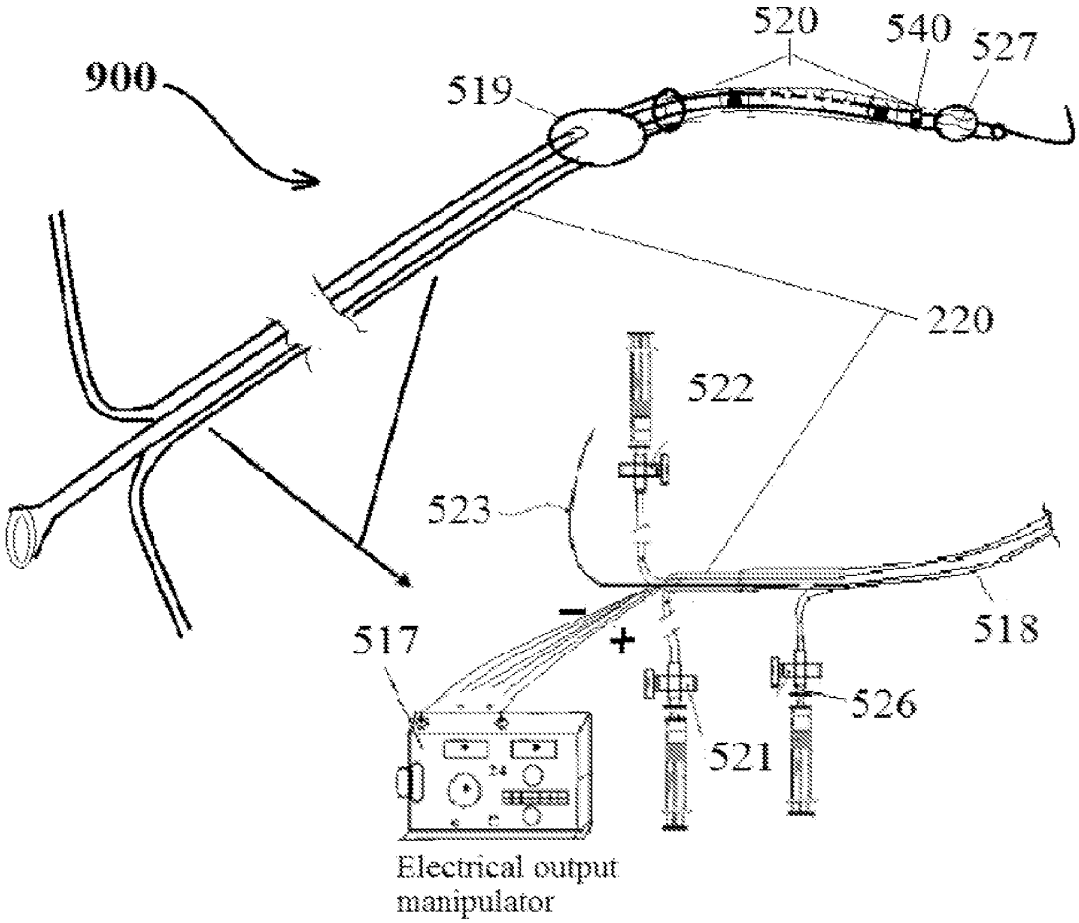

FIG. 9

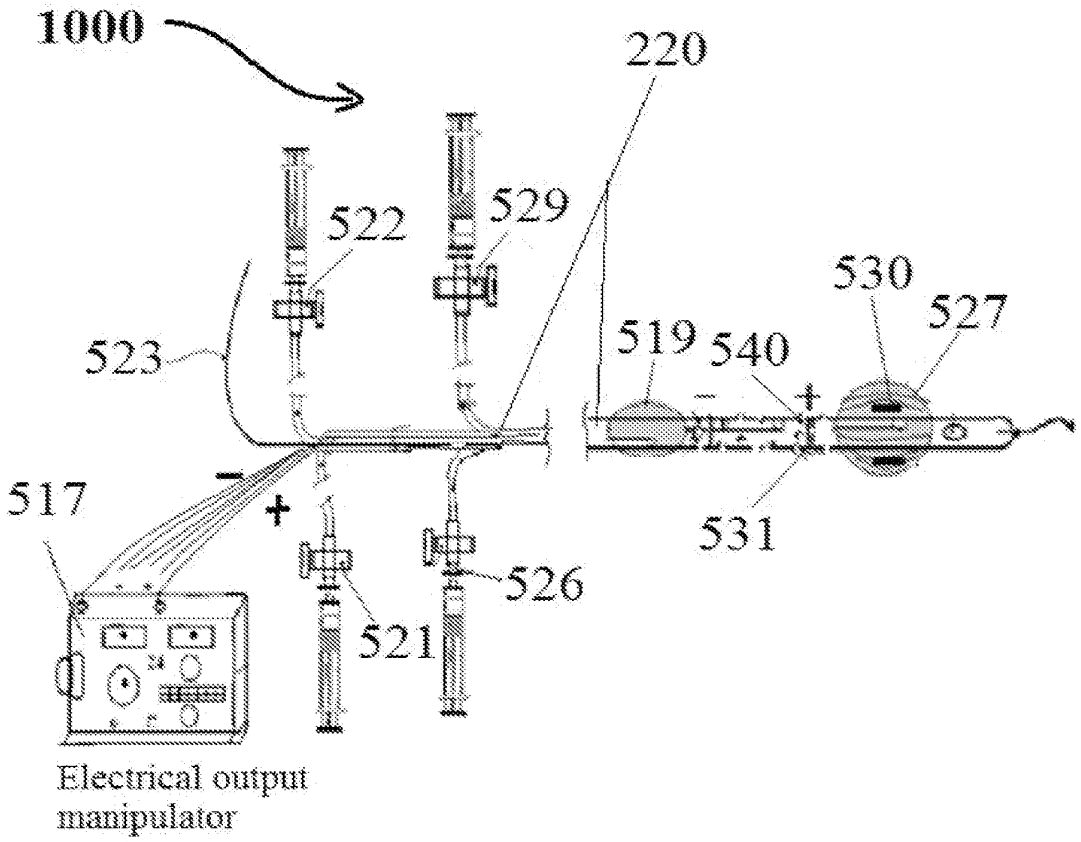

FIG. 10

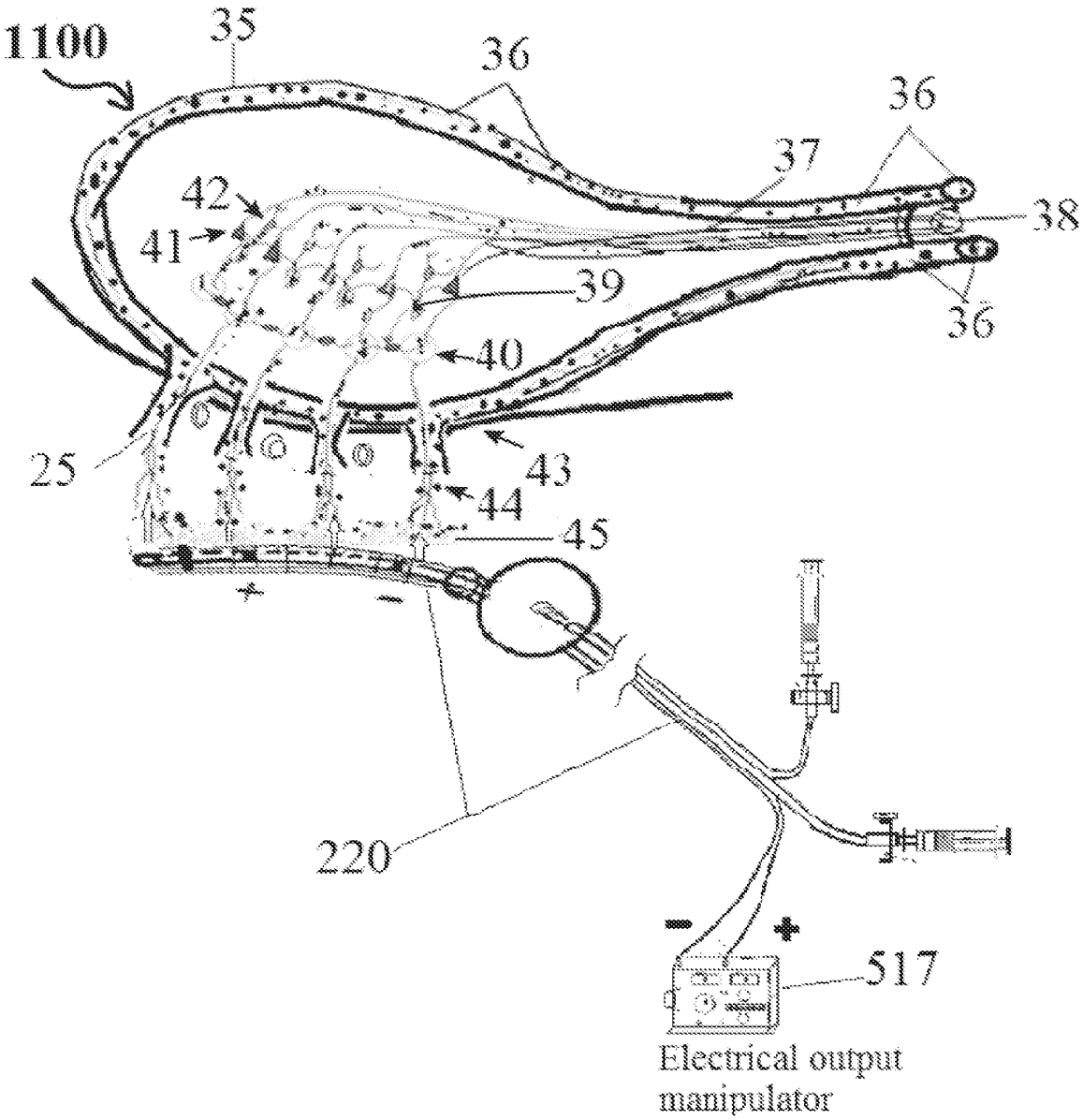

FIG. 11

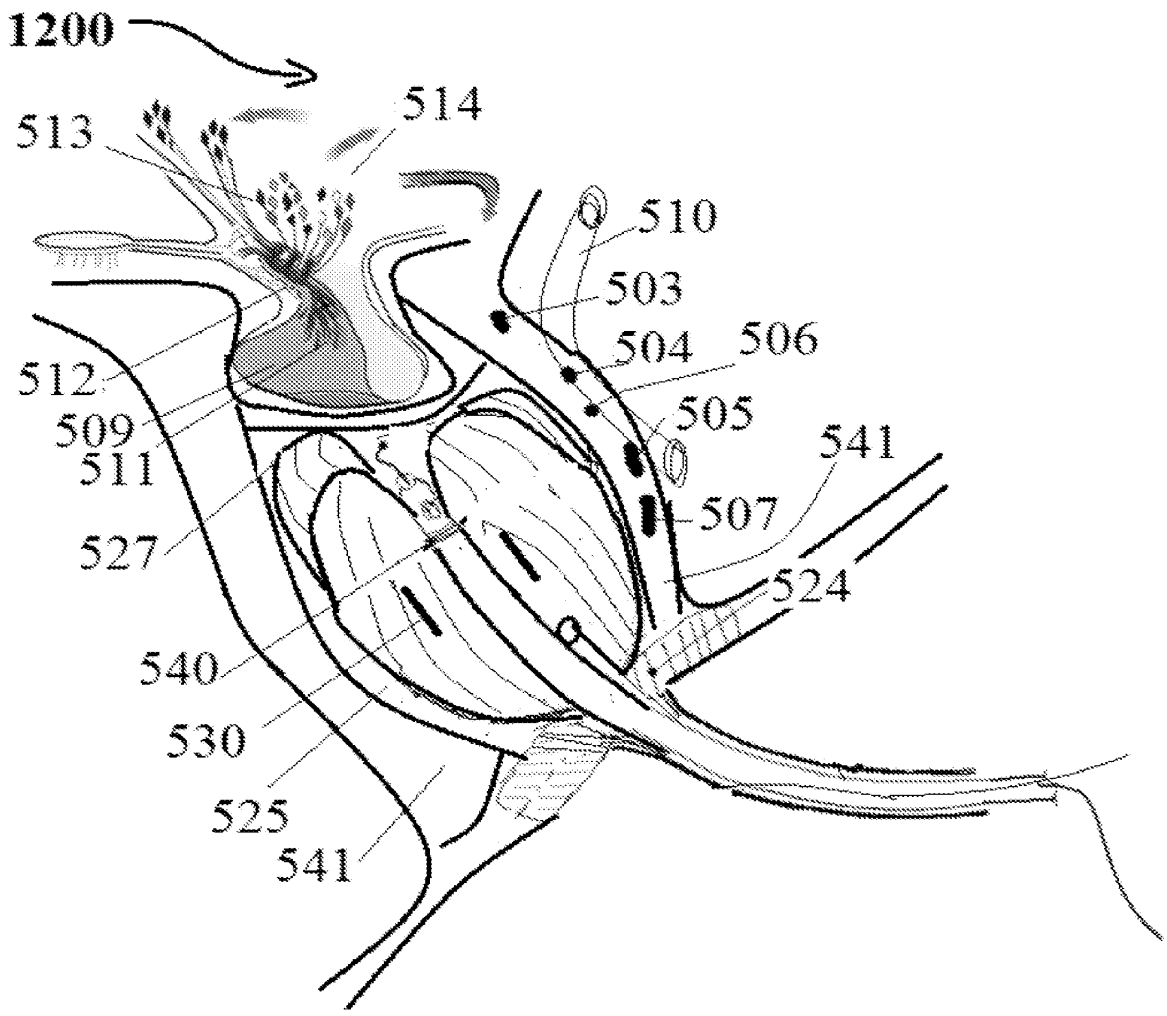

FIG. 12

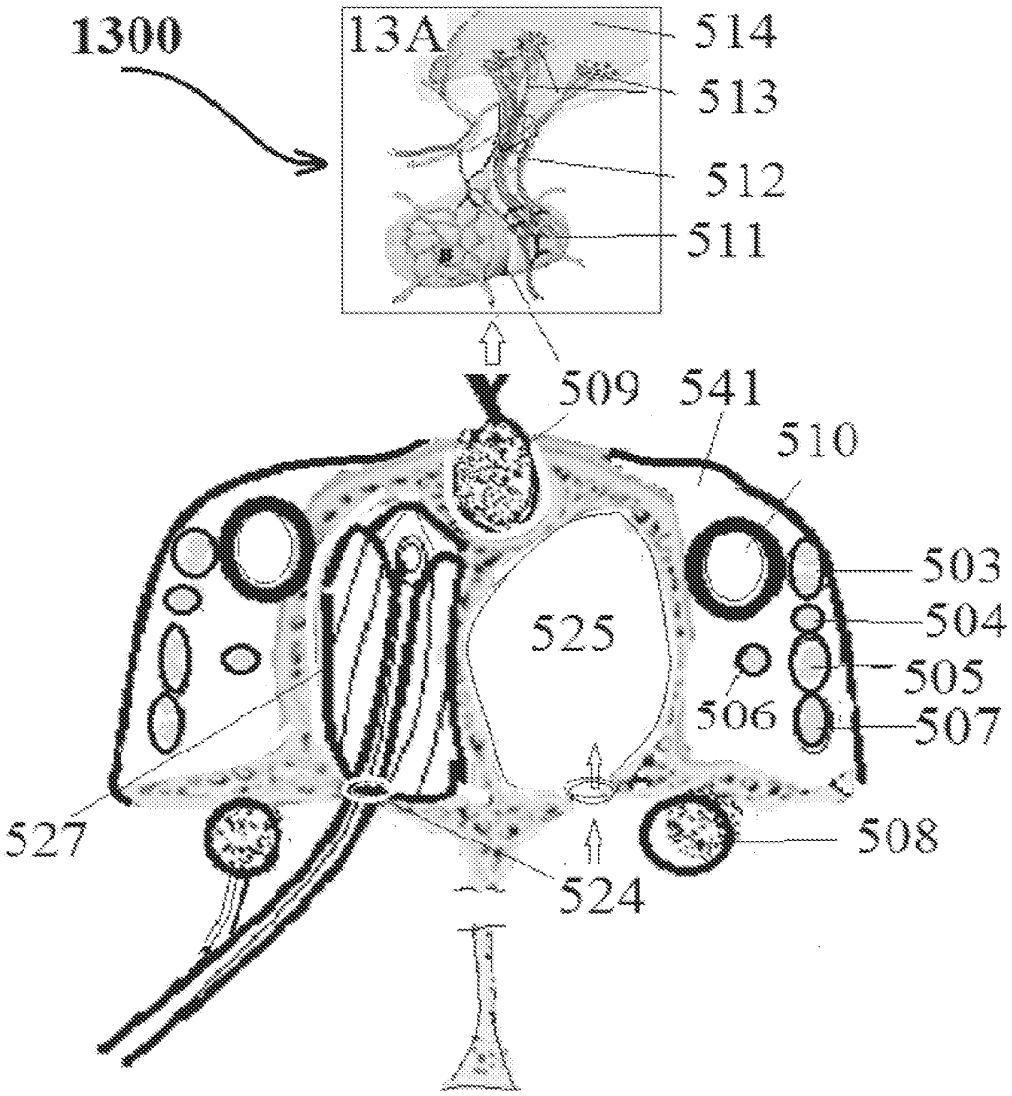

FIG. 13

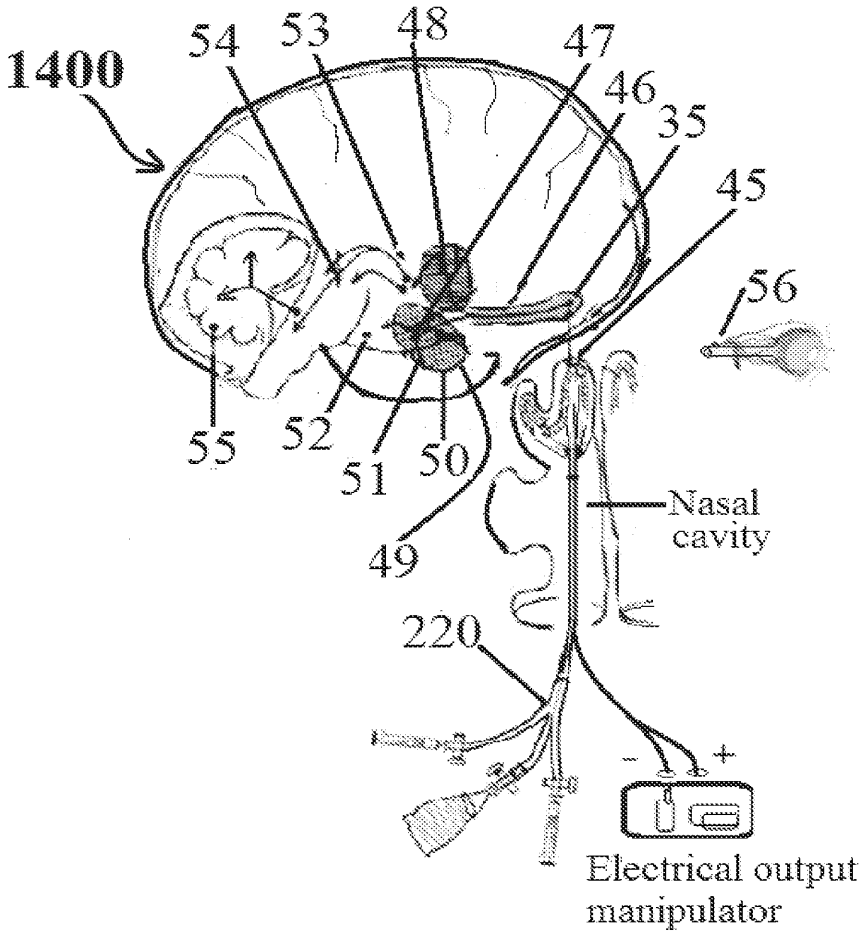

FIG. 14

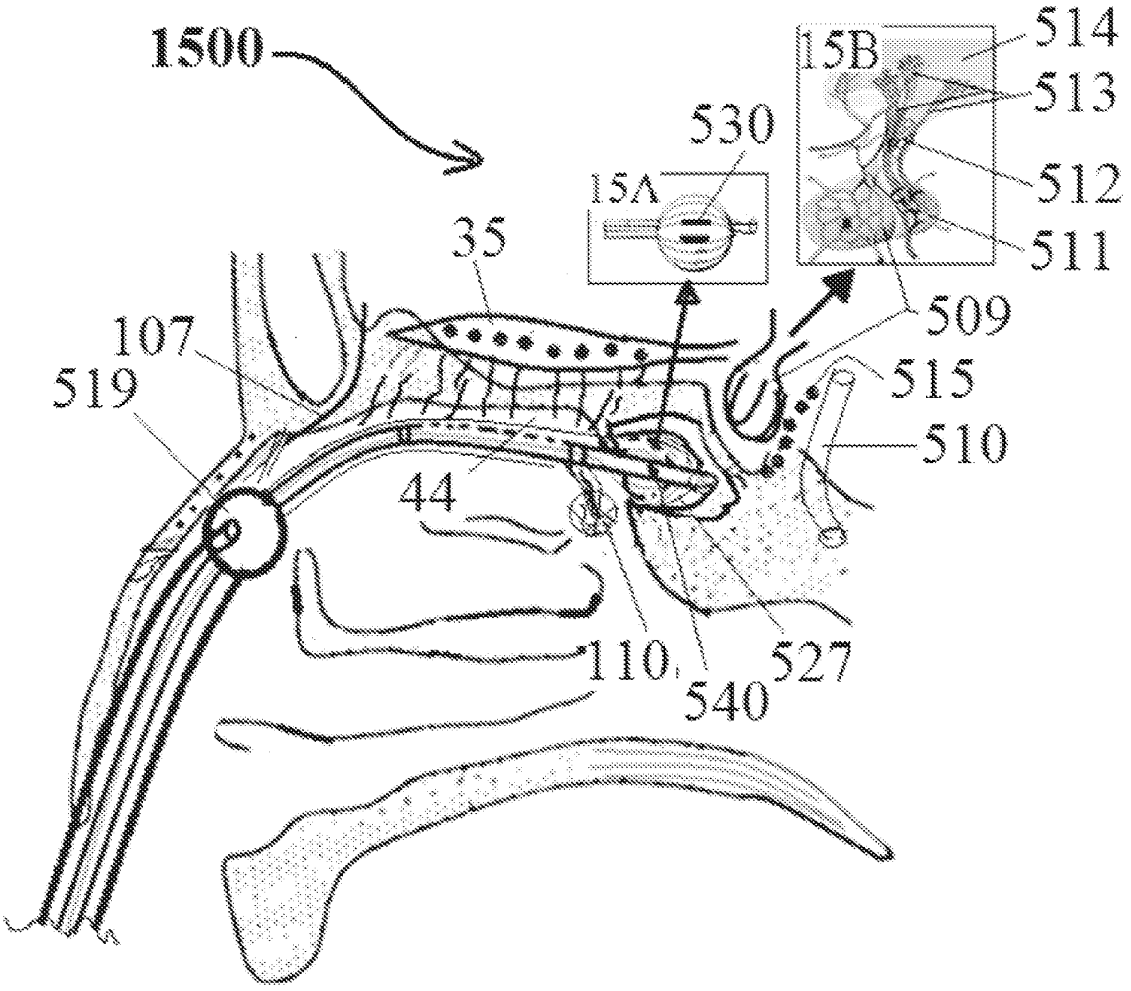

FIG. 15

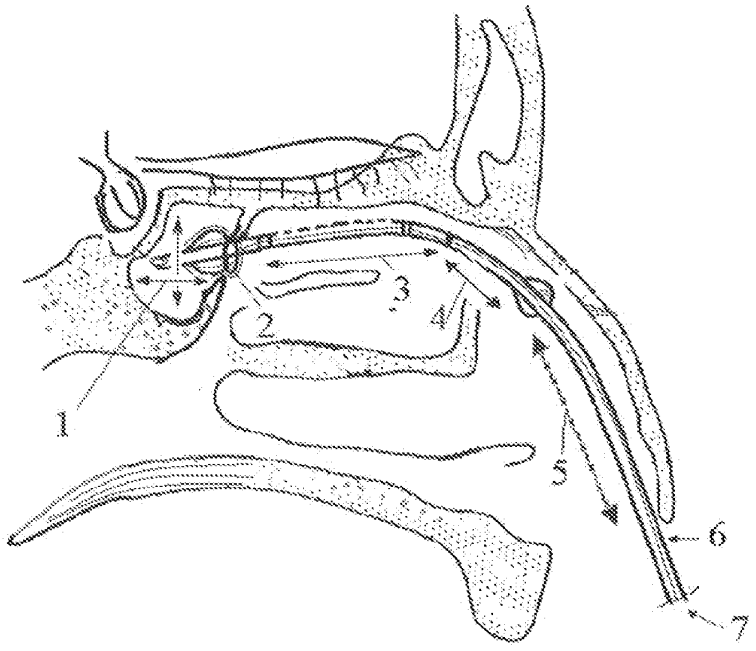

Figure 16

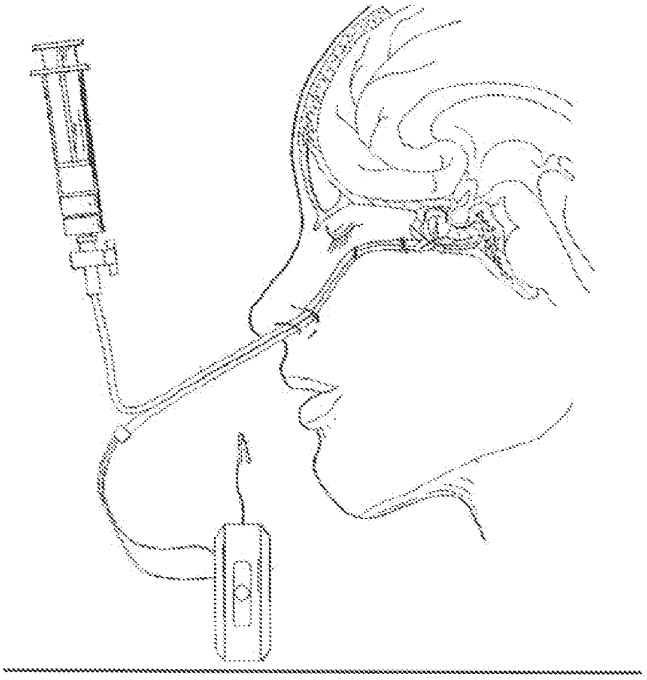

Figure 17

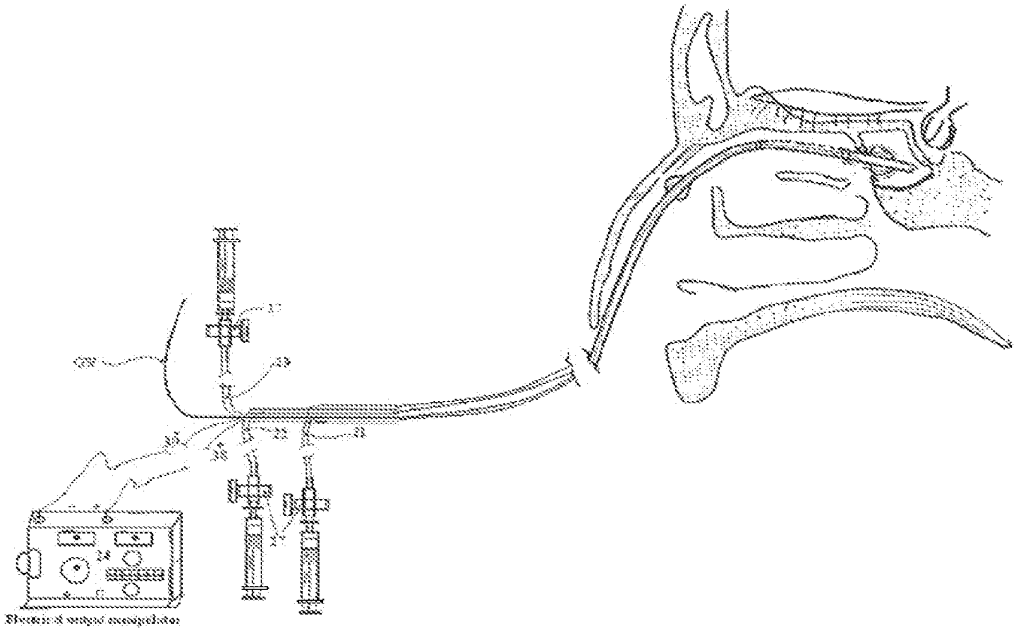

Figure 18

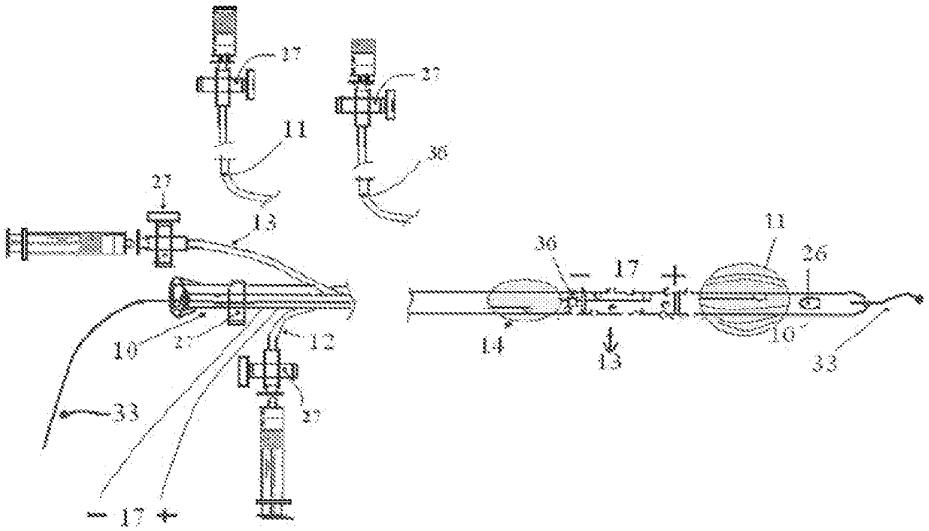

Figure 19

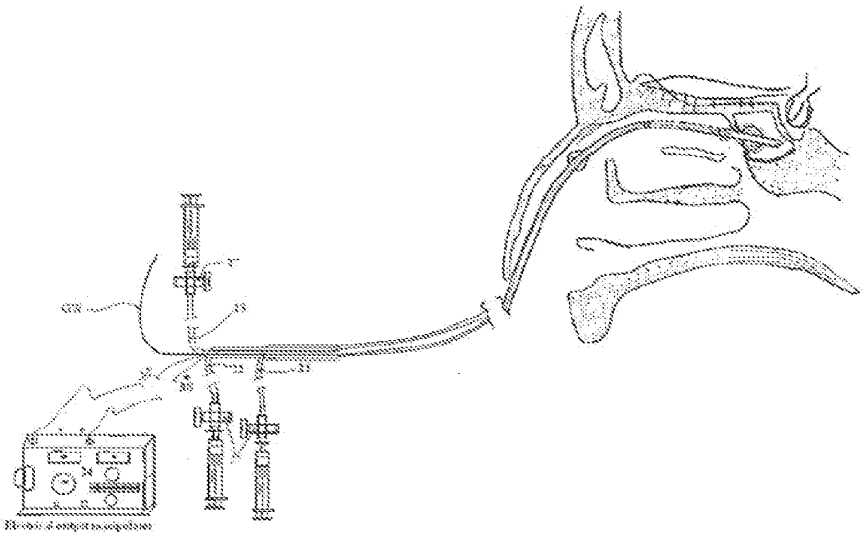

Figure 20

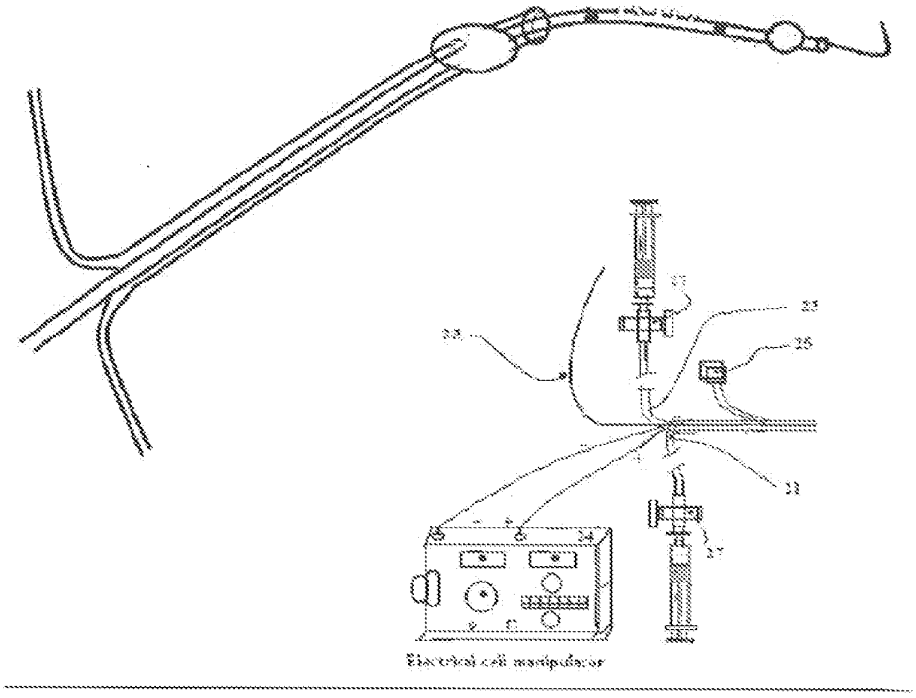

Figure 21

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US14/47566

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61N 1/30 (2014.01)
CPC - A61N 1/00, 1/30, 1/303, 1/306
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8): A61N 1/30 (2014.01)
CPC: A61N 1/00, 1/30, 1/303, 1/306

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Database(s) Searched (Patent and Non-Patent Literature (NPL), Including Sub-Databases and Files Searched) and Search Terms Used: MicroPatent (US-G, US-A, EP-A, EP-B, WO, JP-bib, DE-C,B, DE-A, DE-T, DE-U, GB-A, FR-A); ESpacenet; Google/Google Scholar; IP.com; PubMED/MEDLINE: array, balloon, bipolar*, electrode*, sphenoid*, sinus*, nasal*, olfactor*, mucosa*, stimulat*

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2012/0323214 A1 (SHANTHA, TR) December 20, 2012; figure 5-10; paragraphs [0173]-[0178]	1, 17-18 --- 2, 3/1, 3/2, 4/3/1, 4/3/2
Y	US 2011/0130708 A1 (PERRY, M et al) June 2, 2011; paragraph [0090]	2, 3/1, 3/2, 4/3/1, 4/3/2
A	US 2006/0058854 A1 (ABRAMS, R et al) March 16, 2006; figure 1; paragraphs [0016], [0018], [0029]	2, 3/1, 3/2, 4/3/1, 4/3/2

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
06 November 2014 (06.11.2014)	24 NOV 2014
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US14/47566

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 5-16 and 19-34
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

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2 April 2015 (02.04.2015)

WIPO | PCT

(10) International Publication Number
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A61B 17/02 (2006.01)

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(22) International Filing Date:
30 September 2014 (30.09.2014)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/884,547 30 September 2013 (30.09.2013) US
62/015,468 22 June 2014 (22.06.2014) US

(71) Applicant: **NIDUS MEDICAL, LLC** [US/US]; 75 Barry Lane, Atherton, California 94027 (US).

(72) Inventor: **SAADAT, Vahid**; 75 Barry Lane, Atherton, California 94027 (US).

(74) Agents: **HAN, Johney U.** et al.; Levine Bagade Han LLP, 2400 Geng Road, Suite 120, Palo Alto, California 94303 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

[Continued on next page]

(54) **Title**: APPARATUS AND METHODS FOR TREATING RHINITIS

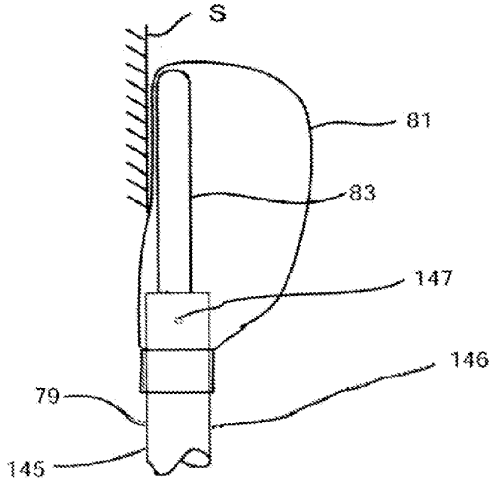


Figure 6H

(57) **Abstract**: Apparatus and methods for treating conditions such as rhinitis are disclosed herein where a distal end of a probe shaft is introduced through the nasal cavity where the distal end has an end effector with a first configuration having a low-profile which is shaped to manipulate tissue within the nasal cavity. The distal end may be positioned into proximity of a tissue region having a post nasal nerve associated with a middle or inferior nasal turbinate. Once suitably positioned, the distal end may be reconfigured from the first configuration to a second configuration which is shaped to contact and follow the tissue region and the post nasal nerve may then be ablated via the distal end. Ablation may be performed using various mechanisms, such as cryotherapy, and optionally under direct visualization.

WO 2015/048806 A2

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

APPARATUS AND METHODS FOR TREATING RHINITIS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Patent Application No. 61/884,547 filed September 30, 2013 and 62/015,468 filed June 22, 2014, each of which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] The present invention is related to devices and methods for ablating regions of tissue. More particularly, the present invention is related to devices and methods for ablating regions of tissue such as through cryogenic ablation of tissue regions within the nasal cavity for treating conditions such as rhinitis.

BACKGROUND OF THE INVENTION

[0003] The human nose is responsible for warming, humidifying and filtering inspired air. The nose is mainly formed of cartilage, bone, mucous membranes and skin. The right and left nasal cavities extend back to the soft palate, where they merge to form the posterior choanae. The posterior choanae opens into the nasopharynx. The roof of the nose is formed, in part, by a bone known as the cribriform plate. The cribriform plate contains numerous tiny perforations through which sensory nerve fibers extend to the olfactory bulbs. The sensation for smell occurs when inhaled odors contact a small area of mucosa in the superior region of the nose, stimulating the nerve fibers that lead to the olfactory bulbs.

[0004] The nasal turbinates are three bony processes that extend inwardly from the lateral walls of the nose and are covered with mucosal tissue. These turbinates serve to increase the inerior surface area of the nose and to impart warmth and moisture to air that is inhaled through the nose. The mucosal tissue that covers the turbinates is capable of becoming engorged with blood and swelling or becoming substantially devoid of blood and shrinking, in response to changes in physiologic or environmental conditions. The curved edge of each turbinate defines a passage way known as a meatus. For example, the inferior meatus is a passageway that passes beneath the inferior turbinate. Ducts, knows as the nasolacrimal ducts, drain tears from the eyes into the nose through openings located within the inferior meatus. The middle meatus is a passageway that extends inferior to the middle turbinate. The middle meatus contains the semilunar hiatus, with openings or Ostia leading

into the maxillary, frontal, and anterior ethmoid sinuses. The superior meatus is located between the superior and medial turbinates.

[0005] The turbinates are autonomically innervated by nerves arising from the Vidian nerve which contains sympathetic and parasympathetic afferents that can modulate the function of the turbinates to either increase (parasympathetic) or decrease (sympathetic) activity of the submucosal layer. The pterygoid canal carries both parasympathetic and sympathetic fibers, namely the vidian nerve, to the sphenopalatine ganglion. Exclusive of the sphenopalatine foramen (SPF) contents, additional posterolateral neurovascular rami project from the sphinopaletine ganglion via multiple individual postganglionic rami to supply the nasal mucosa . The most common locations for these rami are within 1 cm posterosuperior to the horizontal attachment of the inferior turbinate, within 5 mm anteroinferior to this attachment, and the palatine bone via a foramen distinct from the SPF. Also, Blier, et.al showed that interfascicle anastomotic loops in some cases, are associated with at least 3 accessory nerves. Based on Blier et.al work each accessory nerve could be proximally traced directly to the PPG or greater palatine nerve.

[0006] Rhinitis is defined as inflammation of the membranes lining the nose, characterized by nasal symptoms, including itching, rhinorrhea, and/or nasal congestion. Chronic Rhinitis affects tens of millions of people in the US and is a leading cause for patients to seek medical care. Medical treatment has been shown to have limited effects for chronic rhinitis sufferers and requires daily medication use or onerous allergy treatments and up to 20% of patients may be refractory.

[0007] In addition to the medications turbinate reduction surgery (RF and micro-debridement) both have temporary duration of effect of 1-2 years and can result in complications including mucosal sloughing, acute pain and swelling, overtreatment and bone damage. Additionally, turbinate reduction does not treat the symptom of rhinorrhea. It is thought that parasympathetic effect of the vidian nerve predominates so that, on transecting it, the result is decreased rhinitis and congestion. This pathophysiology has been confirmed as surgical treatment of the vidian nerve has been tried with great success; however, the procedure is invasive, time consuming and potentially can result in dry eyes due to autonomic fibers in the vidian nerve that supply the lacrimal glands.

[0008] Golding-Wood, who recommended cutting the parasympathetic nerve fibers in the vidian canal to decrease the parasympathetic tone to the nasal mucosa, introduced a different approach for the treatment of hypersecretion in 1961. Various approaches to the

vidian canal were subsequently developed, and the method was widely employed in the 1970s. However, the original technique was abandoned at the beginning of the 1980s because of its irreversible complications such as dry eyes.

[0009] Recent studies have shown that selectively interrupting the Post Nasal Nerves (PNN) in patients with chronic rhinitis improves their symptoms while avoiding the morbidities associated with vidian neurectomy.[1] The study by Ikeda et.al suggests that the effect of an anticholinergic drug on nasal symptoms resembled that of PNN resection in patients with chronic rhinitis. Based on his study the glandular mucosal acinar cells were significantly reduced after the PNN resection. The reduction in glandular cells may be explained by decreased secretion of the nerve growth factor or epidermal growth factor regulated by acetylcholine, a major neurotransmitter of parasympathetic systems.

[0010] Posterior nasal neurectomy, initially developed by Kikawada in 1998 and later modified by Kawamura and Kubo, is an alternative method in which neural bundles are selectively cut or cauterized from the sphenopalatine foramen. Autonomic and sensory nerve fibers that pass through the foramen anatomically branch into the middle and inferior turbinate and are distributed around the mucosal layer of the nose. Therefore, selective neurectomy at this point enables physicians to theoretically avoid surgical complications such as inhibition of lacrimal secretion.

SUMMARY OF THE INVENTION

[0011] The Posterior Nasal Nerves (PNN) innervate, inferior, middle, and inferior turbinates. Ablating these nerves leads to a decrease in or interruption of parasympathetic nerve signals that contribute to congestion and rhinorrhea in patients with chronic rhinitis (allergic or vasomotor). The devices and methods described herein are configured to be used for ablating one or more of these branches to reduce or eliminate rhinitis, e.g., ablating the Posterior Nasal Nerves (PNN).

[0012] Generally, several various apparatus and methods may be used to ablate the PNN as described below. One method for treating the tissue region within a nasal cavity in proximity to the PNN may be comprised of introducing a distal end of a probe shaft through the nasal cavity, wherein the distal end has an end effector with a first configuration having a low-profile which is shaped to manipulate tissue within the nasal cavity. The distal end may be positioned into proximity of the tissue region having the PNN associated with a middle or inferior nasal turbinate. Once suitably positioned, the distal end may be reconfigured from the first configuration to a second configuration,

which is shaped to contact and follow the tissue region. The distal end may then be used to ablate the PNN within the tissue region utilizing a number of different tissue treatment mechanisms, e.g., cryotherapy, as described herein.

[0013] In treating the tissue region in one variation, the distal end may be positioned specifically into proximity of the tissue region which is surrounded by the middle nasal turbinate, inferior nasal turbinate, and lateral wall forming a cul-de-sac and having the PNN associated with the middle or inferior nasal turbinate. The distal end may be reconfigured to treat the tissue region accordingly.

[0014] Various configurations for the distal end may be utilized in treating the tissue region so long as the distal end is configured for placement within the narrowed confines of the nasal cavity and more specifically within the confines of the cul-de-sac defined by the tissue region surrounding the middle nasal turbinate, inferior nasal turbinate, and lateral nasal tissue wall.

[0015] One example of a surgical probe configured for ablating the tissue region within such narrowed confines includes a surgical probe apparatus having a surgical probe shaft comprising an elongated structure with a distal end and a proximal end, an expandable structure attached to the distal end of the probe shaft, the expandable structure having a deflated configuration and an expanded configuration. A lumen may be defined through the shaft in fluid communication with an interior of the expandable structure. A member may be attached to the distal end and extend within the expandable structure which encloses the member such that the member is unattached to the interior of the expandable structure. Moreover, the member may define an atraumatic shape, which is sized for pressing against and manipulating through the expandable structure the lateral nasal wall or other tissue proximate to the PNN.

[0016] An example of utilizing such a structure in treating the tissue region may generally comprise advancing the distal end of the surgical probe shaft through the nasal cavity and into proximity of the tissue region having PNN associated with a middle or inferior nasal turbinate and introducing a cryogenic fluid into the expandable structure attached to the distal end of the probe shaft such that the expandable structure inflates from a deflated configuration into an expanded configuration against the tissue region.

[0017] As described above, a position of the member relative to the tissue region may be adjusted where the member is attached to the distal end of the probe shaft and extends within the expandable structure, which encloses the member such that the member is unattached to an interior of the expandable structure. The practitioner may apply a

pressure against the distal end such that the member is pressed against the interior of the expandable structure which in turn is pressed against the tissue region having the PNN, wherein the member defines an atraumatic shape which is sized for pressing against and manipulating the tissue region. The member may be maintained against the interior of the expandable structure and the tissue region until the tissue region is cryogenically ablated.

[0018] Any of the ablation devices herein can be used to ablate a single nerve branch or multiple nerve branches.

[0019] One aspect of this invention is a surgical probe configured for ablating the posterior nasal nerve associated with a nasal turbinate. The surgical probe, in one example, comprises a surgical shaft with a proximal end and a distal end, a surgical hand piece disposed on the proximal end, and a coiled spring-like structure disposed on the distal end. The coiled spring-like structure is a hollow structure comprising a closely pitched wire coil forming a central lumen, and an outer surface. The surgical hand piece comprises a pressurized liquid cryogen reservoir and a user actuated liquid cryogen flow control valve. There is at least one liquid cryogen path through the probe shaft in fluidic communication with the liquid flow control valve within the hand piece, and the spring-like coiled structure.

[0020] The pressurized cryogen liquid reservoir contains a liquid cryogen, e.g., nitrous oxide, but may also be another cryogenic liquid such as liquid carbon dioxide, or a liquid chlorofluorocarbon compound, etc. The distal spring-like structure may be configured as a liquid cryogen evaporator, either as a closed liquid cryogen evaporator, or as an open liquid cryogen evaporator.

[0021] In the closed evaporator configuration the inner central lumen of the spring-like structure is lined with a polymeric liner. Liquid cryogen is introduced into the central lumen through liquid cryogen supply line that is connected to the liquid cryogen reservoir in the handle, and runs coaxially through the probe shaft. The evaporated liquid cryogen may be vented to the room, e.g., through the probe shaft to a vent port in the hand piece, or in the vicinity of the proximal end of the probe shaft. No liquid or gas cryogen is introduced into the patient's nasal cavity.

[0022] In the open liquid cryogen evaporator configuration, the evaporated cryogen may exit the central lumen of the spring-like structure between the wire coils, and into the nasal cavity of the patient. Precautions to prevent the patient from inhaling the cryogen gas may be taken. As an example, a distal occlusion balloon may be used to occlude the distal nasal passageway.

[0023] The surgical probe may be configured so that the surgeon can press the distal spring like structure against the lateral nasal wall proximate to the target posterior nasal nerve. The spring-like structure is configured to conform to the morphology of the lateral nasal wall and to evenly engage the lateral nasal wall with a substantially uniform contact pressure. The probe shaft may have a length between, e.g., approximately 4 cm and 10 cm, and a diameter between, e.g., approximately 1 mm and 4 mm. The distal spring-like structure may have an outer diameter that approximates the diameter of the probe shaft, or may be larger or smaller in diameter. The extended length of the spring-like structure may be between, e.g., approximately 0.5 cm and 1.5 cm.

[0024] The surgical probe may be supplied with the distal spring-like structure configured straight and coaxial with the probe shaft. In another embodiment, the distal spring like structure is supplied with a lateral curve with the proximal end of the spring-like structure in a tangential relationship with the distal end of the probe shaft. In another embodiment, the surgical probe may be supplied with the distal spring-like structure in a loop configuration where both ends of the spring-like structure are in a substantially tangential relationship with the distal end of the probe shaft.

[0025] The distal spring-like structure is substantially flexible along its axis; however, the structure may also be at least partly malleable and configured for form shaping by the user. Form shaping of the spring-like structure may be done manually by the surgeon, or alternatively the surgical probe may be supplied with the distal spring like structure in various predetermined/factory configurations. Various lengths, shapes, and diameters of the spring-like structure of the surgical probe may be produced and supplied to the end user.

[0026] In one embodiment, the distal spring-like structure is configured as a cryogenic liquid evaporator, where cryogenic liquid is delivered to the central lumen of the distal spring like structure. The liquid then evaporates at a low temperature, which causes the outer surface of the spring-like structure to reach a temperature that is sufficiently cold to ablate surrounding tissue and the function of the target posterior nasal nerve. The surgical probe may be configured so that the temperature of the outer surface of the spring-like structure is between -20 Deg. C. and -50 Deg. C. during liquid cryogen evaporation.

[0027] The surgical hand piece may comprise a factory filled liquid cryogen reservoir, and a user actuated cryogen flow control valve. The surgical hand piece may be configured so that it is held by the user like a pistol having a pistol grip where the cryogen flow valve actuator is configured like a pistol trigger. In an alternate embodiment, the

surgical hand piece is configured for the surgeon to grip it substantially like a writing utensil, with a button located in the vicinity of the index finger configured to actuate the cryogen flow control valve. In a third embodiment, the surgical hand piece may be configured to be held by the surgeon substantially like a pistol or a writing utensil, with a pistol like trigger configured to actuate a cryogen flow control valve, and a button in the vicinity of the index finger configured to actuate the same or a second cryogen control valve.

[0028] In another embodiment of this invention, the distal spring-like structure is encompassed by an expandable membranous structure. The expandable membranous structure may be a hollow bulbous structure with a single ostium configured for pressure tight bonding to the distal end of the probe shaft. The expandable membranous structure may be configured as a liquid cryogen evaporation chamber. Liquid cryogen is introduced into the expandable membranous structure from the encompassed spring-like structure.

[0029] The evaporated cryogen may be exhausted into the room through the probe shaft to a vent port in the hand piece, or in the vicinity of the proximal end of the probe shaft. The surgical probe is configured so that the expandable membranous structure expands to a predetermined shape in response to liquid cryogen evaporation. The pressure within the expandable membranous structure during cryogen evaporation may be regulated. The regulation means may comprise a pressure relief valve disposed in the gas exhaust path. The expandable membranous structure may be formed from an elastomeric material such as silicone rubber, or a urethane rubber. Alternatively, the expandable membranous structure may be formed from a substantially non-elastomeric material such as polyurethane or PET. The expandable membranous structure is configured so the shape and the size of the structure matches the shape and the size of the cul-de-sac of the lateral nasal wall defined by the tail of the middle turbinate, lateral nasal wall and the inferior turbinate, which is the target location for the ablation of the posterior nasal nerves for the treatment of rhinitis. Matching the size and shape of the expandable membranous structure to the size and shape of the target anatomy facilitates optimal tissue freezing and ablation of posterior nasal nerves. The expandable membranous structure may have an expanded diameter between approximately 3 mm and 12 mm in one radial axis, and may be configured such that the expanded diameter in one radial axis is different than another radial axis.

[0030] The probe shaft may be straight and rigid, or alternatively may be substantially malleable and configured for form shaping by the user. The probe shaft may be straight and rigid in the proximal region, and substantially malleable in the distal region

and configured for form shaping by the user.

[0031] The surgical probe may be configured with a camera and a light source disposed in the vicinity of the distal end of the probe shaft. The camera and light source may be configured to provide the surgeon with images of the nasal anatomy in order to identify anatomical landmarks for guiding the surgical placement of the distal spring-like structure against the lateral nasal wall proximate to the target posterior nasal nerve. The camera and light source may be further configured to image tissue freezing to provide the surgeon with visual feedback on the progress of a cryo-ablation of the nasal tissue innervated by posterior nasal nerves.

[0032] The surgical probe may also be configured with at least one temperature sensor disposed in the vicinity of the distal end. The temperature sensor may be configured to sense a temperature indicative of cryogen evaporation temperature, or a temperature indicative of a tissue temperature of surgical interest. Signals from the at least one temperature sensor may be used to servo-control the flow of cryogen in order to control a tissue temperature or to control the evaporation temperature. A temperature sensor may also be used in an informational display, or for system alarms or interlocks.

[0033] The surgical probe may be configured to automatically adjust the flow rate of liquid cryogen in response to one or more of the following parameters: evaporator temperature, evaporator pressure, tissue temperature, evaporator exhaust gas temperature, or elapsed cryogen flow time. The flow rate may be adjusted in a continuous analog manner, or by an alternating on/off flow modulation.

[0034] Another aspect of this invention is a method for treating rhinitis by ablating posterior nasal nerves associated with a middle or inferior nasal turbinate. The method may comprise inserting the distal end of a surgical probe configured for cryoneurolysis into a nostril of a patient with the surgical probe comprising a hollow probe shaft that is, e.g., substantially rigid. The surgical hand piece disposed on the proximal end of the probe shaft may comprise a liquid cryogen reservoir and, e.g., a user actuated liquid cryogen flow control valve. A cryogen liquid evaporator comprising, e.g., a spring-like structure configured as a liquid cryogen evaporator, may be disposed on the distal end of the probe shaft. The distal spring-like structure may be positioned against the lateral nasal wall proximate to a target posterior nasal nerve and then a flow of liquid cryogen to the spring-like structure may be activated for a period of time sufficient to cryo-ablate a target area in the nose containing posterior nasal nerves.

[0035] The method may further involve the targeting of at least one additional

posterior nasal nerve, either within the ipsilateral nasal cavity, or a posterior nasal nerve in a contralateral nasal cavity.

[0036] The method may comprise the use of a surgical probe which has an expandable membranous or non-membranous structure that encompasses the distal spring-like structure and which is configured as an expandable liquid cryogen evaporation chamber. The expandable membranous structure may be configured to be a predetermined size and shape that matches the size and shape of the nasal wall anatomy proximate to the target posterior nasal nerve. The surgical probe may be configured so the expandable membranous structure expands to its predetermined size and shape in response to liquid cryogen evaporation within.

[0037] The method may comprise controlling the flow of the liquid cryogen into the evaporation chamber based on at least one predetermined parameter, which may comprise one or more of the following parameters: cryogenic liquid flow rate, cryogenic liquid flow elapsed time, cryogenic liquid evaporation pressure, cryogenic liquid evaporation temperature, cryogenic gas exhaust temperature, visual determination of tissue freezing, ultrasonic determination of tissue freezing, or the volume of cryogenic liquid supplied by the cryogenic liquid reservoir.

[0038] The method may comprise determining the location of the target posterior nasal nerve, which may involve one or more of the following targeting techniques: endoscopic determination based on the nasal anatomical landmarks, electrical neuro-stimulation of the target posterior nasal nerve while observing the physiological response to the stimulation, electrical neuro-blockade, while observing the physiological response to the blockade, or identification of the artery associated with the target posterior nasal nerve using, e.g., ultrasonic or optical doppler flow techniques.

[0039] Yet another aspect comprises an embodiment of a surgical probe which is configured for ablation where the surgical probe comprises a surgical probe shaft comprising an elongated structure with a distal end and a proximal end, an expandable structure attached to the distal end of the probe shaft, the expandable structure having a deflated configuration and an expanded configuration, a member attached to the distal end and extending within the expandable structure such that the member is unattached to an interior of the expandable structure, wherein the member defines a flattened shape which is sized for placement against a lateral nasal wall proximate to a posterior nasal nerve, and a lumen in fluid communication with the interior of the expandable structure.

[0040] In use, such a surgical probe may be used for treating a tissue region within

a nasal cavity, generally comprising advancing a distal end of a surgical probe shaft through the nasal cavity and into proximity of the tissue region having a posterior nasal nerve associated with a middle or inferior nasal turbinate, introducing a cryogenic liquid into an expandable structure attached to the distal end of the probe shaft such that the expandable structure inflates from a deflated configuration into an expanded configuration against the tissue region, positioning a member relative to the tissue region, wherein the member is attached to the distal end of the probe shaft and extends within the expandable structure such that the member is unattached to an interior of the expandable structure, and wherein the member defines a flattened shape which is sized for placement against the tissue region proximate to the posterior nasal nerve, and maintaining the member against the tissue region until the posterior nasal nerve is cryogenically ablated.

[0041] One aspect of the invention is a cryo-surgical probe apparatus for ablation of PNN function comprising a handle at the proximal end, a probe shaft with a spatula shaped cryo-ablation element mounted in vicinity of the distal end of the shaft, whereby the handle is configured for housing a cryogen source, and controlling the flow of the cryogen to the cryo-ablation element, and the geometric parameters of the probe shaft and cryo-ablation element are optimally configured for cryo-ablation of nasal mucosa containing PNN according to the surgical methods disclosed here within.

[0042] One embodiment of this invention is a cryo-surgical probe apparatus for ablation of nasal mucosa innervated by PNN comprise a handle at the proximal end, a probe shaft with a bullet shaped cryo-ablation element mounted in vicinity of the distal end of the shaft, whereby the handle is configured for housing a cryogen source, and controlling the flow of the cryogen to the cryo-ablation element, and the geometric parameters of the probe shaft and cryo-ablation element are optimally configured for cryo-ablation of PNN according to the surgical methods disclosed here within.

[0043] Another embodiment of this invention is a cryo-surgical probe apparatus for ablation of PNN function comprising a handle at the proximal end, a probe shaft with a bullet shaped cryo-ablation element mounted in vicinity of the distal end of the shaft, whereby the handle is configured for housing a cryogen source, and controlling the flow of the cryogen to the cryo-ablation element, wherein the probe shaft is configured with user operable deflectable distal segment, and the geometric parameters of the probe shaft and cryo-ablation element are optimally configured for cryo-ablation of PNN according to the surgical methods disclosed here within.

[0044] Another embodiment of this invention is a cryo-surgical probe apparatus for

ablation of PNN comprising a handle at the proximal end, a probe shaft with a cylindrically shaped cryo-ablation element mounted in vicinity of the distal end of the shaft, whereby the handle is configured for housing a cryogen source, and controlling the flow of the cryogen to the cryo-ablation element, wherein the cryo-ablation element comprises a linear segmented cryo-ablation element, and the geometric parameters of the probe shaft and cryo-ablation element are optimally configured for cryo-ablation of PNN according to the surgical methods disclosed here within.

[0045] Another embodiment of this invention is a cryo-surgical probe apparatus for ablation of PNN comprising a handle at the proximal end, a probe shaft with a cylindrically shaped cryo-ablation element mounted in vicinity of the distal end of the shaft, whereby the handle is configured for housing a cryogen source, and controlling the flow of the cryogen to the cryo-ablation element, wherein the cryo-ablation element comprises a semi-circular cryo-ablation element, and the geometric parameters of the probe shaft and cryo-ablation element are optimally configured for cryo-ablation of target tissue containing PNN according to the surgical methods disclosed here within.

[0046] Another embodiment of this invention is a cryo-surgical probe apparatus for ablation of PNN function comprising a handle at the proximal end, a probe shaft with a cylindrically shaped cryo-ablation element mounted in vicinity of the distal end of the shaft, whereby the handle is configured for housing a cryogen source, and controlling the flow of the cryogen to the cryo-ablation element, wherein the cryo-ablation element comprises a spiraled cryo-ablation element, and the geometric parameters of the probe shaft and cryo-ablation element are optimally configured for cryo-ablation of target nasal tissue containing PNN according to the surgical methods disclosed here within.

[0047] Another embodiment of this invention is a cryo-surgical probe apparatus for ablation of PNN comprising a proximal end, a probe shaft with a cryo-ablation element comprising a balloon mounted in vicinity of the distal end of the shaft, whereby the proximal end is configured for receiving a cryogen from a cryogen source with the cryogen source comprising a means controlling the flow of the cryogen to the cryo-ablation element, and the geometric parameters of the probe shaft and cryo-ablation element are optimally configured for cryo-ablation of PNN according to the surgical methods disclosed here within.

[0048] Another embodiment of this invention is a cryo-surgical probe apparatus for ablation of PNN comprising a handle at the proximal end, a probe shaft with a cylindrically shaped cryo-ablation element comprising a balloon mounted in vicinity of the distal end of

the shaft, whereby the handle is configured for housing a cryogen source, and controlling the flow of the cryogen to the cryo- ablation element, and the geometric parameters of the probe shaft and cryo-ablation element are optimally configured for cryo-ablation of target nasal tissue containing PNN according to the surgical methods disclosed here within.

[0049] Another embodiment of this invention is a cryo-surgical probe apparatus for ablation of PNN comprising a handle at the proximal end, a probe shaft with a cylindrically shaped cryo-ablation element mounted comprising a balloon with two lateral chambers disposed in the vicinity of the distal end of the shaft, whereby the handle is configured for housing a cryogen source, and controlling the flow of the cryogen to the cryo-ablation element, wherein one chamber of the balloon is configured as a cryogen expansion chamber, and the second chamber is configured as a thermal insulation chamber, and the geometric parameters of the probe shaft and cryo-ablation element are optimally configured for cryo-ablation of PNN according to the surgical methods disclosed here within.

[0050] Another embodiment of this invention is a cryo-surgical probe apparatus for ablation of PNN comprising a handle at the proximal end, a probe shaft with a "T" shaped cryo-ablation element comprising a balloon mounted in vicinity of the distal end of the shaft, whereby the handle is configured for housing a cryogen source, and controlling the flow of the cryogen to the cryo-ablation element, and the geometric parameters of the probe shaft and cryo-ablation element are optimally configured for cryo-ablation of PNN according to the surgical methods disclosed here within.

[0051] Another embodiment of this invention is a cryo-surgical probe apparatus for ablation of PNN function comprising a handle at the proximal end, a probe shaft with a "J" shaped cryo-ablation element comprising a balloon mounted in vicinity of the distal end of the shaft, whereby the handle is configured for housing a cryogen source, and controlling the flow of the cryogen to the cryo-ablation element, and the geometric parameters of the probe shaft and cryo-ablation element are optimally configured for cryo-ablation of PNN according to the surgical methods disclosed here within.

[0052] Another embodiment of this invention is a cryo-surgical probe apparatus for ablation of PNN comprising a handle at the proximal end, a probe shaft with a cryo-ablation element mounted in vicinity of the distal end of the shaft, whereby the handle is configured for housing a cryogen source, and controlling the flow of the cryogen to the cryo-ablation element, wherein a suction means associated with the cryo-ablation element is configured for stabilizing the position of the cryo-ablation element against the target

tissue, and the geometric parameters of the probe shaft and cryo-ablation element are optimally configured for cryo-ablation of PNN according to the surgical methods disclosed here within.

[0053] One aspect of this is a method for cryo-surgical ablation of PNN comprising placing a film of oil or gel on the surface of a cryo-ablation element, then pressing the cryo-ablation element against the lateral wall of a nasal cavity adjacent to a PNN, then ablating the function of the PNN with the cryo-ablation element, whereby the oil or gel prevents frozen nasal tissue from adhering to the cryo-ablation element.

[0054] In another aspect of this invention is an electrosurgical probe apparatus for ablation of PNN comprising a handle at the proximal end, a probe shaft with a radiofrequency (RF) ablation element comprising at least one radiofrequency (RF) electrode mounted in the vicinity of the distal end of the shaft, an electrical connector in the vicinity of the handle configured to connect the RF ablation element to a source of radiofrequency energy, whereby the geometric parameters of the probe shaft and RF ablation element are optimally configured for RF ablation of PNN function according to the surgical methods disclosed here within.

[0055] One embodiment of this invention is an electrosurgical probe apparatus for ablation of PNN comprising a handle at the proximal end, a probe shaft with a radiofrequency (RF) ablation element comprising at least one radiofrequency (RF) electrode mounted in the vicinity of the distal end of the shaft, an electrical connector disposed in the vicinity of the handle configured to connect the RF ablation element to a source of radiofrequency energy, and a fluid connector disposed in the vicinity of the handle to connect at least one fluid port associated with the RF ablation element with a source of pressurized liquid, whereby the geometric parameters of the probe shaft and RF ablation element are optimally configured for RF ablation of PNN according to the surgical methods disclosed here within.

[0056] Another embodiment of this invention is an electrosurgical probe apparatus for ablation of PNN comprising a handle at the proximal end, a probe shaft with a radiofrequency (RF) ablation element comprising at least one radiofrequency (RF) electrode mounted in the vicinity of the distal end of the shaft, an electrical connector disposed in the vicinity of the handle configured to connect the RF ablation element to a source of radiofrequency energy, whereby the geometric parameters of the probe shaft and RF ablation element are optimally configured for RF ablation of PNN according to the surgical methods disclosed here within, wherein the RF ablation element comprises a

monopolar electrosurgical configuration comprising one or more electrodes.

[0057] Another embodiment of this invention is an electrosurgical probe apparatus for ablation of PNN comprising a handle at the proximal end, a probe shaft with a radiofrequency (RF) ablation element comprising at least one radiofrequency (RF) electrode mounted in the vicinity of the distal end of the shaft, an electrical connector disposed in the vicinity of the handle configured to connect the RF ablation element to a source of radiofrequency energy, whereby the geometric parameters of the probe shaft and RF ablation element are optimally configured for RF ablation of PNN according to the surgical methods disclosed here within, wherein the RF ablation element comprises a bi-polar electrosurgical configuration comprising two or more electrodes.

[0058] Another embodiment of this invention is an electrosurgical probe apparatus for ablation of PNN comprising a handle at the proximal end, a probe shaft with a radiofrequency (RF) ablation element comprising at least one radiofrequency (RF) electrode mounted in the vicinity of the distal end of the shaft, an electrical connector disposed in the vicinity of the handle configured to connect the RF ablation element to a source of radiofrequency energy, whereby the geometric parameters of the probe shaft and RF ablation element are optimally configured for RF ablation of PNN according to the surgical methods disclosed here within, wherein the RF ablation element is disposed in the vicinity of the distal end of the shaft on a cylindrical, "J" shaped, "U" shaped or "T" shaped structure.

[0059] Another embodiment of this invention is an electrosurgical probe apparatus for ablation of PNN function comprising a handle at the proximal end, a probe shaft with a radiofrequency (RF) ablation element comprising at least one radiofrequency (RF) electrode mounted in the vicinity of the distal end of the shaft, an electrical connector disposed in the vicinity of the handle configured to connect the RF ablation element to a source of radiofrequency energy, whereby the geometric parameters of the probe shaft and RF ablation element are optimally configured for RF ablation of PNN according to the surgical methods disclosed here within, wherein the RF ablation element is configured in a lateral or radial arrangement.

[0060] Another embodiment of this invention is n electrosurgical probe apparatus for ablation of PNN function comprising a handle at the proximal end, a probe shaft with a radiofrequency (RF) ablation element comprising at least one radiofrequency (RF) electrode mounted in the vicinity of the distal end of the shaft, an electrical connector disposed in the vicinity of the handle configured to connect the RF ablation element to a

source of radiofrequency energy, whereby the geometric parameters of the probe shaft and RF ablation element are optimally configured for RF ablation of PNN according to the surgical methods disclosed here within, wherein the RF ablation element comprises a circular array of domed electrodes disposed on a flat electrically insulative surface, with the domed electrodes optionally associated with a fluid irrigation port.

[0061] Another embodiment of this invention is an electrosurgical probe for ablation of PNN function comprising a handle at the proximal end, a probe shaft with a radiofrequency (RF) ablation element comprising at least one radiofrequency (RF) electrode mounted in the vicinity of the distal end of the shaft, an electrical connector disposed in the vicinity of the handle configured to connect the RF ablation element to a source of radiofrequency energy, whereby the geometric parameters of the probe shaft and RF ablation element are optimally configured for RF ablation of PNN according to the surgical methods disclosed here within, wherein the RF ablation element comprises a linear array of domed electrodes disposed on a flat electrically insulative surface, with the domed electrodes optionally associated with a fluid irrigation port, and a needle configured for injecting a liquid into a sub-mucosal space.

[0062] Another embodiment of this invention is an electrosurgical probe apparatus for ablation of PNN comprising a handle at the proximal end, a probe shaft with a radiofrequency (RF) ablation element comprising at least one radiofrequency (RF) electrode mounted in the vicinity of the distal end of the shaft, an electrical connector disposed in the vicinity of the handle configured to connect the RF ablation element to a source of radiofrequency energy, whereby the geometric parameters of the probe shaft and RF ablation element are optimally configured for RF ablation of PNN according to the surgical methods disclosed here within, wherein the RF ablation element comprises at least one needle configured for interstitial RF ablation.

[0063] Another embodiment of this invention is an electrosurgical probe apparatus for ablation of PNN comprising a handle at the proximal end, a probe shaft comprising a distal and proximal end, and an integrated circuit comprising an RF generator disposed in the vicinity of the handle and an RF ablation element disposed in the vicinity of the distal end of the shaft, whereby the geometric parameters of the probe shaft and RF ablation element are optimally configured for RF ablation of PNN according to the surgical methods disclosed here within.

[0064] In another aspect of this invention is an ultrasonic energy emitting probe apparatus for ablation of PNN comprising a handle at the proximal end, a probe shaft with

an ultrasonic energy ablation element comprising at least one ultrasonic energy emitter mounted in the vicinity of the distal end of the shaft, an electrical connector in the vicinity of the handle configured to connect the ultrasonic energy emitter to an ultrasonic energy generator, whereby the geometric parameters of the probe shaft and ultrasonic energy emitter are optimally configured for ultrasonic energy ablation of PNN according to the surgical methods disclosed here within.

[0065] In another embodiment of this invention is an ultrasonic energy emitting probe apparatus for ablation of PNN comprising a handle at the proximal end, a probe shaft with an ultrasonic energy ablation element comprising at least one ultrasonic energy emitter mounted in the vicinity of the distal end of the shaft, an electrical connector in the vicinity of the handle configured to connect the ultrasonic energy emitter to an ultrasonic energy generator; at least one fluid path in communication between at least one fluid connector in the vicinity of the handle and the ultrasonic energy emitter configured to cool the ultrasonic energy emitter during ultrasonic energy emission, whereby the geometric parameters of the probe shaft and ultrasonic energy emitter are optimally configured for ultrasonic energy ablation of PNN according to the surgical methods disclosed here within.

BRIEF DESCRIPTION OF THE DRAWINGS

[0066] Figure 1 is an internal lateral view of the nasal canal showing the relevant nasal anatomy and the targeted region of the lateral nasal wall for cryo-ablation of posterior nasal nerve function.

[0067] Figure 2 is a schematic illustration of a surgical probe configured for cryo-ablation of posterior nasal nerve function for the treatment of rhinitis.

[0068] Figure 3A is a view of the distal end of a surgical probe shaft with the spring-like structure coaxial to the surgical probe shaft.

[0069] Figure 3B is a view of the distal end of a surgical probe shaft with the spring-like structure comprising a lateral curve in a tangential relationship with the surgical probe shaft.

[0070] Figure 3C is a view of the distal end of a surgical probe shaft with the spring-like structure comprising a loop or a continuous structure.

[0071] Figure 4A is a side view of the distal end of the surgical probe shaft with the spring-like structure coaxial to the surgical probe shaft encompassed by an expandable membranous structure in an unexpanded state.

[0072] Figure 4B is a view of the distal end of the surgical probe shaft with the

spring-like structure coaxial to the surgical probe shaft encompassed by an expandable membranous structure in an expanded state.

[0073] Figure 5A is a side view of the distal end of a surgical probe shaft with the spring-like structure comprising a lateral curve in a tangential relationship with the surgical probe shaft encompassed by an expandable membranous structure in an unexpanded state.

[0074] Figure 5B is a view of the distal end of the surgical probe shaft with the spring-like structure comprising a lateral curve in a tangential relationship with the surgical probe shaft encompassed by an expandable membranous structure in an expanded state.

[0075] Figure 5C is a side view that is 90 degrees from the first side view of Figure 5A.

[0076] Figure 5D is a view that is 90 degrees from the first side view of Figure 5B.

[0077] Figure 6A is a view of the distal end of a surgical probe shaft with the spring-like structure comprising a loop encompassed by an expandable membranous structure in an unexpanded state.

[0078] Figure 6B is a view of the distal end of the surgical probe shaft with the spring-like structure comprising a loop encompassed by an expandable membranous structure in an expanded state.

[0079] Figure 6C is a view that is 90 degrees from the first side view of Figure 6A.

[0080] Figure 6D is a view that is 90 degrees from the first side view of Figure 6B.

[0081] Figure 6E is a view of the distal end of a surgical probe shaft with the structure comprising a continuous member encompassed by a non-distensible structure.

[0082] Figure 6F is a view that is 90 degrees from the first side view of Figure 6E.

[0083] Figure 6G is a view of the embodiment of Figure 6E when pressed longitudinally against a tissue region for treatment.

[0084] Figure 6H is a view of the embodiment of Figure 6E when pressed laterally against a tissue region for treatment.

[0085] Figure 7 is a cross sectional schematic view of the distal end of a surgical probe where the spring-like structure is configured as a closed cryogenic liquid evaporator.

[0086] Figure 8 is a cross sectional schematic view of the distal end of a surgical probe where the spring-like structure is encompassed by an expandable membranous structure with the membranous structure configured as a liquid cryogen evaporation chamber.

[0087] Figure 9 is an internal lateral view of the nasal canal showing a surgical probe with the spring-like structure pressed against a lateral nasal wall in position for a

cryo-ablation of a posterior nasal nerve function.

[0088] Figure 10A is a front view illustration the distal end of a paddle balloon ablation probe with its expandable structure in its un-expanded state. Figure 10B is a side view illustration of Figure 10A. Figure 10C is a front view illustration of the distal end of a paddle balloon ablation probe with its expandable structure in its expanded state. Figure 10D is a side view illustration of Figure 10C.

[0089] Figure 11A is a front view illustration of the distal end of a paddle porous balloon ablation probe. Figure 11B is a side view illustration of Figure 11A.

[0090] Figure 12A is a front view illustration the distal end of a paddle double balloon ablation probe with its expandable structure in its un-expanded state. Figure 12B is a side view illustration of Figure 12A. Figure 12C is a front view illustration of the distal end of a paddle double balloon ablation probe with its expandable structure in its expanded state. Figure 12D is a side view illustration of Figure 12C.

[0091] Figure 13A through 13D are schematic sectional coronal illustrations of a nasal cavity depicting the surgical access to a middle meatus and cryogenic ablation of a sphenopalatine brand and foramen.

[0092] Figure 14A is an internal lateral view of the nasal cavity showing an anatomical target for ablation of parasympathetic nervous function of the middle turbinate. Figure 14B is an internal lateral view of the nasal cavity showing an anatomical target for ablation of posterior nasal nerves. Figure 14C is an internal lateral view of the nasal cavity showing an anatomical target for ablation of posterior nasal nerves using an intermittent line of ablation. Figure 14D is an internal lateral view of the nasal cavity showing an anatomical target for ablation of posterior nasal nerves.

[0093] Figure 15A is a schematic illustration of a cryosurgical probe configured for cryo-ablation of posterior nasal nerves comprising a spatula shaped cryosurgical tip. Figure 15B defines a section view of the cryosurgical probe's cryosurgical tip. Figure 15C is a cross sectional view of the cryosurgical probe's tip.

[0094] Figure 16A is a schematic illustration of the distal end of an alternative embodiment of the cryosurgical probe comprising a bullet shaped cryo-ablation element at the distal end of an angled shaft. Figure 16B is a schematic illustration of the distal end of an alternative embodiment of the cryosurgical probe comprising a bullet shaped cryo-ablation element at the distal end of a user deflectable probe shaft. Figure 16C is a schematic illustration of the distal end of an alternative embodiment of the cryosurgical probe where the cryo-ablation element is configured for producing multiple discrete cryo-

ablations simultaneously.

[0095] Figure 17A is a schematic illustration of the distal end of an alternative embodiment of the cryosurgical probe comprising a semi-circular cryo-ablation element. Figure 17B is a schematic illustration of the ablation morphology resulting from use of the semi-circular cryo-ablation element. Figure 17C is a schematic illustration of the distal end of an alternative embodiment of the cryosurgical probe comprising a spiraled cryo-ablation element.

[0096] Figure 18A is a schematic illustration of cryo-ablation balloon probe configured for cryo-ablation of posterior nasal nerves. Figure 18B is a schematic illustration of the distal end of the cryo-ablation balloon probe detailing the geometry of the cryo-ablation balloon. Figure 18C is a schematic illustration of an alternate embodiment of the cryo-ablation balloon probe comprising an insulating chamber within the cryo balloon structure. Figure 18D is a schematic illustration of the distal end of an alternative embodiment of the cryo-ablation balloon probe comprising a tee shaped cryo-ablation balloon. Figure 18E is a schematic illustration of the distal end of an alternative embodiment of the cryo-ablation balloon probe comprising a "J" shaped cryo-ablation balloon.

[0097] Figure 19A is a schematic illustration of the distal end of an alternate embodiment a cryo-ablation probe comprising a cryo-ablation element with suction stabilization. Figure 19B is a cross sectional view of the distal end of the alternative embodiment showing the configuration of the cryo-ablation element and the suction stabilization means.

[0098] Figure 20A is a schematic illustration of a radiofrequency (RF) ablation probe configured for ablation of the posterior nasal nerves with a bi-polar ring electrode ablation element on an "J" shaped distal probe shaft. Figure 20B is a schematic illustration of the distal end of an alternative embodiment of an RF ablation probe comprising a bi-polar ring electrode ablation element on an "J" shaped distal probe shaft. Figure 20C is a schematic illustration of an alternative embodiment of the distal end of an RF ablation probe comprising a bi-polar electrode ablation element on an "J" shaped distal probe shaft with the electrodes disposed in a lateral array. Figure 20D is a schematic illustration of an alternative embodiment of the distal end of an RF ablation probe comprising a bi-polar electrode ablation element on a "U" shaped distal probe shaft with the electrodes disposed in a lateral array. Figure 20E is a schematic illustration of the distal end of an alternative embodiment of an RF ablation probe comprising a bi-polar electrode ablation element on a

user deployable "T" shaped structure.

[0099] Figure 21A is a schematic illustration of an RF ablation probe configured for ablation of posterior nasal nerves comprising an array of RF ablation electrodes disposed on a planar surface and a fluid irrigation means associated with the electrodes. Figure 21B is a schematic illustration of the distal end of the RF ablation probe showing the arrangement of the ablation electrodes and the associated fluid irrigation means.

[0100] Figure 22A is a schematic illustration of an alternative RF ablation probe comprising an electrode array disposed on a planar surface; a fluid irrigation means associated electrodes, and a deployable needle configured for injecting a liquid into a sub-mucosal space. Figure 22B is a schematic illustration of the distal end of the alternative embodiment RF ablation probe showing the arrangement of the ablation electrodes and the associated fluid irrigation means. Figure 22C is a schematic illustration of the distal end of the alternative embodiment RF ablation probe showing the arrangement of the ablation electrodes and the associated fluid irrigation means with the needle deployed.

[0101] Figure 23A is a schematic illustration of an RF interstitial needle ablation probe configured for interstitial ablation of the parasympathetic nervous function of a nasal turbinate(s). Figure 23B is a schematic illustration of the distal end of the RF interstitial needle ablation probe.

[0102] Figure 24A is a cross sectional view of the distal end of an RF interstitial needle ablation comprising a deployable and retractable array of RF ablation needles configured for lateral deployment showing the needle array retracted. Figure 24B is a cross sectional view of the distal end of an RF interstitial needle ablation comprising a deployable and retractable array of RF ablation needles configured for lateral deployment showing the needle array deployed. Figure 24C is a cross sectional view of the distal end of an RF interstitial needle ablation comprising a deployable and retractable array of RF ablation needles configured for axial deployment showing the needle array retracted. Figure 24D is a cross sectional view of the distal end of an RF interstitial needle ablation comprising a deployable and retractable array of RF ablation needles configured for axial deployment showing the needle array deployed.

[0103] Figure 25A is a schematic illustration of an integrated flexible circuit configured for use with an RF ablation probe comprising an RF energy source and control circuits at one end, and an RF ablation electrode array at the opposite end. Figure 25B is a schematic illustration of the RF ablation electrode array of the flexible circuit mounted on the distal shaft of an RF ablation probe that is configured for ablation of posterior nasal

nerves.

[0104] Figure 26A is an in situ schematic illustration of the RF ablation probe depicted in Figures 22A through 22C showing the needle injecting an anesthetic into the sub-mucosal space prior to an RF ablation of posterior nasal nerves. Figure 26B is an in situ schematic illustration of the resulting ablation.

[0105] Figure 27 is an in situ schematic illustration of an ablation of posterior nasal nerves using the RF interstitial needle ablation probe depicted in Figures 23A and 23B.

[0106] Figure 28 is an in situ illustration of the ablation of the posterior nasal nerves at the ablation target depicted in Figure 14D.

[0107] Figure 29 is an in situ illustration of the ablation of the posterior nasal nerves at the ablation target depicted in Figure 24A.

[0108] Figure 30 is an in situ illustration of the ablation of the posterior nasal nerves at the ablation target area depicted in Figure 14B.

[0109] Figure 31A is a schematic illustration of the ablation probe and an insulated probe guide configured to protect the nasal septum from thermal injury during an ablation of the posterior nasal nerves. Figure 31B is an in situ illustration of an ablation probe configured for ablation of the posterior nasal nerves which comprises an insulating structure configured to protect the nasal septum. Figure 31C is an in situ illustration of an ablation probe configured for ablation of the parasympathetic nervous function of posterior nasal nerves which comprises a space creating structure configured to protect the nasal septum.

DETAILED DESCRIPTION OF THE INVENTION

[0110] Figure 1 is an internal view of the nasal cavity showing the relevant nasal anatomy. Shown for orientation is the lateral nasal cavity wall 4, the nose 1, nostril 2, and the upper lip 3. The superior turbinate 5, middle turbinate 6, and inferior turbinate 7 are depicted along with the associated nerves relevant to this invention shown in dashed lines. The posterior nasal nerves 10,11 and 12 are responsible for the parasympathetic control of the nasal mucosa including turbinates. These posterior nasal nerves (PNNs) originate from the sphenopalatine ganglion. At times other accessory posterior nasal nerves (APNNs) may originate from the greater palatine nerve or from the bony plate underneath the mucosa.

[0111] Figure 2 is a schematic illustration of surgical probe 29, which is configured for cryo-ablation of posterior nasal nerve function for the treatment of rhinitis. Surgical probe 29 comprises: probe shaft 20, with shaft distal end 21 and shaft proximal end 27; surgical hand piece 23, e.g., with pistol grip 24, finger grip 25, pistol trigger flow control

valve actuator 26, button flow control flow valve actuator 22, finger grip barrel 28, cryogen reservoir housing 29; and distal end effector 30 (e.g., spring-like structure) with end effector proximal end 31, and end effector distal end 32. Surgical probe shaft 20 is between, e.g., approximately 1 mm and 4 mm in diameter, and between, e.g., approximately 4 cm and 10 cm in length. Surgical probe shaft 20 may be fabricated from various biocompatible materials such as a surgical grade stainless steel hypodermic tube, or may alternatively be fabricated from a polymeric extrusion. Surgical probe shaft 20 comprises at least one liquid cryogen delivery channel between shaft distal end 21 and shaft proximal end 27. Probe shaft 20 is substantially rigid in one variation, and may also be configured to be malleable and shape formable by the user. The distal end effector 30 is shown having multiple variations described herein and may be optionally interchanged depending upon which particular embodiment is utilized by a practitioner.

[0112] Although probe shaft 20 is depicted to be straight, it is well within the scope of this invention probe shaft 20 may be manufactured with at least one curved segment. Surgical hand piece 23 is disposed on the proximal end 22 of probe shaft 20. Surgical hand piece 23 comprises a liquid cryogen reservoir, not shown, that may be conventionally supplied with liquid cryogen and configured for a single patient use. Alternatively, surgical hand piece 23 may be configured for use with a user replaceable liquid cryogen reservoir in the form of a cartridge. Liquid cryogen cartridges are readily commercially available from many sources. In yet another alternative, a reservoir separate from the device may be fluidly coupled to the hand piece 23. Surgical hand piece 23 may further comprise a liquid cryogen flow control valve, not shown, that may be disposed in fluidic communication with the liquid cryogen reservoir and the liquid cryogen channel in probe shaft 20.

[0113] Surgical device 29 may be configured to be held like a pistol by the surgeon or practitioner using pistol grip 24, or the surgeon or practitioner may hold surgical device 29 like a writing utensil using finger grips 25, with finger grip barrel 28 residing between the thumb and index finger of the surgeon. Surgical device 29 may be configured with, e.g., two or more liquid cryogen flow control valve actuators comprising pistol trigger liquid cryogen flow control actuator 26, which may be used to control the flow of liquid cryogen when the surgeon holds surgical device 29 using pistol grip 24. Liquid cryogen flow control actuator button 22 may be used to control the flow of liquid cryogen when the surgeon holds surgical device 29 by finger grips 25. Probe shaft 20 may be configured to be rotatably coupled to the surgical device 29 to facilitate positioning of distal end effector 30 (e.g., spring–like structure) without having to rotate the surgical device 29 excessively.

Distal end effector 30 (e.g., spring–like structure) , with end effector proximal end 31, and end effector distal end 32 is disposed on the distal end 21 of probe shaft 20 as shown. Distal end effector 30 (e.g., spring–like structure) is configured as a liquid cryogen evaporator, and is configured to be pressed against the lateral nasal wall within the cul-de-sac described above for cryo-ablation of at least one posterior nasal nerve. The construction and the function of distal end effector 30 (e.g., spring–like structure) , and alternative embodiments are described in detail below.

[0114] Surgical device 29 may be configured as a simple mechanical device that is void of electronics as shown. Alternatively, surgical device 29 may be configured with at least one electronic function. In one embodiment, a temperature sensor may be disposed in the vicinity of distal end effector 30 (e.g., spring–like structure) and used to measure, display, or control a temperature of surgical interest. A temperature sensor may be configured to sense the temperature of evaporating cryogen within distal end effector 30 (e.g., spring–like structure) . A temperature sensor may also be configured to sense the temperature of a tissue of surgical interest. The liquid cryogen control valve 22 may also optionally comprise a servo mechanism configured to respond to a sensed temperature to modulate the flow of cryogen in order to control a desired surgical parameter.

[0115] In addition to a temperature sensing capability, surgical device 29 may be configured with a camera and/or a light source disposed in the vicinity of distal end 21 of probe shaft 20. The camera and light source may be used, e.g., to identify nasal anatomical landmarks, and may be used to guide the placement of distal end effector 30 (e.g., spring–like structure) against the lateral nasal wall for a cryo-ablation of the function of a target posterior nasal nerve. An ultrasonic or optical doppler flow sensor may also be disposed in the vicinity of distal end 21 of probe shaft 20 and be used, e.g., to locate the major artery associated with the target posterior nasal nerve, as a means for locating the target posterior nasal nerve. In addition, one or more electrodes may be disposed in the vicinity of distal end 21 of probe shaft 20, which may be used for electrical stimulation or electrical blockade of the function of a target posterior nasal nerve using the observed physiological response to the stimulation or blockade to confirm correct surgical positioning of distal end effector 30 (e.g., spring–like structure) prior to a cryo-ablation, and/or to confirm effectiveness of a cryo-ablation by the determination of a change in the physiological response from before and after a cryo-ablation.

[0116] Any number of temperature sensing, endoscopic instruments, servo controlled cryogen control valves, ultrasonic or optical doppler flow detection, and/or

electrical nervous stimulation and blockade mechanisms may be optionally incorporated into the devices described herein. Also, providing a surgical probe as described here with a liquid cryogen reservoir that is external to the probe hand piece is also within the scope of this invention.

[0117] Figure 3A is a schematic illustration of an alternative end effector embodiment, which comprises spring-like structure 39 which is configured in a coaxial arrangement with probe shaft 20. Figure 3B is a schematic illustration of the distal end of an alternative embodiment surgical probe 43 which comprises spring-like structure 44, which is configured with a lateral curve as shown with proximal end 46 in a tangential relationship with the distal end 21 of probe shaft 20. Figure 3C is a schematic illustration of the distal end of an alternative embodiment surgical probe 48, with spring-like structure 49 configured as a loop structure as shown, with both ends of spring-like structure 49 in a substantially tangential relationship with distal end 21 of probe shaft 20. The three alternate spring-like structure embodiments 39, 44, and 49 depicted in Figures 3A, 3B, and 3C are configured as liquid cryogen evaporators, where the outer surface of each spring-like structure may achieve a temperature between, e.g., approximately -20 Deg. C to -90 Deg. C., in response to liquid cryogen evaporation within. As previously described, the end effector described here may be optionally replaced by any of the other end effector embodiments described herein.

[0118] Spring-like structures 39, 44, and 49 are substantially flexible and are configured to conform to the morphology of a lateral nasal wall proximate to a target posterior nasal nerve with a substantially uniform contact pressure. Spring-like structures 39, 44, and 49 may be configured to be partially malleable and form shapeable by the user, while retaining a spring-like resilience during use. Spring-like structures 39 and 44 comprise distal end 40 and 45 respectively, and proximal end 41 and 46 respectively. Spring-like structures 39 and 44 comprise end cap 38, which functions as a pressure bulkhead defining the distal end of the liquid cryogen evaporator that resides within, which is described in detail below. Spring-like structures 39, 44, and 49 comprise a tightly coiled wire that forms a central chamber, and an outer surface. A thin polymeric liner is disposed on the inner surface of the central chamber and functions to contain the evaporating cryogen within the central chamber. Cryogen is introduced into the central chamber through a liquid cryogen supply line, which runs through probe shaft 20, and is in fluidic communication with the liquid cryogen flow control valve and the liquid cryogen reservoir previously described. Evaporated cryogen gas may be vented into the room out of the

central chamber, through probe shaft 20, then out of a vent port disposed in the vicinity of proximal end 22 of probe shaft 20, not shown, or disposed in the surgical hand piece, also not shown. The construction and function of the disclosed embodiments of the spring-like structures is described in detail below.

[0119] Figure 4A is a schematic illustration of a side view of the distal end of alternative embodiment surgical probe 55 comprising expandable membranous structure 58 encompassing spring-like structure 57 in an un-expanded state. Figure 4B is a schematic illustration of a side view of the distal end of surgical probe 55 with expandable structure or expandable membranous structure in an expanded state. In the depicted embodiment, expandable membranous structure 58 is configured as a liquid cryogen evaporation chamber. Liquid cryogen is introduced into the interior of expandable membranous structure 58 from spring-like structure 57. Surgical probe 55 is configured so expandable membranous structure 58 expands to a predetermined size and shape in response to liquid cryogen evaporation within. While structure 58 may be expandable to a predetermined size and shape, the structure 58 may be comprised of a non-distensible material while in other variations, structure 58 may alternatively be comprised of a distensible material which allows for the expanded size and shape to vary depending upon the volume of cryogen introduced. Surgical probe 55 is configured such that the outer surface of expandable membranous structure 58 will be between approximately -20 Deg. C to -90 Deg. C. during cryogen evaporation within. The expanded size or shape of expendable membranous structure 58 is configured to substantially contact the surface of the cul-de-sac (element 13 in Figure 1 which indicates the region of tissue region defined and surrounded by the middle nasal turbinate, inferior nasal turbinate, and lateral wall) when pressed against the lateral nasal wall be the surgeon. Expandable membranous structure 58 may be configured to form a hollow bulbous structure in its expanded state, and comprises a single ostium 59 configured for adhesive bonding to distal end 62 of probe shaft 56 using adhesive bond 60. Cryogen exhaust vent 61 comprises at least one fenestration in distal end 62 of probe shaft 40, which is in fluidic communication with a proximal vent port, not shown, and the room. A pressure relief valve, not shown, may be disposed in the fluid path between the interior of expandable membranous structure 58 and the room to control the pressure within expandable membranous structure 58, and the degree of expansion during liquid cryogen evaporation. The construction and functionality of surgical probe embodiments comprising an expandable membranous structure are described in detail below.

[0120] Figure 5A is a schematic illustration of a side view of the distal end of

alternate embodiment of surgical probe 68 comprising expandable membranous structure 69 encompassing spring-like structure 70. Spring-like structure 70 is configured with a lateral bend as depicted. Expandable membranous structure 69 is depicted in its un-expanded state. Figure 5B is a schematic illustration of the same side view in Figure 5A of alternate embodiment surgical probe 68 with expandable membranous structure 69 in its expandable state. Figure 5C is a schematic side view illustration taken at view A-A from Figure 5A. Figure 5D is a schematic side view illustration taken at view B-B from Figure 5B. Surgical probe 68 is configured with expandable membranous structure 69 functioning as a liquid cryogen evaporation chamber as depicted in Figures 4A and 4B. Liquid cryogen enters the interior of expandable membranous structure 69 from encompassed spring-like structure 70. Evaporated cryogen gas exits the interior of expandable membranous structure 69 through fenestration(s) 144 in distal end 143 of probe shaft 141 and exits surgical probe 68 proximally into the room. Spring-like structure 70 is configured to pre-tension membranous structure 69 in one radial axis to a greater extent than a second radial axis in a manner that causes expansion to be constrained in the radial axis with greatest pre-tensioning. In Figure 5A and 5B, spring-like structure 70 is configured to pre-tension expandable membranous structure 69 to a greater extent in the radial axis that is normal to the view axis. In Figure 5C and 5D, spring-like structure 70 is configured to pre-tension expandable membranous structure 69 to a greater extent in the radial axis that is parallel to the view axis. Figure 5A and Figure 5C depict surgical probe 68 with expandable membranous structure 69 in its un-expanded state. Figure 5B and 5D depict surgical probe 68 with expandable membranous structure 69 in its expanded state. Pre-tensioning of expandable membranous structure 69 provides a means for achieving a predetermined expanded shape for optimal matching of the morphology of the target area of the lateral nasal wall.

[0121] Figure 6A is a schematic illustration of a side view of the distal end of alternate embodiment of surgical probe 79 comprising expandable membranous structure 80 encompassing spring-like structure 82. Spring-like structure 82 is configured as a loop structure as depicted. Expandable membranous structure 80 is depicted in its un-expanded state. Figure 6B is a schematic illustration of the same side view in Figure 6A of alternate embodiment surgical probe 79 with its expandable membranous structure 80 in its expandable state. Figure 6C is a schematic side view illustration taken at view C-C from Figure 6A. Figure 6D is a schematic side view illustration taken at view D-D from Figure 6B. Surgical probe 79 is configured with expandable membranous structure 80 functioning

as a liquid cryogen evaporation chamber as depicted in Figures 4A and 4B. Liquid cryogen enters the interior of expandable membranous structure 80 from encompassed spring-like structure 82. Evaporated cryogen gas exits the interior of expandable membranous structure 69 through fenestration(s) 147 in distal end 146 of probe shaft 145 and exits surgical probe 79 proximally into the room. Spring-like structure 82 is configured to pre-tension expandable membranous structure 80 in one radial axis to a greater extent than a second radial axis in a manner that causes expansion to be constrained in the radial axis with greatest pre-tensioning. In Figure 6A and 6B, spring-like structure 82 is configured to pre-tension membranous structure 80 to a greater extent in the radial axis that is normal to the view axis. In Figure 6C and 6D, spring-like structure 82 is configured to pre-tension expandable membranous structure 80 to a greater extent in the radial axis that is parallel to the view axis. Figure 6A and Figure 6C depict surgical probe 79 with expandable membranous structure 80 in its un-expanded state. Figure 6B and 6D depict surgical probe 79 with expandable membranous structure 80 in its expanded state. Pre-tensioning of expandable membranous structure 80 provides a means for achieving a predetermined expanded shape for optimal matching of the morphology of the target area of the lateral nasal wall.

[0122] Another alternative embodiment is illustrated in the side view of Figure 6E which shows a structure or member 83 which is formed into a looped and elongated structure having arcuate edges for presenting an atraumatic surface. Rather than being formed as a spring like structure, the structure 83 may be formed of a relatively rigid wire or member instead which maintains its configuration when pressed against a tissue surface. Structure 83 may form a continuous structure which defines an opening there through such as a looped or elongated and looped member which is open through the loop. The structure 83 may be contained entirely within the expandable structure 81 which may be formed to have a predefined shape which is distensible or non-distensible when inflated by the cryogen. Moreover, the expandable structure 81 may be formed to surround the structure 83 entirely without being supported by or attached to the structure 83 itself. Such a structure 83 may provide a configuration which presents a low-profile as the device is advanced into and through the nasal cavity and between the nasal turbinate tissues. Yet because of the relatively flattened shape and rigidity and integrity of the structure 83, the structure 83 may be used to manipulate, move, or otherwise part the tissues of the nasal cavity without having to rely upon the expandable structure 81. Additionally, the low-profile enables the structure 83 to be positioned desirably within the narrowed confines of,

e.g., the cul-de-sac in proximity to the posterior nasal nerves (as shown by cul-de-sac 13 shown in Figure 1). When the expandable structure 81 is in its deflated state, it may form a flattened shape and when inflated, the expandable structure 81 may inflate into a configuration which remains unsupported by or attached to the structure 83. Because the structure 83 may be formed of a member which solid along its length, the cryogen may be introduced directly into the expandable structure 81 through a distal opening defined in the probe shaft 145.

[0123] Alternatively, structure 83 may be formed of a hollow tubular member which itself is formed into the continuous or looped shape. In such an embodiment, the cryogen may be optionally introduced through the hollow tubular member and dispersed within the interior of the expandable structure 81 through one or more openings which may be defined along the tubular member. In yet another alternative, the structure 83 may be formed into a flattened shape rather than a looped shape. In this configuration, the structure may be either solid or hollow such that that cryogen may be introduced through the structure and into the interior of the expandable structure 81 via one or more openings defined along the structure.

[0124] The structure 83 may extend and remain attached to the probe shaft 145, but the remainder of the structure 83 which extends within the expandable structure 81 may remain unattached or unconnected to any portion of the expandable structure 81. Hence, once the expandable structure 81 is inflated by the cryogen, the structure 83 may be adjusted in position or moved via manipulating the probe shaft 145 relative to the interior of the expandable structure 81 to enable the targeted positioning and cooling of the tissue region when in contact against the outer surface of the expandable structure 81. For instance, the structure 83 may press laterally upon a particular region of the underlying tissue to stretch or thin out the contacted tissue region to facilitate the cryogenic treatment. When the structure 83 is adjusted in position relative to the expandable structure 81, the expandable structure 81 may remain in a static position against a contacted tissue region allowing for limited repositioning of the structure 83 within.

[0125] Alternatively in other variations, the structure 83 may be attached along the interior of the expandable structure 81 partially at particular portions of the structure 83 or along the entirety of the structure 83. For instance, structure 83 may be attached, adhered, or otherwise coupled over its entirety to expandable structure 81 while in other variations, a distal portion of structure 83 may be attached, adhered, or otherwise coupled to a distal portion of the expandable structure 81 while in yet other variations, portions of the

structure 83 may be attached, adhered, or otherwise coupled to the expandable structure 81 along its side portions. Any of these variations may be optionally utilized depending upon the desired interaction and treatment between the structure 83, expandable structure 81, and underlying tissue region to be treated.

[0126] In yet another alternative variation, the lumen 84 for introducing the cryogen into the interior of the expandable structure 81 may be extended past the distal end of the probe shaft such that the cryogen is released within the interior at a more distal location. As shown, the cryogen lumen 84 may be supported along the structure 83, e.g., via a bar or member 85 which extends across the structure 83. This particular variation may allow for the cryogen to be introduced into the distal portion of the interior of the expandable member 81. Either this variation or the variation where the cryogen is released from an opening of the probe shaft may be utilized as desired.

[0127] Figure 6F shows a side view of the embodiment of Figure 6E illustrating how the structure 83 can be formed from a relatively flattened configuration relative to the inflated expandable structure 81. Because of the structural integrity of structure 83 and its relatively flattened profile, the structure 83 may provide for targeted treatment of the tissue when contacted by the device. Figure 6G shows the side view of the inflated expandable structure 81 when pressed in a longitudinal direction by its distal tip against the underlying tissue surface S. The relative strength of the structure 83 provides for the ability to press the device against the tissue surface such that the remainder of the expandable structure 81 may maintain its inflated configuration to potentially insulate the other surrounding tissue regions. Figure 6H likewise shows the device when the structure 83 is pressed laterally along its side against the tissue surface S such that the structure 83 lies flat. The contacted tissue region may be treated while the remainder of the surrounding tissue is potentially insulated by the expanded structure 81.

[0128] While the treatment end effector is designed for application along the tissue region defined by the cul-de-sac, the same end effector may be used in other regions of the nasal cavity as well. For instance, once the ablation is performed along the cul-de-sac, the end effector may then be moved to an adjacent tissue region, e.g., region immediately inferior to the cul-de-sac, and ablation treatment may be effected again. Additionally and/or alternatively, the end effector may also be used to further treat additional tissue regions, e.g., posterior aspect of the superior, middle, and/or inferior turbinates (any one, two, or all three regions). In either case, once the cul-de-sac has been ablated, the end effector may remain in place until the tissue region has thawed partially or completely

before the end effector is moved to the adjacent tissue region for further treatment.

[0129] Once the treatment is completed, or during treatment itself, the tissue region may be assessed utilizing any number of mechanisms. For instance, the tissue region may be visually assessed utilizing an imager during and/or after ablation.

[0130] As described herein, the device may be utilized with a temperature sensor, e.g., thermistor, thermocouple, etc., which may be mounted along the shaft, within or along the expandable structure 81, along the structure 83, etc., to monitor the temperature not only of the cryogen but also a temperature of the tissue region as well under treatment.

[0131] Additionally and/or alternatively, the expandable structure 81 may also be vibrated while maintaining the structure 83 against the interior of the expandable structure 81 and the tissue region utilizing any number of vibrational actuators which may be mounted anywhere along the device as appropriate. The vibrations may be applied directly against the tissue region or, e.g., through a layer of gel to facilitate the vibrational contact with the tissue.

[0132] Additionally and/or alternatively, other biocompatible agents may be used in combination with the cryogenic treatment. For instance, in one variation, an anesthetic may be applied to the tissue region to be treated prior to or during the cryogenic treatment. This and other alternative features described may be utilized not only with the variation shown and described in Figures 6E and 6F but with any other embodiments described herein.

[0133] Figure 7 is a cross sectional schematic illustration of the distal end of a generic surgical probe 89, which represents the construction and functionality of previously described surgical probe end effectors described above. Depicted is the distal end of probe shaft 90, liquid cryogen supply line 91, wire coil 92, inner liner 93, end cap 94, metering orifices 95, liquid cryogen 96, liquid cryogen evaporation chamber 97, and cryogen exhaust path 98. Liquid cryogen evaporation chamber is defined by central channel 134 and inner liner 93 of wire coil 92, end cap 94 at its distal end, probe shaft 90 at its proximal end. Wire coil 92 may be welded to end cap 94 and probe shaft 90 as shown. Alternatively, adhesive may be used for assembly. Probe shaft 90 may be formed from a surgical grade stainless steel hypodermic tube with an outside diameter between, e.g., approximately 1 mm and 4 mm. Wire coil 92 comprises a tightly coiled flat wire with a coil pitch that approximates the axial thickness 136 of wire 135 as shown. Wire 135 may be a stainless steel wire, or may alternatively be a nickel titanium super elastic alloy wire. Wire 135 has an axial thickness 136 between, e.g., approximately 0.5 mm and 1.5 mm, and a radial

thickness 137 between, e.g., approximately 0.1 mm and 0.5 mm. Wire 135 may alternatively be a round wire with a diameter between, e.g., approximately 0.25 mm and 1.0 mm.

[0134] Inner liner 93 is depicted being disposed on the inner wall of wire coil 92. Inner liner 93 is configured to provide a fluid tight seal of wire coil 92. Inner liner 93 may be a polymeric material such as polyethylene, or PTFE. Alternatively a polymeric line may be disposed on the outer surface 133 to provide a fluid tight seal of wire coil 92. Cryogen supply line 91 in fluidic communication with the supply of liquid cryogen in the liquid cryogen reservoir and liquid cryogen flow control valve in the surgical hand piece, not shown. Cryogen supply line 91 may be made from a thin walled tube with a high pressure rating such as a polyimide tube. Cryogen supply line 91 delivers liquid cryogen 96 into liquid cryogen evaporation chamber 97 through metering orifice(s) 95. Liquid cryogen supply line 91 has an inner diameter between, e.g., approximately 0.2 mm and 0.8 mm, and a wall thickness between, e.g., approximately 0.05 mm and 0.5 mm.

[0135] Metering orifices 95 are configured to comprise a distribution of fenestrations in the distal end of liquid cryogen supply line 91 as shown, and are configured to distribute liquid cryogen 96 into liquid cryogen evaporation chamber 97 in a substantially uniform manner. The diameter and number of metering orifices 95 are configured such that the flow of liquid cryogen 96 into liquid cryogen evaporation chamber 97 is sufficient to lower the temperature of outer surface 133 to between, e.g., approximately - 20 Deg. C., and -50 Deg. C. during liquid cryogen evaporation in order to effect a cryo-ablation, while limiting the flow of liquid cryogen 96 into liquid cryogen evaporation chamber 97 so that substantially all liquid cryogen evaporates within liquid cryogen evaporation chamber 97. As depicted, liquid cryogen evaporation chamber 97 is an empty space. Alternatively, liquid cryogen evaporation chamber 97 may comprise a porous material configured to absorb the liquid cryogen 96 and prevent the liquid cryogen from leaving liquid cryogen evaporation chamber 97 while in a liquid state. Cryogenic gas leaves liquid cryogen evaporation chamber 97 through central channel 139, and is vented into the room.

[0136] Figure 8 is a cross sectional schematic illustration of the distal end of generic surgical probe 104 representing the construction and functionality of surgical probe embodiments 55, 68, and 79 previously described and depicted in Figures 4A and 4B, Figures 5A through 5D, and Figures 6A through 6D, respectively. Depicted is the distal end of probe shaft 105, wire coil structure 106, end cap 107, liquid cryogen supply line

108, expandable membranous structure 109, in its expanded state, ostium 110, adhesive bond 111 between ostium 110 and probe shaft 105, cryogen gas exhaust vent 112, exhaust gas flow path 113, pressure bulkhead 114, liquid cryogen evaporation chamber 115, and liquid cryogen 116. Wire coil 106, probe shaft 105, end cap 107, and cryogen supply line 108 are substantially similar to corresponding elements described in detail and depicted in Figure 7, therefore, no further description is warranted. Expandable membranous structure 109, ostium 110, adhesive bond 111, cryogen gas exhaust vent 112, and exhaust gas flow path 113 are substantially similar to corresponding elements described in detail and depicted in Figure 4A, 4B, 5A through 5D, and 6A through 6D, therefore no further description is warranted. Liquid cryogen chamber 139 is defined by spring coil 106, end cap 107, and pressure bulkhead 114. Liquid cryogen 116 enters liquid cryogen chamber 139 through liquid cryogen supply line 108, and through liquid cryogen ports 137. Wire coil 106 is configured to meter liquid cryogen 116 from liquid cryogen chamber 139 into liquid cryogen evaporation chamber 115 in a manner that sprays liquid cryogen 116 in the direction of interior surface 141 of expandable membranous structure 109 so that the liquid cryogen rapidly evaporates upon contact with inner surface 141. A perforated polymeric liner, not shown, disposed upon wire coil 106 may be used to provide proper metering and spatial distribution of liquid cryogen 116.

[0137] Figure 9 is an internal view of the nasal cavity showing surgical probe 148 comprising an expandable membranous structure 123, configured as a liquid cryogen evaporator in position for a cryo-ablation of at least one posterior nasal nerve associated with middle nasal turbinate 129, or inferior nasal turbinate 128. Probe shaft 122 is associated with a surgical hand piece, not shown. Endoscope 126, proximal end not shown, with field of view 127 is positioned to guide the correct surgical placement of spring-like structure 125, and expandable membranous structure 123 against lateral nasal wall 130 at region 124 posterior to the middle turbinate as shown. Expandable membranous structure 123 is depicted in an expanded state. Alternatively, an endoscopic imaging means may be incorporated into the surgical probe 148, along its shaft, which may comprise a CCD or CMOS imager

[0138] Figures 10A thru 10D are schematic illustrations of the distal end 151 of alternative embodiment paddle balloon probe 150. Depicted is probe shaft 154, expandable structure 153, and paddle structure 152. Figure 10A is a front view illustration of distal end 151 with expandable structure 153 in an un-expanded state. Expandable structure 153 is maintained in its un-expanded state during introduction to, and removal from the target region of the

nasal anatomy. Suction may be applied by a suction means to maintain expandable structure 153 in its un-expanded state. Figure 10B is a side view illustration of the distal end 151 of paddle balloon probe 150 with expandable structure 153 in its un-expanded state. Figure 10C is a front view illustration of the distal end 151 of paddle balloon probe 150 with expandable structure 153 in its expanded or inflated state. Figure 10D is a side view illustration of the distal end of paddle balloon probe 150 with expandable structure 153 in its expanded or inflated state. Paddle 152 is configured for access to middle meatus of the lateral nasal wall by means of insertion between the middle nasal turbinate and the inferior nasal turbinate, as illustrated in figures 13A thru 13D below. Paddle structure 152 is a rounded rectangular shape as shown with a major dimension between approximately, e.g. 8mm and 16mm, and a minor dimension between approximately, e.g. 4mm and 10mm. The thickness of paddle structure 152 is between approximately, e.g. 1mm and 3mm. Paddle structure 152 is sufficiently rigid to access the middle meatus between the middle nasal turbinate and the inferior nasal turbinate, and is sufficiently flexible to avoid trauma to the nasal anatomy during use. Expandable structure 153 comprises a membrane that is bonded to paddle structure 152 in a manner that forms a air tight bladder as shown. Paddle balloon probe 150 is configured for introduction of a liquid cryogen into the bladder formed by paddle structure 152 and expandable structure 153, as well as to removed evaporated cryogen from the bladder with an exit to the room. The bladder formed by paddle structure 152 and expandable structure 153 is configured as cryogenic evaporation chamber, and the outer surface of expandable structure 153 is configured as a cryo-ablation surface. Expandable structure 153 is configured apply a force against the middle meatus of the lateral nasal wall between approximately, e.g. 20 grams and 200 grams. Expandable structure 153 is configured for expansion in reaction cryogen evaporation within. Liquid cryogen is introduced into the bladder through probe shaft 154, and evaporated cryogen gas is removed from the bladder and vented to the room trough probe shaft 154. The cryogenic ablation mechanisms and other features are similar to cryo-ablation probe embodiments described above and below.

[0139] Figures 11A and 11 B are schematic illustrations of the distal end 166 of paddle porous balloon probe 163, which is an alternative embodiment of paddle balloon probe 150. Figure 11 A is front view illustration, and Figure 11B is a side view illustration. Paddle porous balloon probe 163 comprises probe shaft 167, porous expandable structure 165, and paddle structure 164. Porous expandable structure 165 is similar to expandable structure 153, described above, comprising a porous membrane versus an air tight

membrane. Porous expandable structure 165 is configured for the venting of evaporated cryogen gas through the pores168 from within the bladder formed by porous expandable structure 165 and paddle structure 164 into the patient's nostril in the immediate vicinity of the surface of the lateral nasal wall that is targeted for cryo-ablation. Venting the cold gas in the vicinity of the targeted lateral nasal wall enhances cooling effectiveness, while precluding the need to vent the evaporated cryogen gas through probe shaft 167, allowing the probe shaft to be smaller in caliber, and therefore less traumatic. The cryogenic ablation mechanisms and other features are similar to cryo-ablation probe embodiments described above and below.

[0140] Figures 12A thru 12D are schematic illustrations of the distal end 179 of double balloon paddle probe 178. Figure 12A is a front view illustration of double balloon paddle probe 178 with expandable structure 181 in its un-expanded state. Figure 12 B is a side view illustration of double balloon paddle probe 178 with expandable structure in its un-expanded state. Figure 12C is a front view illustration of double balloon paddle probe 178 with expandable structure 181 in its expanded state. Figure 12 D is a side view illustration of double balloon paddle probe 178 with its expandable structure 181 in its expanded state. Double balloon paddle probe 178 comprises probe shaft 180, expandable structure 181, paddle structure 182, liquid cryogen port 183, and cryogen gas exhaust port 184. In this embodiment, expandable structure 181 encompasses paddle structure 182 and comprises a single ostium 185, and an adhesive bond 186 which forms an air tight seal of for expandable structure 181. The configuration and function of this embodiment substantially similar to the embodiment depicted in Figures 6A to 6H, with the difference being in this embodiment a paddle structure 182 is encompassed by expandable structure 181, versus a spring-like structure or a formed wire structure encompassed by an expandable structure as depicted in Figures 6A to 6H. Optionally, the distal inner edge of paddle structure 182 and be bonded to the interior of expandable structure 181 by adhesive bond 187.

[0141] Figures 13A through 13D are schematic sectional coronal illustrations of the nasal cavity depicting ablation probe 201 access to the middle meatus 198 between the middle nasal turbinate 6 and inferior nasal turbinate 7. Ablation probe 201 is a generic representation any of the ablation probes disclosed here within that utilize and expandable structure. Figure 13A depicts the thin edge of the distal end of ablation probe 201 being inserted into the thin gap between middle nasal turbinate 6 and inferior nasal turbinate 7. Figure 13B depicts the distal structure of ablation probe 201 behind middle turbinate against the middle meatus 198 in position for an ablation. Figure 13C depicts the initiation

of ablation by activation of the flow of cryogenic liquid into the expandable structure 203 resulting in the inflation of the expandable structure 203 as shown. Please note, as depicted, the expandable structure is most similar to that depicted in Figures 10 and 11, but is not intended imply a preference for those embodiments over the other embodiments disclosed here within. Figure 13D depicts the ablation zone 204 resulting from the application of a cryo-ablation of between approximately, e.g. 20 to 300 seconds. Following ablation, the probe may be removed following a thawing period that may be between approximately, e.g. 20 to 30 seconds. As depicted the sphenopalatine branch, comprising the sphenopalatine artery, sphenopalatine vein, and sphenopalatine nerve, and the sphenopalatine foramen are substantially encompassed by the zone of ablation 204. As previously described, and further described below, the targeted tissue may comprise other locations, including the proximity of accessory posterolateral nerves bounded by a sphenopalatine foramen superiorly, an inferior edge of an inferior turbinate inferiorly, a Eustachian tube posteriorly, or a posterior third of the middle and inferior turbinates anteriorly. Other anatomical targets may include the pterygomaxillary fossa, sphenopalatine ganglion, or vidian nerve.

[0142] Figure 14A is an internal lateral view of the nasal cavity showing target 228 for ablation of the parasympathetic nervous function of middle turbinate 6. Ablation target 228 is directly over the posterior superior lateral nasal branches 11 which innervate middle turbinate 6. Ablation target 228 may be circular as shown or non-circular, with a zone of ablative effect between 1 mm and 4 mm deep. Figure 14B is an internal lateral view of the nasal cavity showing target 246 for ablation of parasympathetic nervous function of superior turbinate 5, middle turbinate 6, and inferior turbinate 7. Ablation target 246 is linier as shown and is directly over posterior inferior lateral nasal branch 10, which innervates inferior turbinate 7, posterior superior lateral nasal branch 11 which innervates middle turbinate 6, and superior lateral nasal branch 12 which innervates superior turbinate 5. The depth of ablative effect is ideally between 1mm and 4mm deep. Figure 14C is an internal lateral view of the nasal cavity showing target 247 for ablation of parasympathetic nervous function of superior turbinate 5, middle turbinate 6, and inferior turbinate 7. Ablation target 246 is linier and segmented as shown with ablation segments directly over posterior inferior lateral nasal branch 10, which innervates inferior turbinate 7, posterior superior lateral nasal branch 11 which innervates middle turbinate 6, and superior lateral nasal branch 12 which innervates superior turbinate 5. The depth of ablative effect is ideally between 1mm and 4mm deep. Figure 2D is an internal lateral view of the nasal

cavity showing target 248 for ablation of the parasympathetic nervous function of middle turbinate 6. Ablation target 228 is directly over the posterior superior lateral nasal branches 11 which innervate middle turbinate 6. Ablation target 248 is oblong as shown and positioned between middle turbinate 6 and inferior turbinate 7 as shown, with a zone of ablative effect between 1 mm and 4 mm deep.

[0143] Figure 15A is a schematic illustration of cryosurgical probe 234 configured for cryo-ablation of parasympathetic nervous function of a nasal turbinate(s) comprising a spatula shaped cryosurgical tip 236. Cryosurgical probe 234 comprises handle 235, probe shaft 237 cryosurgical tip 236 refrigerant cartridge cover 239, and refrigerant control push button 238. Handle 235 may comprise a receptacle, not shown, for receiving a refrigerant filled cartridge, not shown, which may comprise liquid carbon dioxide, which is used for evaporative cryogenic cooling within cryosurgical probe tip 236. Alternatively, the cartridge may comprise a compressed cryogenic gas which may comprise argon or nitrous oxide which is used for Joule-Thompson effect cryogenic cooling within cryosurgical probe tip 236. Those skilled in the art cryosurgical instrumentation are familiar with means for configuring cryosurgical probe 234 for evaporative cryogenic cooling or Joule-Thompson effect cryogenic cooling according to this invention, therefore, further detailed description relating to cryosurgical techniques are not warranted. Refrigerant control push button 238 is in mechanical communication with a valve which is configured to open when push button 238 is depressed by the operator causing the cryogen within the cartridge to flow into cryosurgical probe tip 236 through a conduit within probe shaft 237. Handle 235 further comprises a venting means, not shown for exhausting the expanded cryogen into the atmosphere. Probe shaft 237 is between approximately 2mm and 6mm in diameter, with a length between approximately 4 cm and 10 cm. Figure 15B defines a section view of the cryosurgical probe 234 cryosurgical tip 236. Figure 15C is a cross sectional view of the cryosurgical probe 234 distal end comprising probe shaft 237, refrigerant delivery tube 253, and probe tip 236. Cryogen delivery tube 253 traverses the length of probe shaft 237 in a coaxial relationship and is in fluidic communication with the cryogen cartridge in handle 235 through the cryogen control valve previously described. At the distal end of cryogen delivery tube 253 there is at least one lateral fenestration configured to direct the release of the pressurized cryogen 256 from cryogen delivery tube 253 into expansion chamber 251 of cryosurgical tip 236 in the direction of cryo-ablation surface 249 of cryosurgical tip 236. Cryo-ablation surface 249 is substantially flat. The opposing surface 250 to ablation surface 249 may be cylindrical as shown. By directing the release of

cryogen towards ablation surface 249, ablation surface 249 achieves cryo-ablation temperatures between approximately -20 to -200 degrees centigrade, and opposing surface 250 remains warmer. The expanded cryogen 255 exits expansion chamber 251 through probe shaft 252 and is vented to atmosphere through handle 235 as previously described. Probe shaft 237, cryogen delivery tube 253, and cryosurgical tip 236 may fabricated from a stainless steel as is typical with cryosurgical probes, or may be fabricated with alternative materials as is familiar to those skilled in the art of cryosurgical probes. Probe shaft 237 may configured as shown with curvatures configured for nasal anatomy, or alternatively may be configured as described below.

[0144] Figure 16A is a schematic illustration of the distal end of an alternative embodiment 262 of the cryosurgical probe comprising a bullet shaped cryo-ablation element 263 at the distal end of angled probe shaft 265. In this embodiment pressurized cryogen is released through an orifice in an axial direction into the expansion chamber in the direction cryo-ablation surface 264. The diameter of shaft 265 is between approximately 2mm and 6mm, and the angle of shaft 265 is between approximately 30 and 60 degrees, and the point of bend is between 1 cm and 3 cm from the distal end of ablation element 263. Figure 16B is a schematic illustration of the distal end of an alternative embodiment 266 of the cryosurgical probe comprising a bullet shaped cryo-ablation element 263 at the distal end of a user deflectable probe shaft 267. Deflectable probe shaft 267 comprises distal deflectable segment 268 and a substantially rigid non-deflectable proximal segment 269. Probe shaft 267 diameter is between approximately 2 mm and 6 mm. The border between deflectable distal segment 268 and proximal non-deflectable segment is between approximately 1 cm and 3 cm from the distal end of ablation element 263. The angle of deflection may be between approximately 60 to 120 degrees and may be configured for deflection in one direction, or in two directions as shown. The deflection means comprises at least one pull wire housed within probe shaft 267 and a deflection actuator disposed in the vicinity of the proximal end of probe 266. Those skilled in the art deflectable tipped surgical probes are familiar means for creating a deflectable tipped cryosurgical probe according to this invention. Figure 4C and 4D are schematic illustrations of the distal end of an alternative embodiment 270 of the cryosurgical probe where the cryo-ablation element 274 is configured for producing multiple discrete cryo-ablations simultaneously. Cryo ablation element 274 comprises an expansion chamber, not shown, discrete lateral cryo-ablation surfaces 272, surrounded by thermal insulation 273. Ablation element 274 comprises a hollow bullet shaped metallic structure with lateral protrusions in the surface

forming cryo-ablation surfaces 272, with a thermal insulating material covering all remaining external surfaces of ablation element 274 as shown. As with cryo-surgical probe 234, cryogen is released from cryogen delivery tube in a lateral direction towards cryo-ablation surfaces 272.

[0145] Figure 17A is a schematic illustration of the distal end of an alternative embodiment 280 of the cryosurgical probe comprising a semi-circular cryo-ablation element 282. Cryo-ablation element 282 comprises a continuation of probe shaft 281 formed in a semi-circle as shown. Within the semi-circular section cryogen delivery tube 283 comprises an array of lateral fenestration in the one axial direction relative to semi-circular form, making the corresponding surface of the ablation element 282 the cryo-ablation surface. Figure 17B is a schematic illustration of the ablation 284 morphology in the nasal mucosa 288 resulting from use of the semi-circular ablation element 282. The gap 286 in the ablation provides blood perfusion to the mucosa encompassed by the ablation providing a reduction in tissue sloughing as the result of the ablation, as well as a reduction in the chance of infection, and a reduction of patient discomfort. Figure 17C is a schematic illustration of the distal end of an alternative embodiment 287 of the cryosurgical probe comprising a spiraled cryo-ablation element.

[0146] Figure 18A is a schematic illustration of cryo-ablation balloon probe 294 configured for cryo-ablation of parasympathetic nervous function of a nasal turbinate(s). Cryo-ablation balloon probe 294 comprises balloon 295, probe shaft 296, cryogen delivery tube 297, with lateral fenestrations 298 disposed on the distal end of cryogen delivery tube 297 within balloon 295 as shown. Cryo-ablation balloon probe 294 further comprises proximal hub 299 with cryogen exhaust port 299, cryogen supply port 301. Probe shaft 296 may be rigid or flexible. Balloon 295 functions as a cryogen expansion chamber for either a cryogenic evaporation cooling process or a Joules-Thompson effect cooling process. Pressurized cryogen 256 is delivered to the interior of balloon 295 through cryogen delivery tube 297 under pressure. Cryogen 256 exits cryogen delivery tube 297 through lateral fenestrations 298 as shown, in the radial direction towards the wall of balloon 295. The radial wall of balloon 295 is the cryo-ablation surface. Expanded cryogen 255 exits balloon 295 through probe shaft 296, and is vented to atmosphere through exhaust port 300. Exhaust port 300 may comprise a pressure relief valve, which creates a back pressure to inflate balloon 295 at a predetermined pressure. Cryogen supply port 301 is configured to connect cryogen supply tube 297 to a source of cryogen. Proximal hub 299 may be configured as a handle, and comprise a cryogen control valve. Figure 18B is a schematic

illustration of the distal end of the cryo-ablation balloon probe detailing the geometry of the cryo-ablation balloon. The length 302 of balloon 295 is between approximately 3 mm and 20 mm, and the diameter 303 of balloon 295 is between 1 mm and 5 mm. Figure 18C is a schematic illustration of an alternate embodiment 304 of the cryo-ablation balloon probe 294 comprising an insulating chamber 307 within the cryo balloon 305 structure. Insulating chamber 307 is formed by membrane 306 as shown. Fenestration 308 is a small opening in communication between expansion chamber 311 and insulating chamber 307, which allows insulation chamber to inflate with expanded cryogen gas 255 in a substantially static manner providing thermal insulation to the surface of balloon 305 adjacent to insulation chamber 307. Lateral fenestrations 310 direct pressurized cryogen 301 towards the wall of balloon 305 opposite of insulation chamber 307 forming cryo-ablation surface 312. The length 302 of balloon 305 is between approximately 3 mm and 20 mm, and the diameter of balloon 305 is between approximately 1 mm and 6 mm. Figure 18D is a schematic illustration of the distal end of an alternative embodiment 313 of the cryo-ablation balloon probe 294 comprising a tee shaped cryo-ablation balloon 314. The length 302 of balloon 314 is between approximately 3 mm to 20 mm, and the diameter of balloon 303 is between approximately 1 mm and 6 mm. Cryogen delivery tube 315 is configured to direct pressurized cryogen down the horns 316 of balloon 314 as shown. Figure 18E is a schematic illustration of the distal end of an alternative embodiment 317 of the cryo-ablation balloon probe 294 comprising a "J" shaped cryo-ablation balloon 318. The length 302 of balloon 318 is between approximately 3 mm and 20 mm, and the diameter 303 of balloon 318 is between approximately 1 mm and 6 mm. Cryogen delivery tube 319 is configured to direct pressurized cryogen 256 laterally into the "J" as shown.

[0147] Figure 19A is a schematic illustration of the distal end of an alternate embodiment 325 of cryo-ablation probe 294 comprising a cryo-ablation element 326 with suction stabilization. Figure 19B is a cross sectional view of the distal end of the alternative embodiment 325 showing the configuration of the cryo-ablation element 326 and the suction stabilization means.

[0148] Ablation element 326 is surrounded by suction chamber 329 as shown. Suction chamber 329 is in fluidic communication with a suction source, not shown, by suction tube 331. Suction ports 330 are oriented in the same direction as cryo-ablation surface 332 and are configured to provide suction attachment to the tissue when cryo-ablation surface 332 is placed into contact with the nasal mucosa in the ablation target zone. Probe shaft 325,

cryogen delivery tube 327, and lateral fenestrations 328 have similar function those previously described.

[0149] Figure 20A is a schematic illustration of radiofrequency (RF) ablation probe 338 configured for ablation of the parasympathetic nervous function of a nasal turbinate(s) with a bi-polar ring electrode ablation element 342 on an "J" shaped distal probe tip 341. RF ablation probe 338 comprises handle 339, probe shaft 340, "J" shaped probe tip 341, bipolar ring electrode pair 342, RF activation switch 345, electrical connector 343, and fluid connector 344. Those skilled in the art of RF ablation probes are familiar with the many possible configurations and construction techniques for RF electrodes and probes that are within the scope of this invention, therefore detailed description of the illustrated electrode configurations described below, and their construction techniques is not warranted. Electrical connector 343 is configured for connection to a radiofrequency energy generator, for which there are many commercially available. Fluid connector 344 is configured for connection to source of liquid irrigant. Fluid connector 344 may be in fluidic communication with at least one fluid irrigation port located the vicinity of the RF ablation electrode, and is embodiment specific. RF activation switch 345 allows the user to activate the RF ablation and terminate the RF ablation. Probe shaft 340 is between approximately 2 mm to 6 mm in diameter, and between approximately 4 cm and 10 cm long, but could be longer. The length of "J" tip 341 is between approximately 0.5 cm and 1.5 cm. Ring the spacing between RF electrode pair 342 is between approximately 2 mm and 6 mm. Figure 20B is a schematic illustration of the distal end of an alternative embodiment 346 of RF ablation probe 338 comprising a bi-polar segmented ring electrode ablation element on an "J" shaped distal probe shaft. The gap 348 shown in the ring electrode is on the side opposite of the side configured for RF ablation. The gap 348 in the ring electrodes protect the nasal septum during RF ensuring that RF energy is only applied to the lateral nasal wall at the ablation target. Figure 20C is a schematic illustration of alternative embodiment 349 of the distal end of RF ablation probe 338 comprising a bi-polar electrode ablation element 350 on a "J" shaped distal probe shaft with the electrodes disposed in a lateral array. Figure 20D is a schematic illustration of alternative embodiment 351 of the distal end of RF ablation probe 338 comprising a bi-polar electrode ablation element 352 on a "U" shaped distal probe shaft 353 with the electrodes disposed in a lateral array. Figure 20E is a schematic illustration of the distal end of alternative embodiment 354 of RF ablation probe 338 comprising a bi-polar electrode ablation element 355 on a user deployable "T" shaped structure356. Element 356 is comprised of two halves which can

alternately be collapsed and deployed as in Figure 20E. The two halves of the electrode structure 356 are pivoted to allow them to move laterally relative to the catheter shaft 354. Electrodes 355 can operate in a mono polar, bipolar or multipolar fashion as known in the art.

[0150] Figure 21A is a schematic illustration of alternative embodiment 362 to RF ablation probe 338 configured for ablation of the parasympathetic nervous function of a nasal turbinate(s) comprising an array of RF ablation electrodes 363 disposed on a planar surface with a fluid irrigation means associated with the electrodes. Figure 21B is a schematic illustration of the distal end of the RF ablation probe 362 showing the arrangement of the ablation electrode array 363 and the associated fluid irrigation means. Alternative embodiment 362 comprises distal probe tip 119, probe shaft 369, handle 339, fluid connector 344, and electrical connector 343. Electrode array 363 comprises two or more dome shaped electrodes 365, that are electrically configured into a bipolar pair, meaning that if there are 4 electrodes 365, then two of the electrodes are connectable to one pole of an RF generator, and the second two electrodes are connectable to the opposite pole of the RF generator, etc. Electrodes 365 are dome shaped and protrude from planar surface 366. A fluid port 364 is associated with each electrode 365. All fluid ports are in fluidic communication with fluid connector 344. Fluid ports 364 are configured to irrigate the surface of the nasal mucosa that is contact with electrodes 365 to provide cooling of the mucosa and the electrodes 365, to minimize thermal injury to the surface of the mucosa, and to prevent sticking of the electrodes to the surface of the mucosa. Probe tip 371 is between approximately 4 mm and 8 mm in diameter, and between approximately 3 mm to 8 mm thick. The number of electrodes 365 of electrode array 363 may be between 2 and approximately 10.

[0151] Figure 22A is a schematic illustration of an alternative embodiment 377 of RF ablation probe 362 comprising a linear electrode array 378 disposed on a planar surface; a fluid irrigation ports 387 associated electrodes 379, and a deployable needle 380 configured for injecting a liquid into a sub-mucosal space. Figure 22B is a schematic illustration of the distal end of the alternative embodiment 377 RF ablation probe showing the arrangement of the ablation electrodes 379 and the associated fluid irrigation ports 387. Figure 22C is a schematic illustration of the distal end of the alternative embodiment 377 RF ablation probe showing the arrangement of the ablation electrodes 379 and the associated fluid irrigation ports 387 with the needle 380 deployed. The function, of domed electrodes 379, fluid ports 387, electrical connector 343, fluid connector 344, RF activation

switch 345, handle 382, and shaft 384 all function in essentially the same manner as described for prior embodiment 362. This embodiment has a linear electrode array 378, and a deployable needle configured for injecting a liquid into the sub-mucosal space where the liquid may comprise an anesthetic. Needle actuator 383 provides the user a means actuating needle 380. Fluid connector 389 is in fluidic communication with needle 380, through needle shaft 385, and is configured with a female luer connector for mating with a syringe, not shown. Shaft 384 contains needle shaft 385, electrical cable 386, and provides a conduit for irrigation fluid, not shown.

[0152] Figure 23A is a schematic illustration of an RF interstitial needle ablation probe 395 configured for interstitial ablation of a posterior nasal nerve. Figure 23B is a schematic illustration of the distal end 396 of the RF interstitial needle ablation probe 395. RF interstitial needle probe 395 comprises distal tip 396, probe shaft 398, handle 399, electrical connector 400, fluid connector 401, RF activation switch 402. Distal tip 396 comprises interstitial needle electrode array 397, which comprises more than one interstitial needle 464 Handle, 399, RF activation switch 402, electrical connector 400, and probe shaft 398 function in a manner previously described. Fluid port 401 is in fluidic communication with at least one RF ablation needle 464, with the at least one RF ablation needle 464 being hollow and configured for injecting a liquid into the nasal sub-mucosal space. Each RF ablation needle 464 has a proximal electrically insulating coating 405, and a distal electrically insulating coating 404, forming RF electrode surface 403. Proximal insulator 405, and distal insulator 404 are configured for limiting the ablation effects to the sub-mucosal space, which will be described in further detail below. Interstitial needle electrode array 397 may be configured as a mono-polar electrode array, or a bipolar electrode array. Interstitial needle electrode array 397 may be configured as a linear array, a circular array, a triangular array, or any other geometric form. Interstitial needle electrode array 397 may comprise two or more RF ablation needles 464. RF ablation needles 464 are between approximately 18 and 28 gauge, and between approximately 3 mm and 10 mm long.

[0153] Figure 24A is a cross sectional view of the distal end of an alternative embodiment 411 to RF interstitial needle ablation probe 395 comprising a deployable and retractable array of RF ablation needles 412 configured for lateral deployment showing the needle array retracted. Figure 24B is a cross sectional view of the distal end of an alternative embodiment 411 of RF interstitial needle ablation probe 395 comprising a deployable and retractable array of RF ablation needles configured for lateral deployment showing the

needle array deployed. Interstitial needle array 412 is housed in a hollow sheath with a "J" tip 413 as shown. Linear actuator shaft 414 is in mechanical communication with a user actuator lever at the proximal end not shown. Linear actuator shaft 414 is moved in the distal direction to deploy needle array 412, and moved in the proximal direction to retract needle array 412 as shown. Figure 24C is a cross sectional view of the distal end of an alternative embodiment 415 of RF interstitial needle ablation probe 395 comprising a deployable and retractable array of RF ablation needles configured for axial deployment showing the needle array retracted. Figure 24D is a cross sectional view of the distal end of an alternative embodiment 415 of RF interstitial needle ablation probe 395 comprising a deployable and retractable array of RF ablation needles configured for axial deployment showing the needle array deployed.

[0154] Figure 25A is a schematic illustration of an integrated flexible circuit 421 configured for use with an RF ablation probe comprising an RF energy source and control circuits 422 at one end, and an RF ablation electrode array 423 at the opposite end, connected by electrical conduits 426. Figure 25B is a schematic illustration of the RF ablation electrode array 423 of the flexible circuit mounted on the distal shaft of an RF ablation probe that is configured for ablation of the parasympathetic nervous function of a nasal turbinate. Also shown are optional fluid ports associated with the RF ablation electrode array as shown, with irrigation fluid 427 supplied to irrigation ports 425 through distal shaft 424.

[0155] Figure 26A is an in situ schematic illustration of the RF ablation probe 377 depicted in Figures 10 through 10C showing needle 380 injecting an anesthetic into the sub-mucosal space 433 prior to an RF ablation of the posterior nasal nerve 434. Figure 26B is an in situ schematic illustration of the resulting RF ablation 436 showing the ablation zone 436 encompassing posterior nasal nerve 434, and residing below the mucosal surface 437 due to the cooling effect of liquid irrigant 435.

[0156] Figure 27 is an in situ schematic illustration of an RF ablation of the parasympathetic nerve of a posterior nasal nerve 434 using the RF interstitial needle ablation probe 395 depicted in Figures 11A and 11B showing ablation zone 436 encompassing posterior nasal nerve434 and residing below the mucosal surface 437 due to the arrangement of needle electrode surface(s) 403 and needle insulation zones 404 & 405.

[0157] Figure 28 is an in situ illustration of the ablation of the posterior nasal nervedepicted in Figure 14D. Generic ablation device 441 is shown with cylindrical ablation element 442, which could be a cryo ablation element, an RF ablation element, or

some other type of thermal ablation element. Also shown is endoscope 443, which provides the surgeon an image for positioning ablation element 442 at the target location, and a means for monitoring the ablation.

[0158] Figure 29 is an in situ illustration of the ablation of the posterior nasal nerveof a nasal turbinate at the ablation target depicted in Figure 14B. Generic ablation device 441 is shown with cylindrical ablation element 442, which could be a cryo ablation element, an RF ablation element, or some other type of thermal ablation element. Also shown is endoscope 443, which provides the surgeon an image for positioning ablation element 442 at the target location, and a means for monitoring the ablation.

[0159] Figure 30 is an in situ illustration of the ablation of the posterior nasal nerve using a generic "T" tipped ablation device 448. Generic "T" tipped ablation device 448 is shown with ablation elements 449, which could be cryo ablation elements, RF ablation elements, or some other type of thermal ablation elements. Also shown is endoscope 443, which provides the surgeon an image for positioning ablation element 442 at the target location, and a means for monitoring the ablation.

[0160] Figure 31A is a schematic illustration of generic ablation probe 455 and an insulated probe guide 457 configured to protect the nasal septum from thermal injury during an ablation of the parasympathetic nervous function of a nasal turbinate(s). Probe guide 457 is configured to press ablation element 456 of probe 455 against the lateral wall of a nasal cavity 458 and create a thermally insulative space between the lateral wall of the nasal cavity 458 and the nasal septum 459 as shown in Figures 31B and 31C. Probe guide 457 may be fabricated from foam material, or any other suitable thermally insulative material. Figure 31B is an in situ illustration of generic ablation probe 437 configured for ablation of the posterior nasal nerve which comprises an insulating structure 460 configured to protect the nasal septum 459 from thermal injury. Structure 460 may comprise an inflatable balloon. Figure 31C is an in situ illustration of generic ablation probe 455 configured for ablation of the parasympathetic nervous function of a nasal turbinate(s) which comprises a space creating structure 461 configured to protect the nasal septum 459 from thermal injury. Structure 461 may comprise a deployable wire structure or surgical basket structure.

CLAIMS

What is claimed is:

1. A method for treating a tissue region within a nasal cavity, comprising:

introducing a distal end of a probe shaft through the nasal cavity, wherein the distal end has an end effector with a first configuration having a low-profile which is shaped to manipulate tissue within the nasal cavity;

positioning the distal end into proximity of a tissue region having at least one posterior nasal nerve;

reconfiguring the distal end from the first configuration to a second configuration which is shaped to contact and follow the tissue region; and

ablating the at least one posterior nasal nerve within the tissue region via the distal end.

2. The method of claim 1 wherein ablating the at least one posterior nasal nerve comprises ablating the posterior nasal nerve such that symptoms of rhinitis are reduced.

3. The method of claim 1 wherein introducing a distal end comprises introducing the distal end through a nostril and into the nasal cavity.

4. The method of claim 1 wherein positioning the distal end comprises positioning the distal end at least 2 cm beyond an anterior entrance to a middle meatus.

5. The method of claim 1 wherein positioning the distal end comprises:

advancing the distal end along an upper surface of the inferior nasal turbinate to a mid-portion of the middle nasal turbinate;

advancing the distal end into a middle meatus; and

further advancing the distal end posteriorly up into a cul-de-sac.

6. The method of claim 1 wherein positioning the distal end comprises positioning the distal end between the middle and inferior nasal turbinate.

7. The method of claim 1 wherein positioning the distal end comprises

positioning the distal end relative to the tissue region surrounded by the middle nasal turbinate, inferior nasal turbinate, and lateral wall forming a cul-de-sac.

8. The method on claim 1 wherein positioning the distal end positioning the distal end to contact a lateral nasal wall defined by a tail of a nasal turbinate, lateral wall, and an inferior turbinate.

9. The method of claim 1 wherein positioning the distal end comprises positioning the distal end into proximity of the Pterygomaxillary fossa, sphenopalatine ganglion, sphenopalatine ganglion, or vidian nerve.

10. The method of claim 1 wherein positioning the distal end comprises positioning the distal end into proximity of accessory posterolateral nerves bounded by an sphenopalatine foramen superiorly, an inferior edge of an inferior turbinate inferiorly, a Eustachian tube posteriorly, or a posterior third of the middle and inferior turbinates anteriorly.

11. The method of claim 1 wherein reconfiguring the distal end comprises inflating an expandable structure projecting from the probe shaft into contact against the tissue region.

12. The method of claim 11 further comprising positioning a member extending within the expandable structure, wherein the expandable structure encloses the member such that the member is unattached to the interior of the expandable structure, into contact against the tissue region through the expandable structure.

13. The method of claim 1 wherein ablating the at least one posterior nasal nerve comprises introducing a cryogenic fluid into or through the distal end.

14. The method of claim 1 wherein ablating the at least one posterior nasal nerve comprises cryogenically ablating the tissue region between approximately 20 seconds to 300 seconds.

15. The method of claim 1 wherein ablating the at least one posterior nasal

nerve comprises cryogenically ablating the tissue region between approximately 20 seconds to 120 seconds.

16. The method of claim 1 further comprising introducing an imaging device in proximity to the distal end.

17. The method of claim 1 further comprising visualizing the tissue region while advancing the distal end of the probe shaft through the nasal cavity.

18. The method of claim 17 wherein visualizing comprises visualizing via a CCD or CMOS imager positioned along the surgical probe shaft.

19. The method of claim 17 wherein visualizing comprises visualizing infrared wavelengths.

20. The method of claim 17 wherein visualizing comprises visualizing via a nasal endoscope.

21. The method of claim 20 wherein visualizing comprises advancing the nasal endoscope with the surgical probe shaft.

22. The method of claim 1 further comprising introducing a temperature sensor in proximity to the distal end of the surgical probe shaft.

23. The method of claim 1 further comprising applying a pressure to the tissue region via the distal end with a force of 20 to 200 grams.

24. The method of claim 1 further comprising waiting 10 to 20 seconds after ablating the at least one posterior nasal nerve prior to removing the distal end from the tissue region.

25. The method of claim 1 wherein ablating the at least one posterior nasal nerve comprises ablating the tissue region through a layer of gel.

26. The method of claim 1 further comprising assessing the tissue region during and/or after ablation.

27. The method of claim 26 wherein assessing comprises inspecting the tissue region visually or via ultrasound.

28. The method of claim 26 wherein assessing comprises detecting or a temperature of the tissue region.

29. The method of claim 1 further comprising vibrating the distal end while maintaining the distal end against the tissue region.

30. The method of claim 1 further comprising applying an anesthetic to the tissue region to be treated prior to ablating the post nasal nerve.

31. A method for treating rhinitis, comprising:

introducing a distal end of a probe shaft through the nasal cavity, wherein the distal end has an end effector with a first configuration having a low-profile which is shaped to manipulate tissue within the nasal cavity;

positioning the distal end into proximity of a tissue region surrounded by the middle nasal turbinate, inferior nasal turbinate, and lateral wall forming a cul-de-sac;

reconfiguring the distal end from the first configuration to a second configuration which is shaped to contact and follow the tissue region; and

ablating the at least one posterior nasal nerve within the tissue region via the distal end.

32. The method of claim 31 wherein ablating the at least one posterior nasal nerve comprises ablating the posterior nasal nerves such that symptoms of rhinitis are reduced.

33. The method of claim 31 wherein introducing a distal end comprises introducing the distal end through a nostril and into the nasal cavity.

34. The method of claim 31 wherein positioning the distal end comprises

positioning the distal end at least 2 cm beyond an anterior entrance to a middle meatus.

35. The method of claim 31 wherein positioning the distal end comprises:

advancing the distal end along an upper surface of the inferior nasal turbinate to a mid-portion of the middle nasal turbinate;

advancing the distal end into a middle meatus; and

further advancing the distal end posteriorly up into a cul-de-sac.

36. The method of claim 31 wherein positioning the distal end comprises positioning the distal end between the middle and inferior nasal turbinate.

37. The method on claim 31 wherein positioning the distal end positioning the distal end to contact a lateral nasal wall defined by a tail of a nasal turbinate, lateral wall, and an inferior turbinate.

38. The method of claim 31 wherein positioning the distal end comprises positioning the distal end into proximity of the Pterygomaxillary fossa, sphenopalatine ganglion, sphenopalatine ganglion, or vidian nerve.

39. The method of claim 31 wherein positioning the distal end comprises positioning the distal end into proximity of accessory posterolateral nerves bounded by an sphenopalatine foramen superiorly, an inferior edge of an inferior turbinate inferiorly, a Eustachian tube posteriorly, or a posterior third of the middle and inferior turbinates anteriorly.

40. The method of claim 31 wherein reconfiguring the distal end comprises inflating an expandable structure projecting from the probe shaft into contact against the tissue region.

41. The method of claim 40 further comprising positioning a member extending within the expandable structure, wherein the expandable structure encloses the member such that the member is unattached to the interior of the expandable structure, into contact against the tissue region through the expandable structure.

42. The method of claim 31 wherein ablating the at least one posterior nasal nerve comprises introducing a cryogenic fluid into or through the distal end.

43. The method of claim 31 wherein ablating the at least one posterior nasal nerve comprises cryogenically ablating the tissue region between approximately 20 seconds to 300 seconds.

44. The method of claim 31 wherein ablating the at least one posterior nasal nerve comprises cryogenically ablating the tissue region between approximately 20 seconds to 120 seconds.

45. The method of claim 31 further comprising introducing an imaging device in proximity to the distal end.

46. The method of claim 31 further comprising visualizing the tissue region while advancing the distal end of the probe shaft through the nasal cavity.

47. The method of claim 46 wherein visualizing comprises visualizing via a CCD or CMOS imager positioned along the surgical probe shaft.

48. The method of claim 46 wherein visualizing comprises visualizing infrared wavelengths.

49. The method of claim 46 wherein visualizing comprises visualizing via a nasal endoscope.

50. The method of claim 49 wherein visualizing comprises advancing the nasal endoscope with the surgical probe shaft.

51. The method of claim 31 further comprising introducing a temperature sensor in proximity to the distal end of the surgical probe shaft.

52. The method of claim 31 further comprising applying a pressure to the tissue region via the distal end with a force of 20 to 200 grams.

53. The method of claim 31 further comprising waiting 10 to 20 seconds after ablating the posterior nasal nerves prior to removing the distal end from the tissue region.

54. The method of claim 31 wherein ablating the at least one posterior nasal nerve comprises ablating the tissue region through a layer of gel.

55. The method of claim 31 further comprising assessing the tissue region during and/or after ablation.

56. The method of claim 55 wherein assessing comprises inspecting the tissue region visually or via ultrasound.

57. The method of claim 55 wherein assessing comprises detecting or a temperature of the tissue region.

58. The method of claim 31 further comprising vibrating the distal end while maintaining the distal end against the tissue region.

59. The method of claim 31 further comprising applying an anesthetic to the tissue region to be treated prior to ablating the posterior nasal nerves.

60. A surgical probe configured for ablation, comprising:

a surgical probe shaft comprising an elongated structure with a distal end and a proximal end;

an expandable structure attached to the distal end of the probe shaft, the expandable structure having a deflated configuration and an expanded configuration;

a lumen in fluid communication with an interior of the expandable structure; and

a member attached to the distal end and extending within the expandable structure which encloses the member such that the member is unattached to the interior of the expandable structure,

wherein the member defines an atraumatic shape which is sized for pressing against and manipulating through the expandable structure a lateral nasal wall proximate to at least one posterior nasal nerve.

61. The surgical probe of claim 60 wherein the surgical probe shaft is between 1 mm and 4 mm in diameter and between approximately 4 cm and 10 cm in length.

62. The surgical probe of claim 60 wherein the lumen is defined through the probe shaft.

63. The surgical probe of claim 60 wherein surgical probe shaft is malleable and is configured for shape forming by the user.

64. The surgical probe of claim 60 further comprising a surgical hand piece attached to the proximal end, where the surgical hand piece is configured to be held like writing utensil or like a pistol.

65. The surgical probe of claim 64 wherein the surgical hand piece comprises a flow control valve actuator.

66. The surgical probe of claim 60 further comprising a pressurized reservoir in fluid communication with interior of the expandable structure through the lumen.

67. The surgical probe of claim 66 wherein the reservoir contains a liquid cryogen.

68. The surgical probe of claim 60 wherein the member comprises a looped structure defining an opening therethrough.

69. The surgical probe of claim 60 wherein the member comprises a coiled spring-like structure.

70. The surgical probe of claim 69 wherein the coiled spring-like structure is curved and tangent to the distal end of the surgical probe shaft.

71. The surgical probe of claim 69 wherein the coiled spring-like structure is at least partially malleable and is configured for shape forming by the user.

72. The surgical probe of claim 69 wherein the coiled spring-like structure comprises a tightly coiled metal wire defining a central lumen and an outer surface.

73. The surgical probe of claim 72 wherein the central lumen is in fluidic communication with the lumen.

74. The surgical probe of claim 72 wherein the central lumen comprises a polymeric liner.

75. The surgical probe of claim 60 wherein the expandable structure comprises a distensible or non-distensible material.

76. The surgical probe of claim 60 wherein the expandable structure is configured as a hollow bulbous structure with an ostium configured for fluid tight bonding to the distal end of the surgical probe shaft.

77. The surgical probe of claim 60 wherein the expandable structure is configured to expand to a greater extent in a first radial axis than a second radial axis.

78. The surgical probe of claim 60 further comprising an imaging device in proximity to the distal end of the surgical probe shaft.

79. The surgical probe of claim 60 further comprising a temperature sensor in proximity to the distal end of the surgical probe shaft.

80. The surgical probe of claim 60 further comprising an indicator or marker along the shaft.

81. A method for treating a tissue region within a nasal cavity, comprising:

advancing a distal end of a surgical probe shaft through the nasal cavity and into proximity of the tissue region having at least one posterior nasal nerve;

introducing a cryogenic fluid into an expandable structure attached to the distal end of the probe shaft such that the expandable structure inflates from a deflated configuration

into an expanded configuration against the tissue region;

adjusting a position of a member relative to the tissue region, wherein the member is attached to the distal end of the probe shaft and extends within the expandable structure which encloses the member such that the member is unattached to an interior of the expandable structure;

applying a pressure against the tissue region having the at least one posterior nasal nerve via the member pressing against the interior of the expandable structure, wherein the member defines an atraumatic shape which is sized for pressing against and manipulating the tissue region through the expandable structure; and

maintaining the member against the interior of the expandable structure and the tissue region until the tissue region is cryogenically ablated.

82. The method of claim 81 wherein maintaining the member further comprises cryogenically ablating the at least one posterior nasal nerve such until symptoms of rhinitis are reduced.

83. The method of claim 81 wherein advancing a distal end comprises advancing the distal end through a nostril and into the nasal cavity.

84. The method of claim 81 wherein advancing a distal end comprises advancing the distal end at least 2 cm beyond an anterior entrance to a middle meatus.

85. The method of claim 81 wherein advancing a distal end comprises:

advancing the distal end along an upper surface of the inferior nasal turbinate to a mid-portion of the middle nasal turbinate;

advancing the distal end into a middle meatus; and

further advancing the distal end posteriorly up into a cul-de-sac.

86. The method of claim 81 wherein advancing a distal end comprises positioning the member between the middle and inferior nasal turbinate.

87. The method of claim 81 wherein advancing a distal end comprises positioning the member relative to the tissue region surrounded by the middle nasal turbinate, inferior nasal turbinate, and lateral wall forming a cul-de-sac.

88. The method of claim 81 wherein advancing a distal end comprises positioning the member into proximity of the Pterygomaxillary fossa, sphenopalatine ganglion, sphenopalatine ganglion, or vidian nerve.

89. The method of claim 81 wherein advancing a distal end comprises positioning the member into proximity of accessory posterolateral nerves bounded by an sphenopalatine foramen superiorly, an inferior edge of an inferior turbinate inferiorly, a Eustachian tube posteriorly, or a posterior third of the middle and inferior turbinates anteriorly.

90. The method of claim 81 wherein introducing a cryogenic fluid comprises evaporating the cryogenic fluid within the expandable structure.

91. The method of claim 81 wherein the expandable structure is inflated in response to evaporation of the cryogenic fluid within the interior.

92. The method of claim 81 wherein introducing a cryogenic fluid further comprises expanding the expandable structure to a greater extent in one radial axis compared to a second radial axis.

93. The method on claim 81 wherein adjusting a position of a member further comprises positioning the member to contact a lateral nasal wall defined by a tail of a nasal turbinate, lateral wall, and an inferior turbinate.

94. The method of claim 81 wherein introducing a cryogenic fluid further comprises flowing the cryogenic fluid into the interior between approximately 20 seconds to 300 seconds.

95. The method of claim 81 wherein introducing a cryogenic fluid further comprises flowing the cryogenic fluid into the interior between approximately 20 seconds to 120 seconds.

96. The method of claim 81 wherein the cryogenic fluid comprises nitrous

oxide, liquid nitrogen, or carbon dioxide.

97. The method of claim 81 further comprising introducing an imaging device in proximity to the distal end.

98. The method of claim 81 further comprising visualizing the tissue region while advancing the distal end of the surgical probe through the nasal cavity.

99. The method of claim 98 wherein visualizing comprises visualizing via a CCD or CMOS imager positioned along the surgical probe shaft.

100. The method of claim 98 wherein visualizing comprises visualizing infrared wavelengths.

101. The method of claim 98 wherein visualizing comprises visualizing via a nasal endoscope.

102. The method of claim 101 wherein visualizing comprises advancing the nasal endoscope with the surgical probe shaft.

103. The method of claim 81 further comprising introducing a temperature sensor in proximity to the distal end of the surgical probe shaft.

104. The method of claim 81 wherein advancing a distal end comprises positioning the surgical probe shaft into proximity of an anterior region of middle or inferior nasal turbinate.

105. The method of claim 81 wherein applying a pressure comprises applying a force of 20 to 200 grams via the member pressing against the interior of the expandable structure.

106. The method of claim 81 further comprising stopping the cryogenic fluid and waiting 10 to 20 seconds prior to removing the distal end of the surgical probe shaft from the tissue region.

107. The method of claim 81 wherein maintaining the member comprises ablating the tissue region through a layer of gel.

108. The method of claim 81 further comprising assessing the tissue region during and/or after ablation.

109. The method of claim 108 wherein assessing comprises inspecting the tissue region visually or via ultrasound.

110. The method of claim 81 wherein assessing comprises detecting or a temperature of the tissue region.

111. The method of claim 81 further comprising vibrating the expandable structure while maintaining the member against the interior of the expandable structure and the tissue region.

112. The method of claim 81 further comprising applying an anesthetic to the tissue region to be treated prior to applying a pressure against the tissue region.

113. A method for treating rhinitis, comprising:

advancing a distal end of a surgical probe shaft through the nasal cavity and into proximity of a tissue region surrounded by the middle nasal turbinate, inferior nasal turbinate, and lateral wall forming a cul-de-sac and having at least one posterior nasal nerve;

introducing a cryogenic fluid into an expandable structure attached to the distal end of the probe shaft such that the expandable structure inflates from a deflated configuration into an expanded configuration against the tissue region, wherein the distal end has an attached member which extends within the expandable structure such that the member is unattached to the interior of the expandable structure;

applying a pressure against the tissue region via the member pressing against the interior of the expandable structure, wherein the member defines an atraumatic shape and is unattached to the interior of the expandable structure; and

maintaining the member against the interior of the expandable structure and the

tissue region until the tissue region is cryogenically ablated.

114. The method of claim 113 wherein advancing a distal end comprises advancing the distal end at least 2 cm beyond an anterior entrance to a middle meatus.

115. The method of claim 113 wherein advancing a distal end comprises:

advancing the distal end along an upper surface of the inferior nasal turbinate to a mid-portion of the middle nasal turbinate;

advancing the distal end into a middle meatus; and

further advancing the distal end posteriorly up into a cul-de-sac.

116. The method of claim 113 wherein advancing a distal end comprises positioning the member between the middle and inferior nasal turbinate.

117. The method of claim 113 wherein advancing a distal end comprises positioning the member into proximity of the Pterygomaxillary fossa, sphenopalatine ganglion, sphenopalatine ganglion, or vidian nerve.

118. The method of claim 113 wherein advancing a distal end comprises positioning the member into proximity of accessory posterolateral nerves bounded by an sphenopalatine foramen superiorly, an inferior edge of an inferior turbinate inferiorly, a Eustachian tube posteriorly, or a posterior third of the middle and inferior turbinates anteriorly.

119. The method of claim 113 wherein introducing a cryogenic fluid comprises evaporating the cryogenic fluid within the expandable structure.

120. The method of claim 113 wherein the expandable structure is inflated in response to evaporation of the cryogenic fluid within the interior.

121. The method on claim 113 wherein advancing a distal end further comprises positioning the member to contact a lateral nasal wall defined by a tail of a nasal turbinate, lateral wall, and an inferior turbinate.

122. The method of claim 113 wherein introducing a cryogenic fluid comprises flowing the cryogenic fluid into the interior between approximately 20 seconds to 300 seconds.

123. The method of claim 113 wherein introducing a cryogenic fluid further comprises flowing the cryogenic fluid into the interior between approximately 20 seconds to 120 seconds.

124. The method of claim 113 wherein the cryogenic fluid comprises nitrous oxide, liquid nitrogen, or carbon dioxide.

125. The method of claim 113 further comprising introducing an imaging device in proximity to the distal end.

126. The method of claim 113 further comprising visualizing the tissue region while advancing the distal end of the surgical probe through the nasal cavity.

127. The method of claim 126 wherein visualizing comprises visualizing via a CCD or CMOS imager positioned along the surgical probe shaft.

128. The method of claim 126 wherein visualizing comprises visualizing infrared wavelengths.

129. The method of claim 126 wherein visualizing comprises visualizing via a nasal endoscope.

130. The method of claim 129 wherein visualizing comprises advancing the nasal endoscope with the surgical probe shaft.

131. The method of claim 113 further comprising introducing a temperature sensor in proximity to the distal end of the surgical probe shaft.

132. The method of claim 113 wherein applying a pressure comprises applying a force of 20 to 200 grams via the member pressing against the interior of the expandable

structure.

133. The method of claim 113 further comprising stopping the cryogenic fluid and waiting 10 to 20 seconds prior to removing the distal end of the surgical probe shaft from the tissue region.

134. The method of claim 113 wherein maintaining the member comprises ablating the tissue region through a layer of gel.

135. The method of claim 113 further comprising assessing the tissue region during and/or after ablation.

136. The method of claim 135 wherein assessing comprises inspecting the tissue region visually or via ultrasound.

137. The method of claim 113 wherein assessing comprises detecting or a temperature of the tissue region.

138. The method of claim 113 further comprising vibrating the expandable structure while maintaining the member against the interior of the expandable structure and the tissue region.

139. The method of claim 113 further comprising applying an anesthetic to the tissue region to be treated prior to applying a pressure against the tissue region.

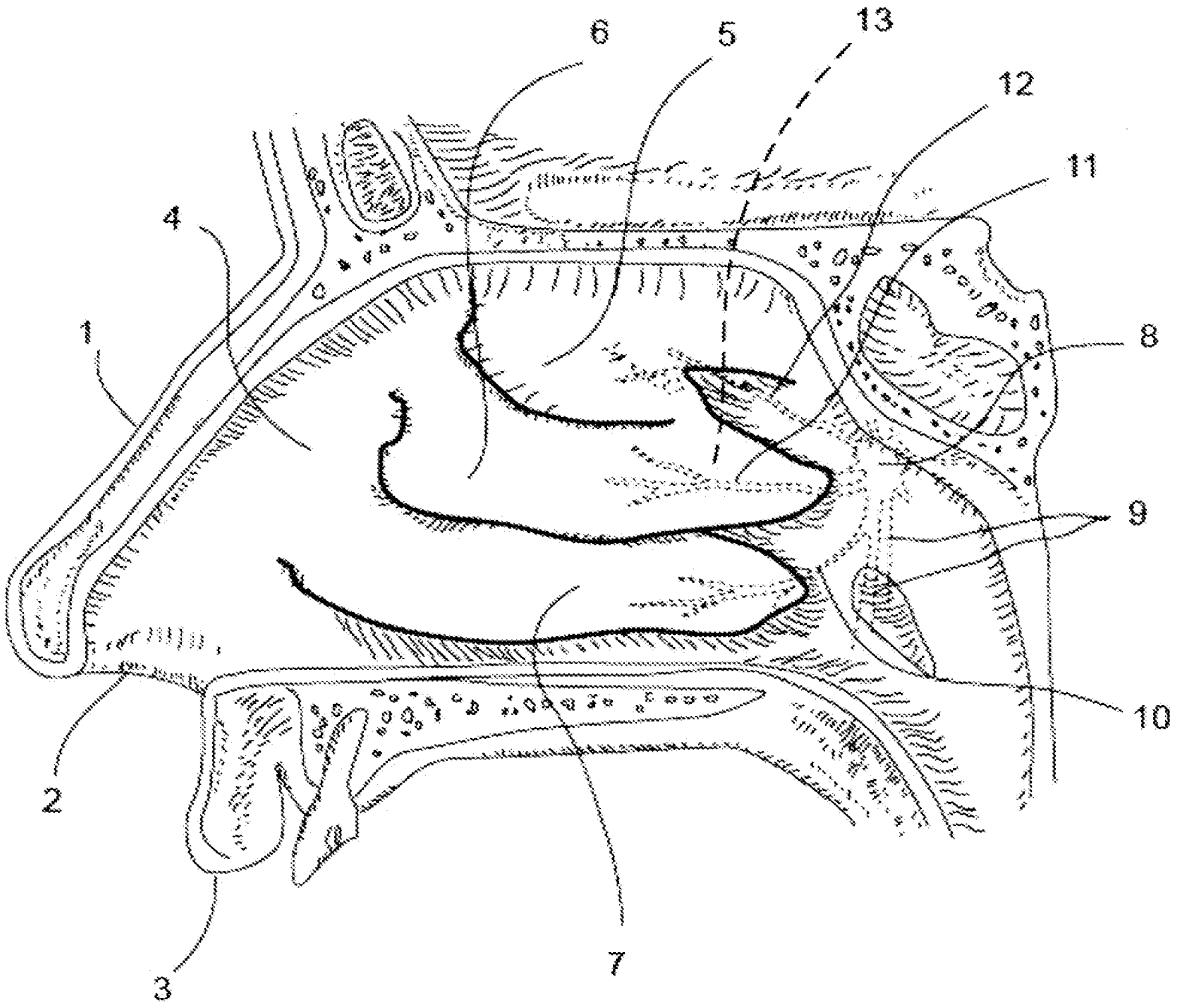


Figure 1

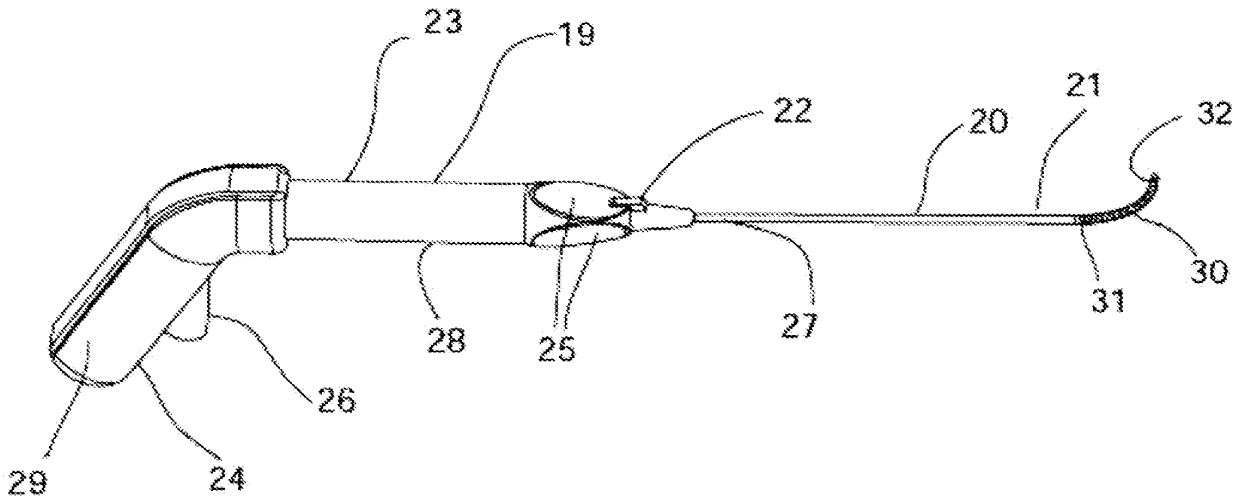


Figure 2

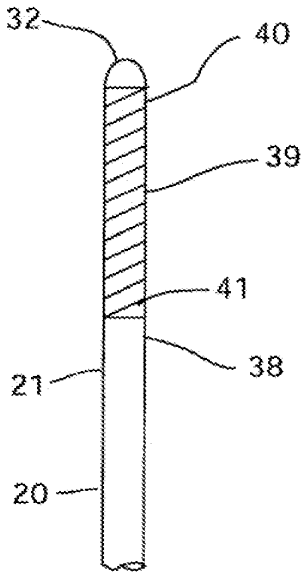


Figure 3A

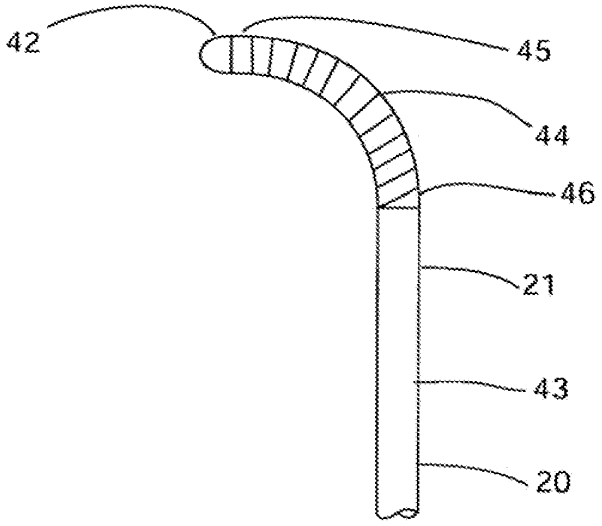


Figure 3B

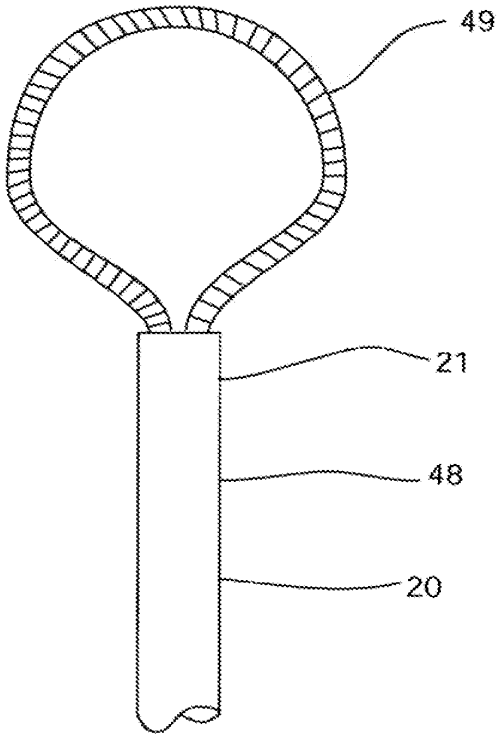


Figure 3C

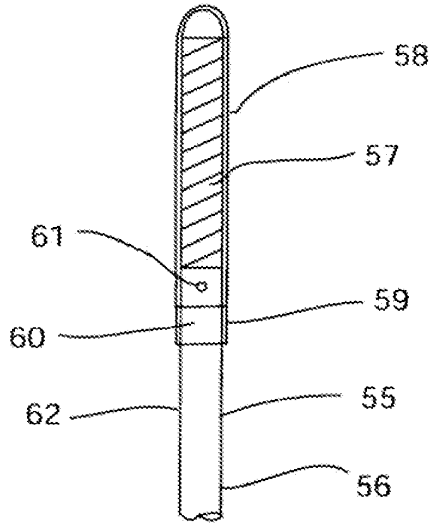


Figure 4A

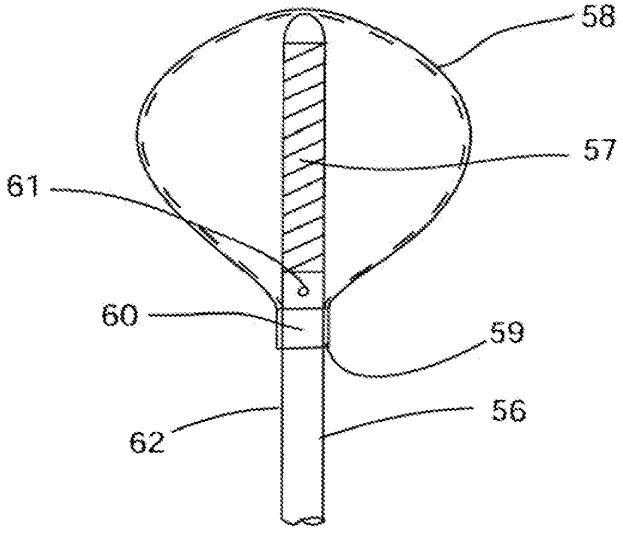


Figure 4B

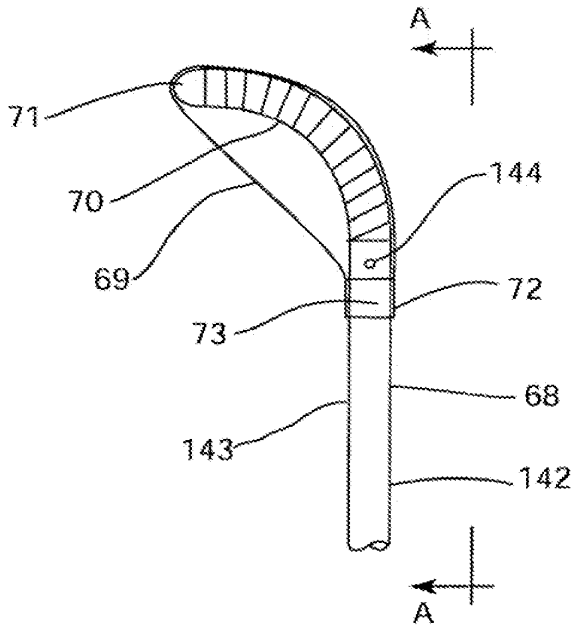


Figure 5A

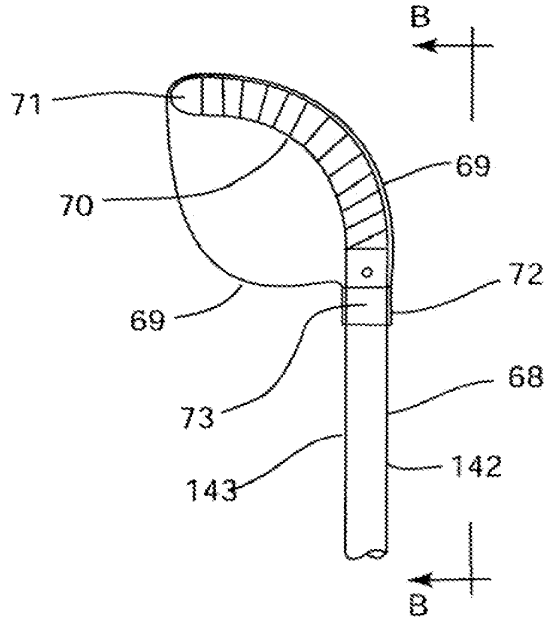
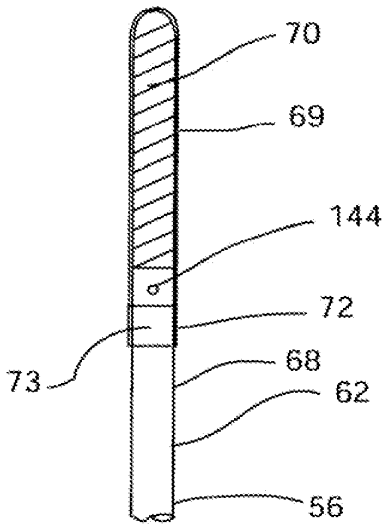
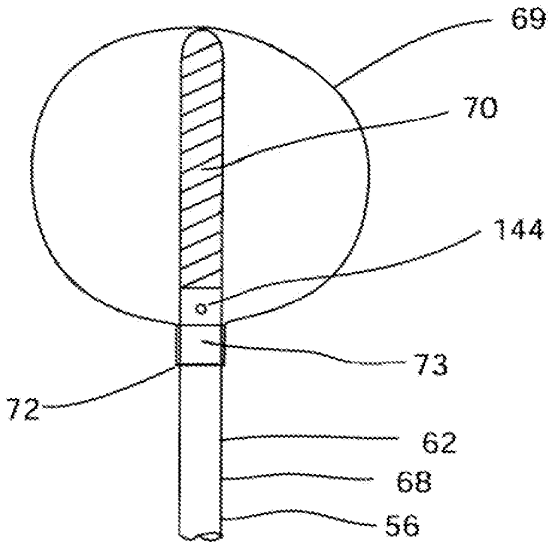


Figure 5B



View A-A

Figure 5C



View B-B

Figure 5D

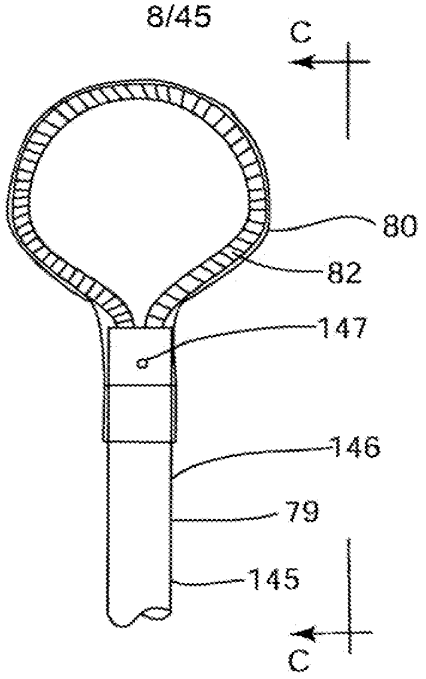


Figure 6A

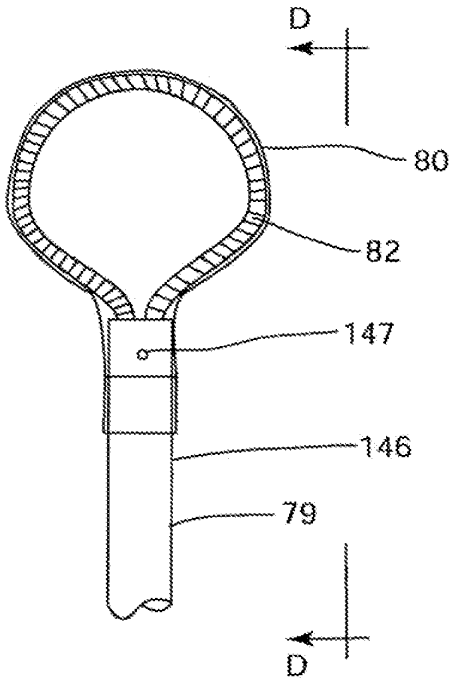
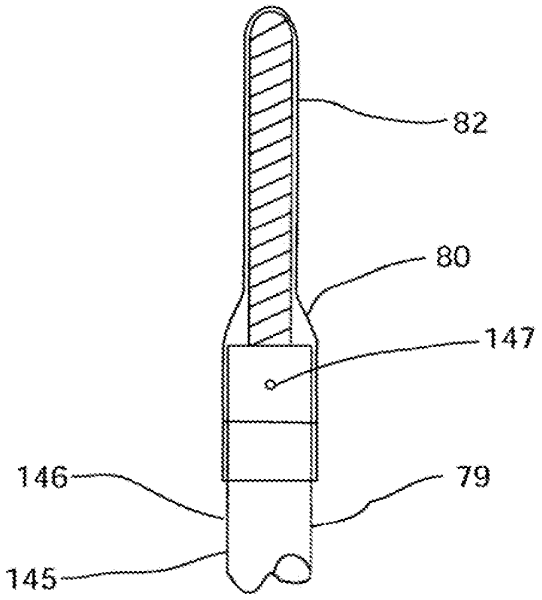
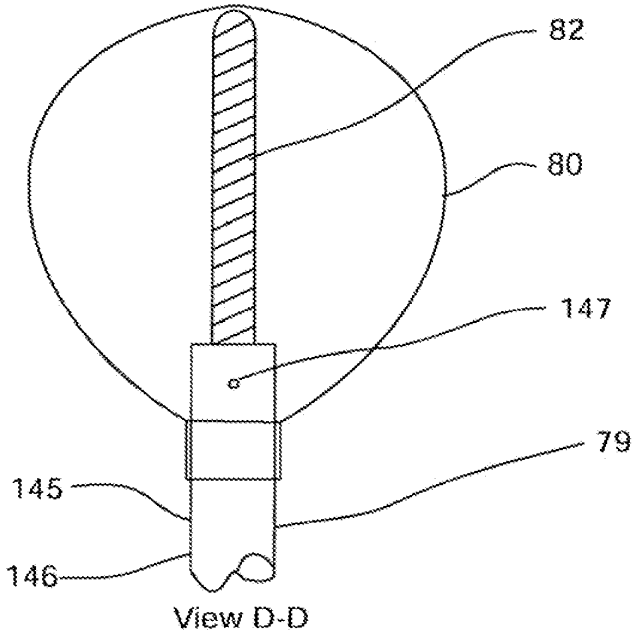


Figure 6B



View C-C

Figure 6C



View D-D

Figure 6D

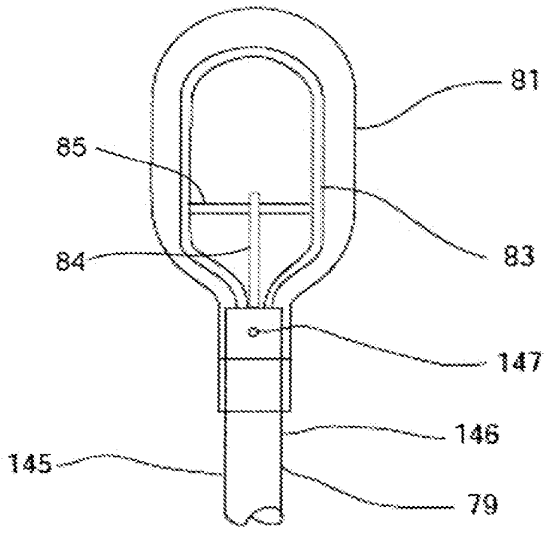


Figure 6E

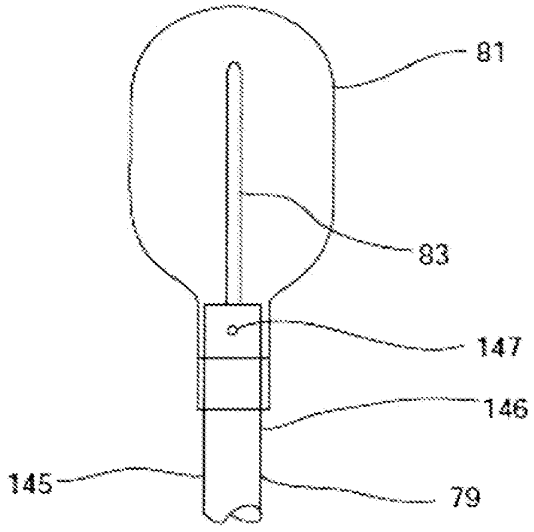


Figure 6F

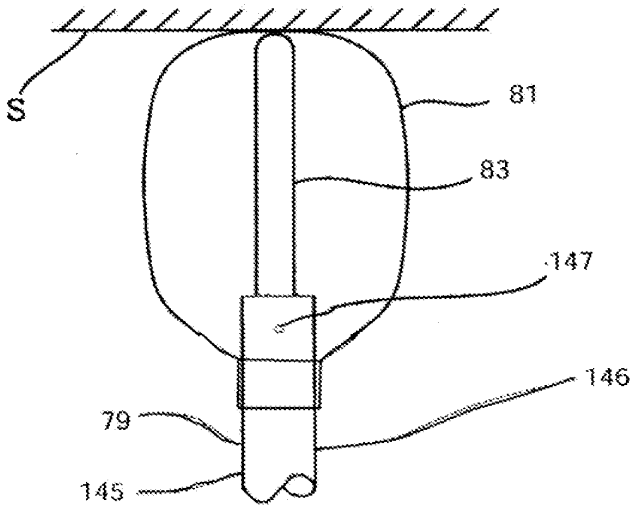


Figure 6G

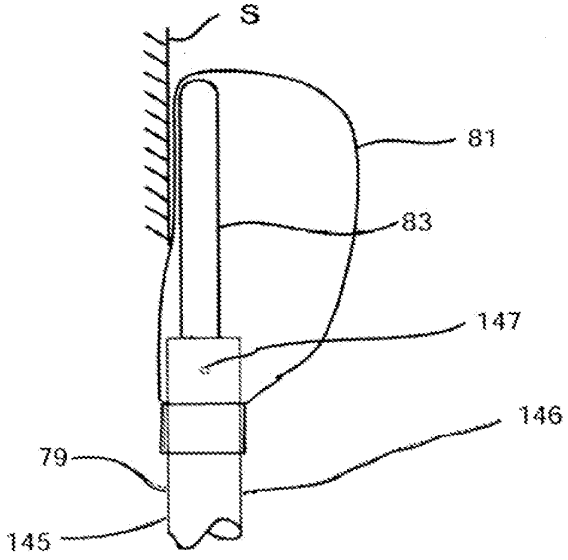


Figure 6H

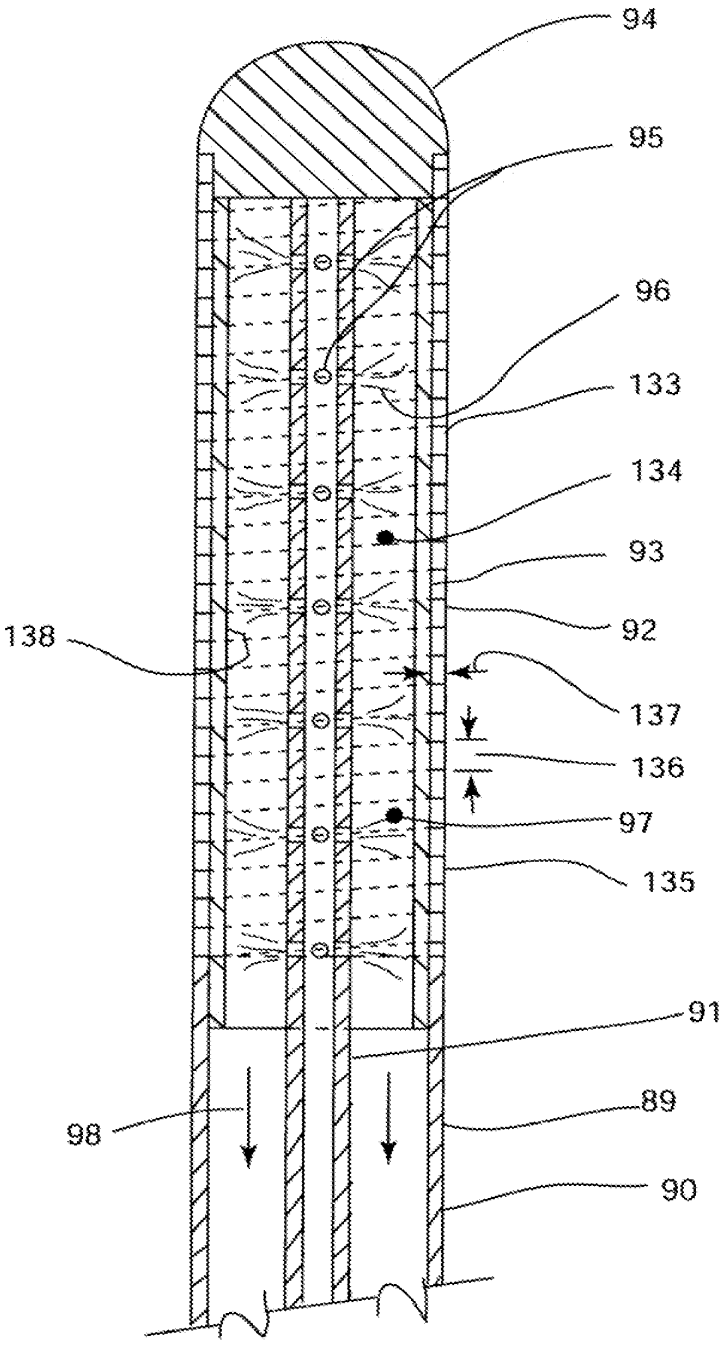


Figure 7

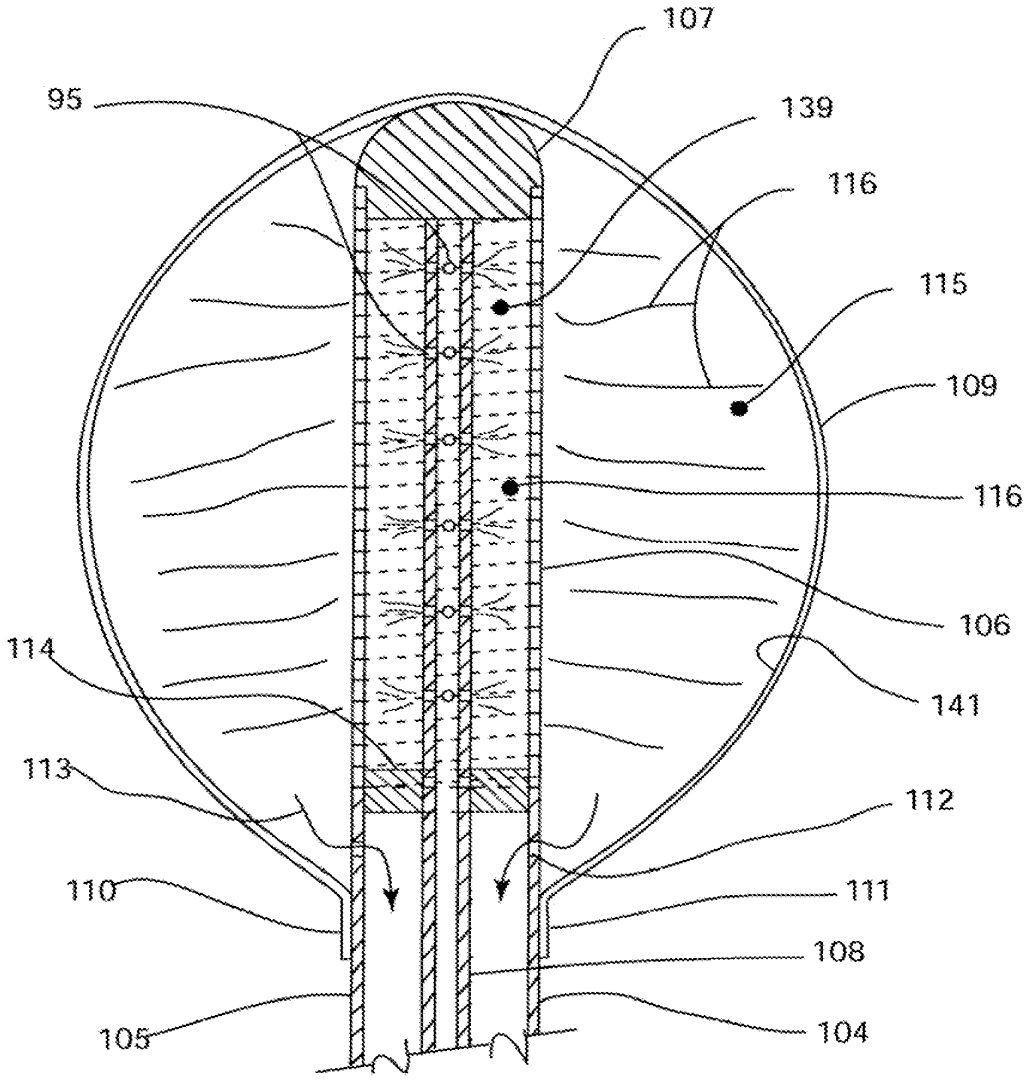

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Figure 8

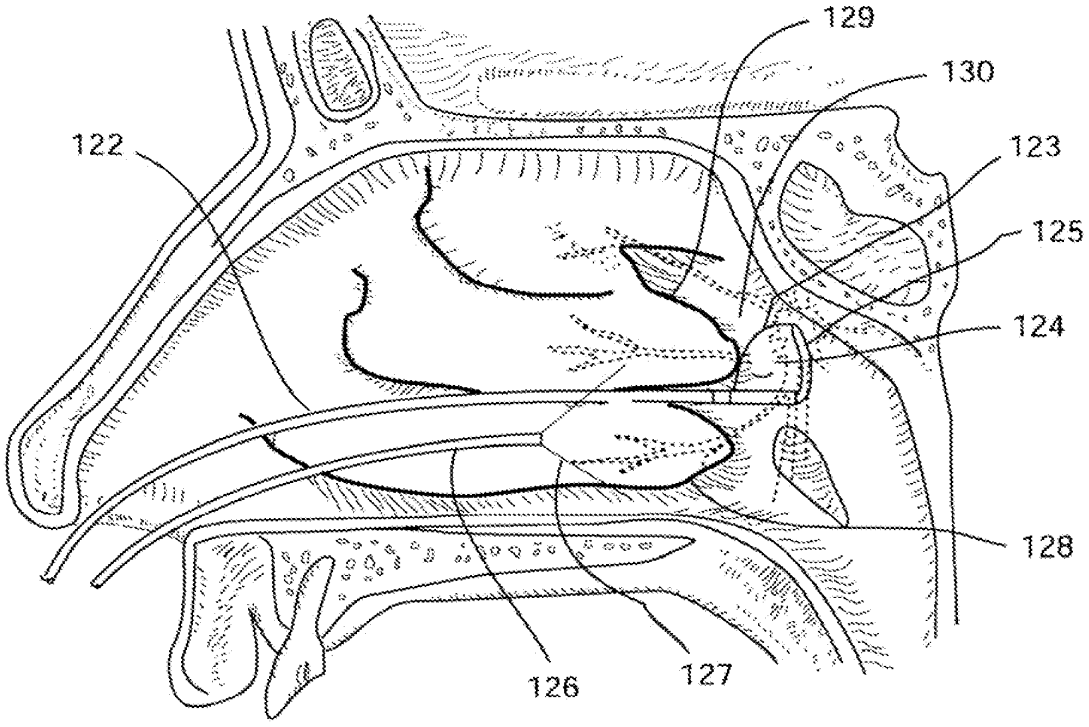


Figure 9

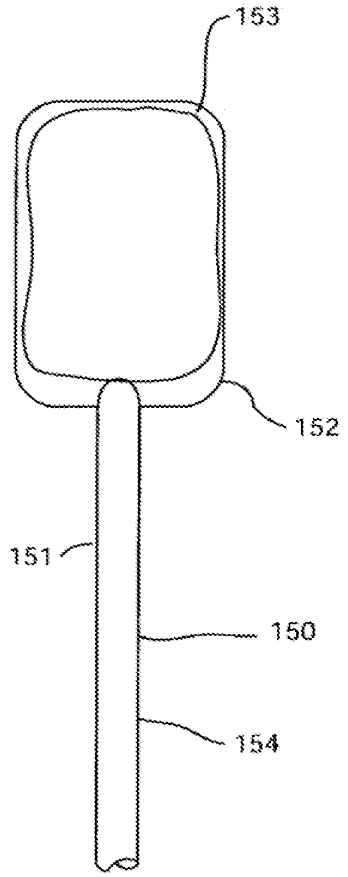


Figure 10A

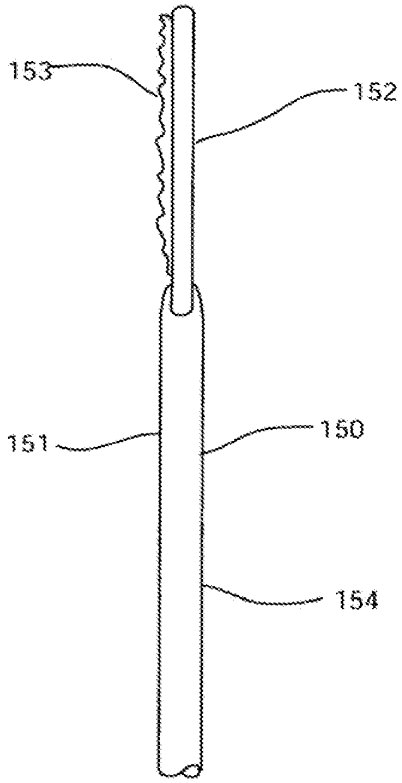


Figure 10B

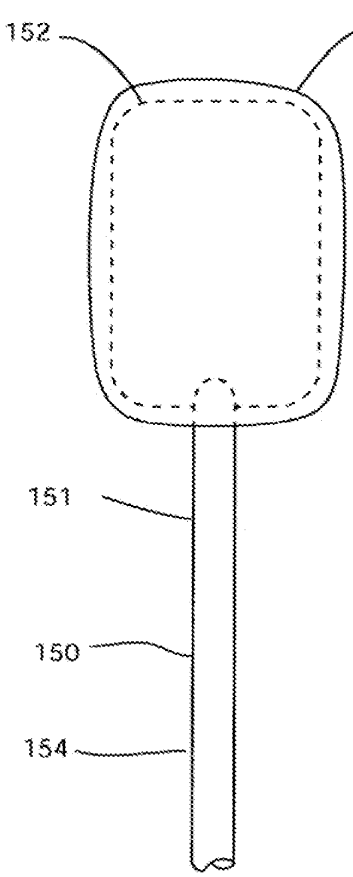


Figure 10C

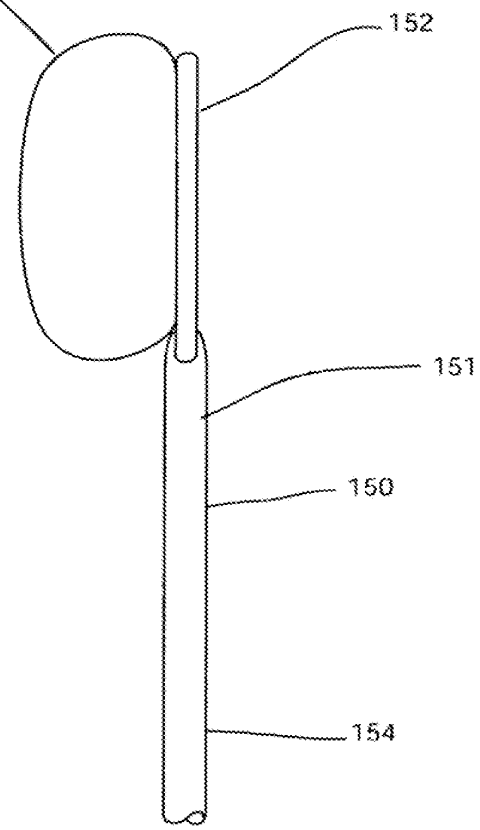


Figure 10D

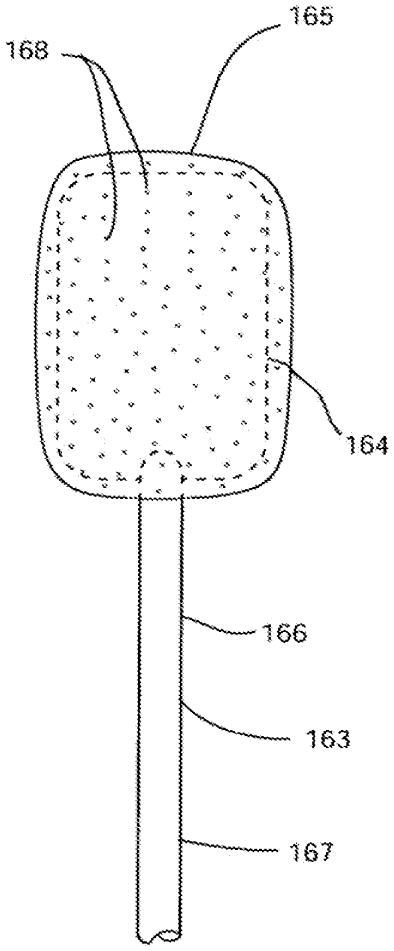


Figure 11A

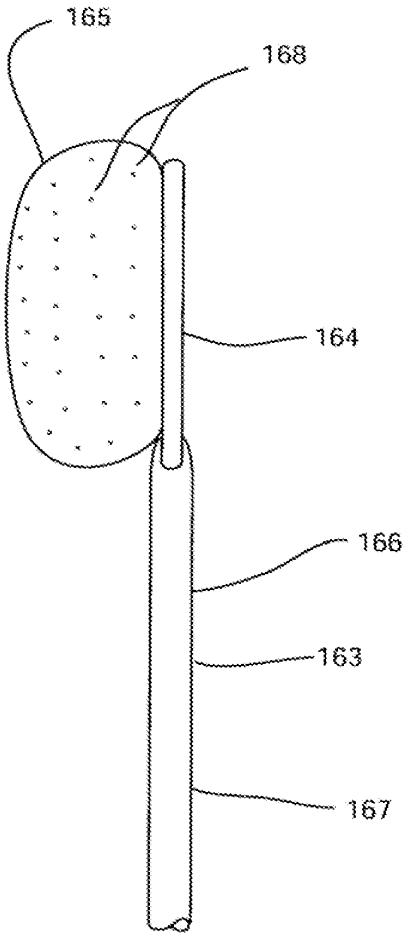


Figure 11B

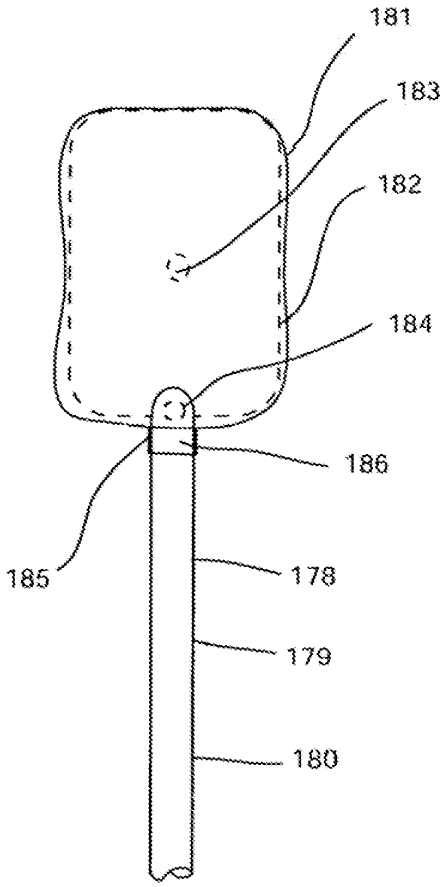


Figure 12A

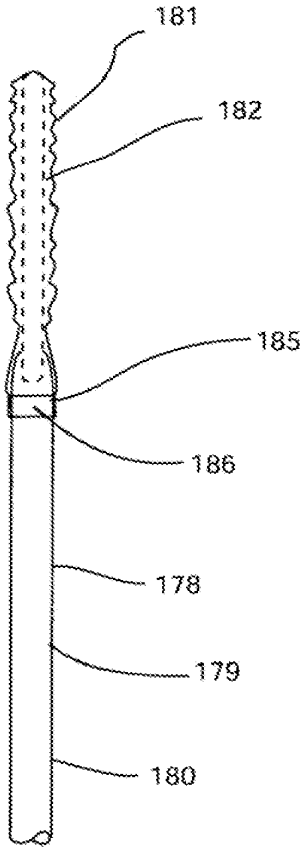


Figure 12B

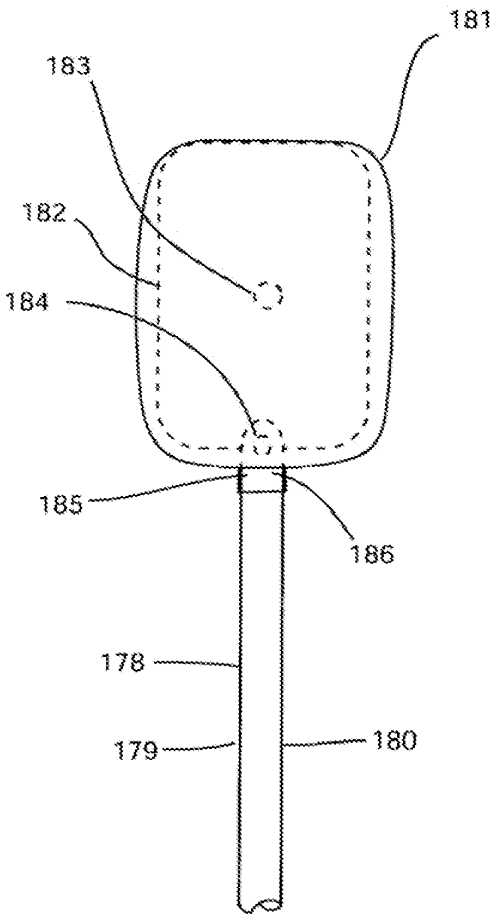


Figure 12C

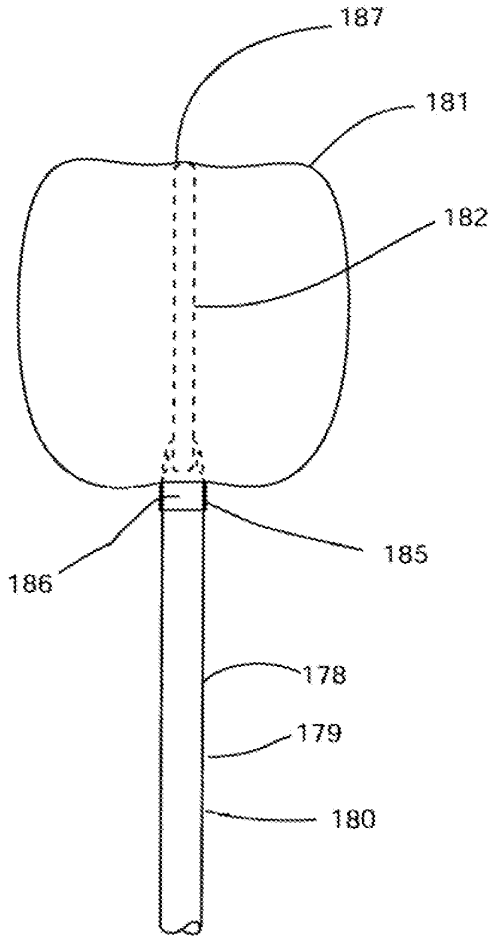


Figure 12D

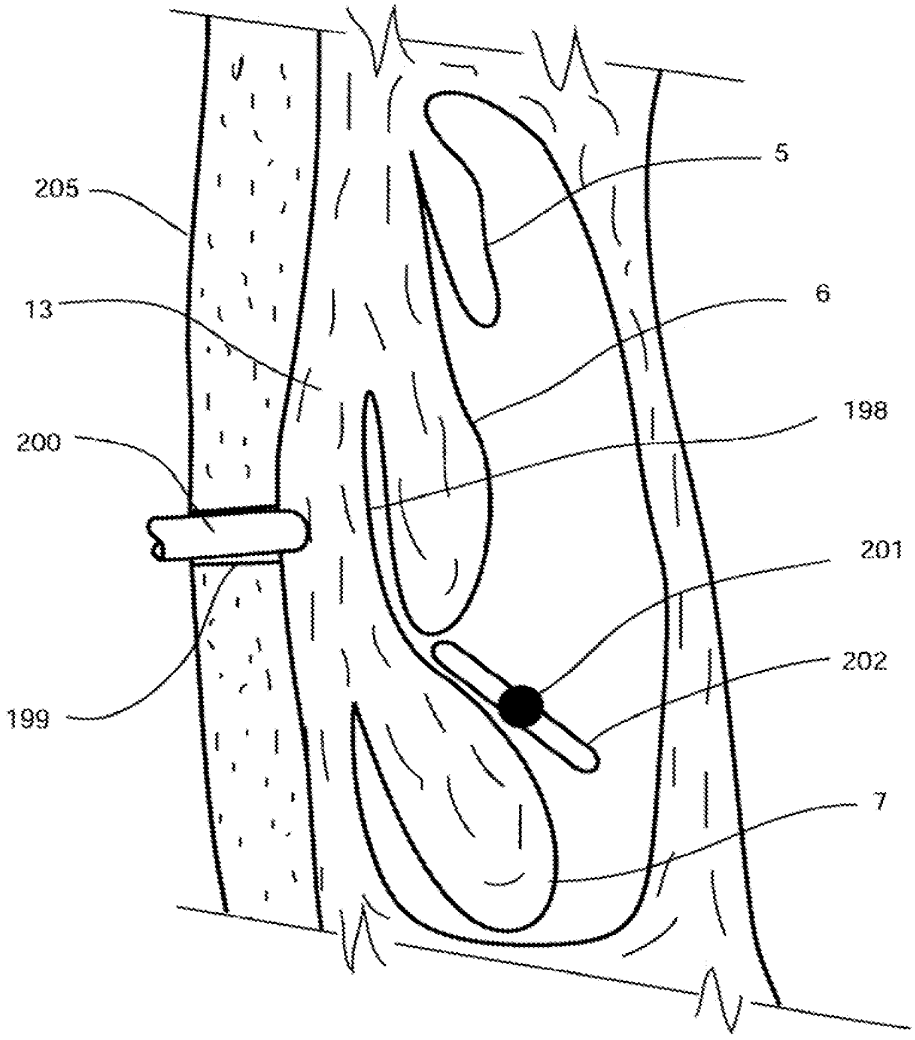


Figure 13A

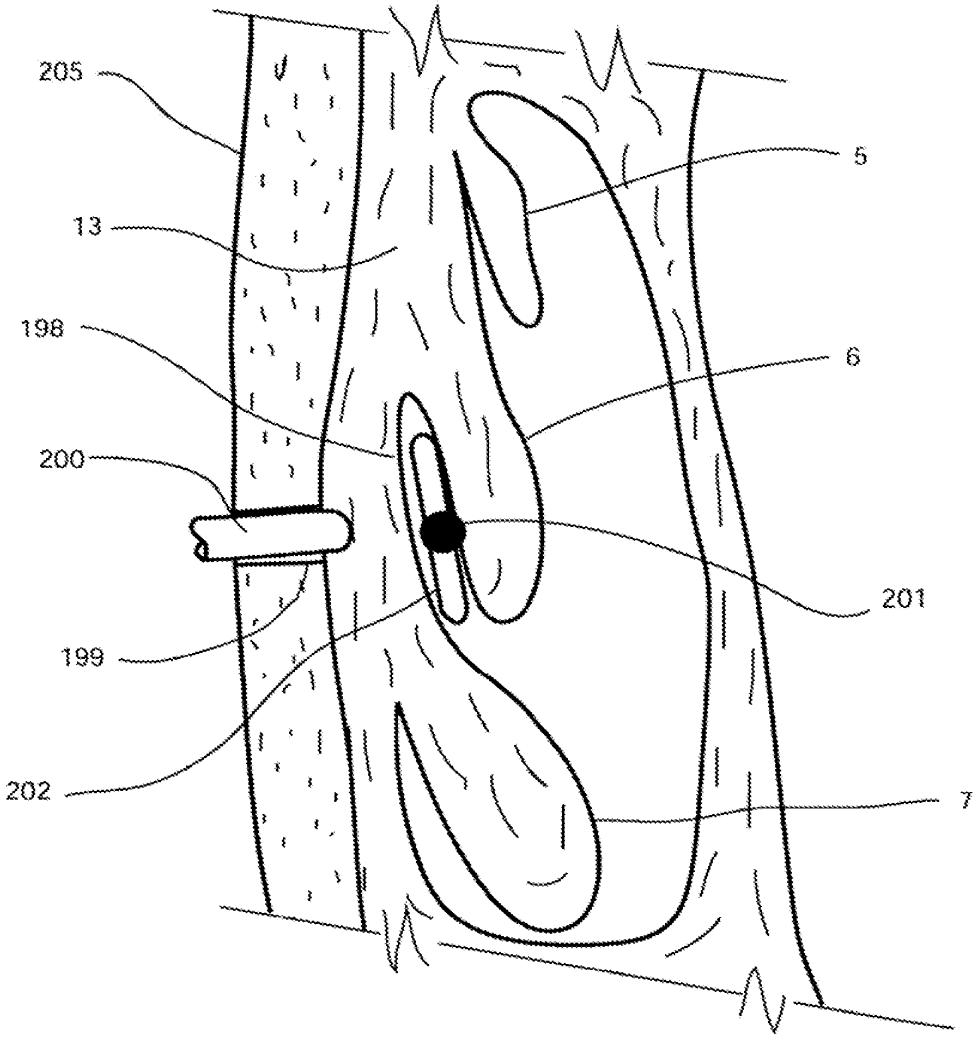


Figure 13B

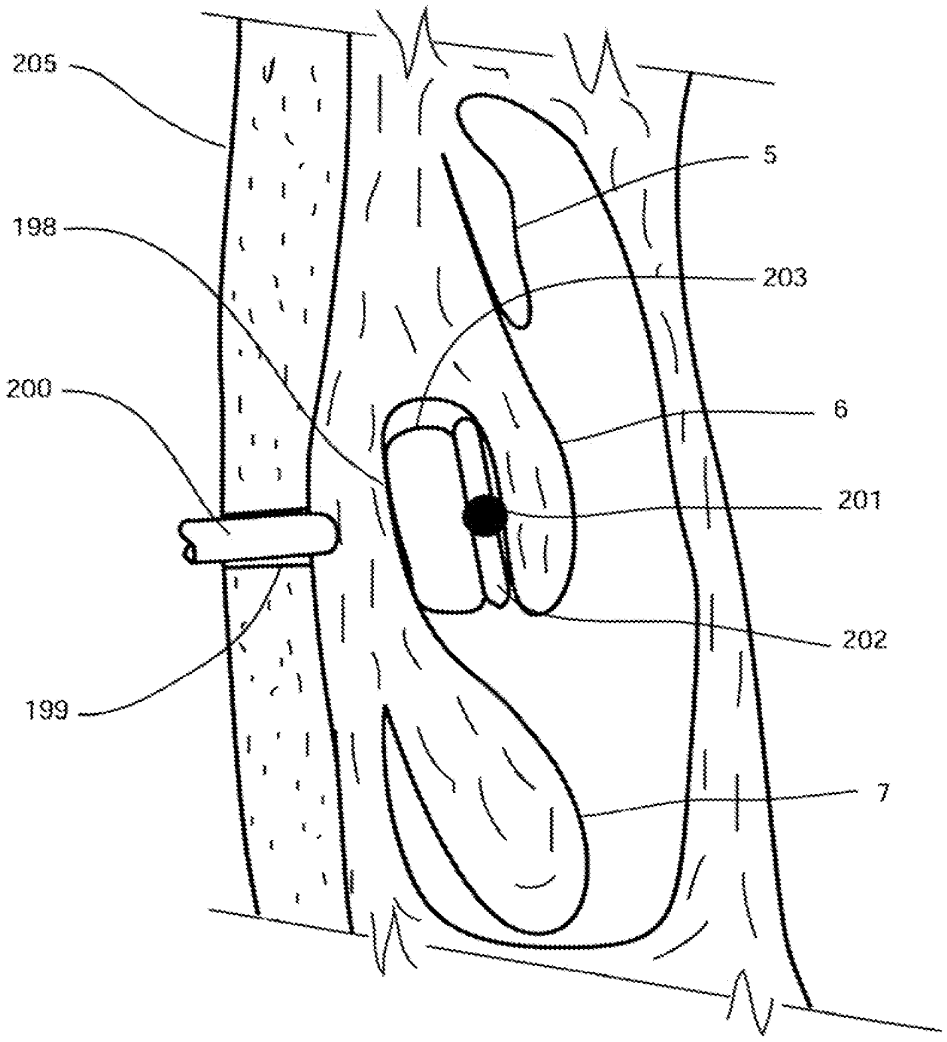


Figure 13C

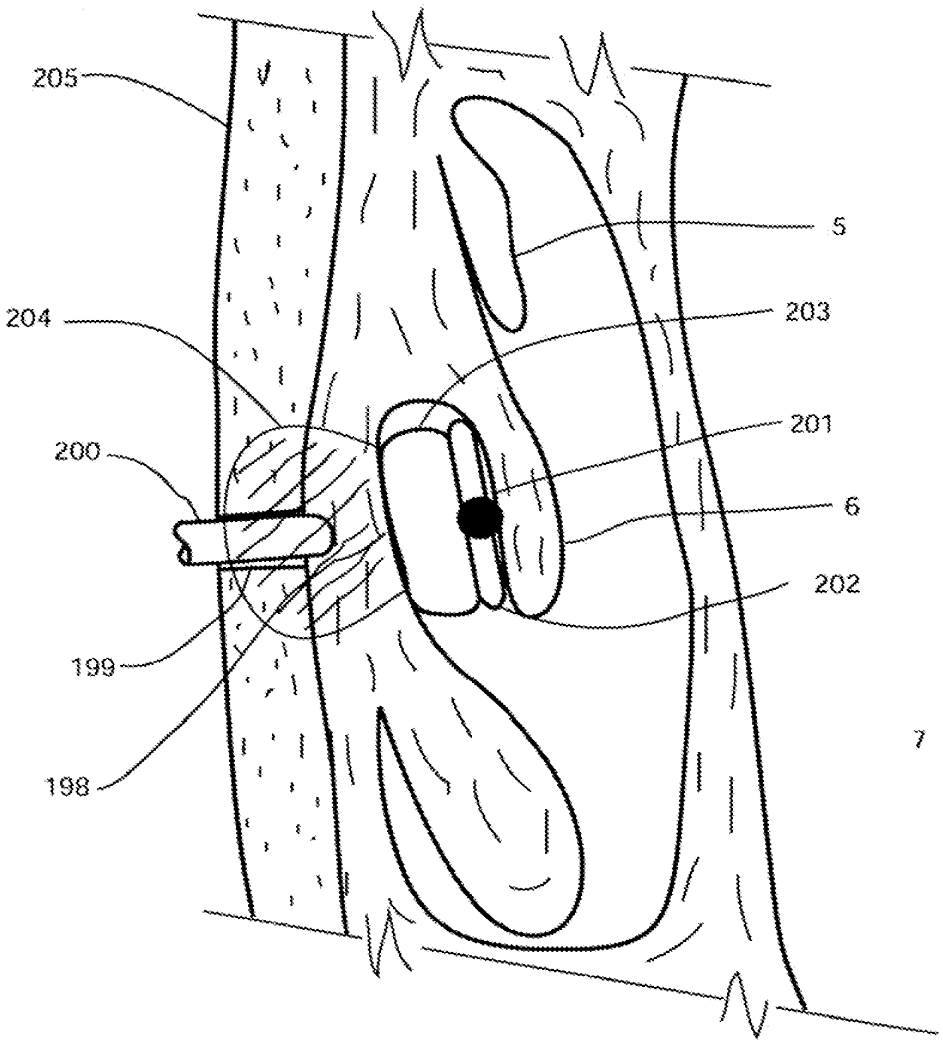


Figure 13D

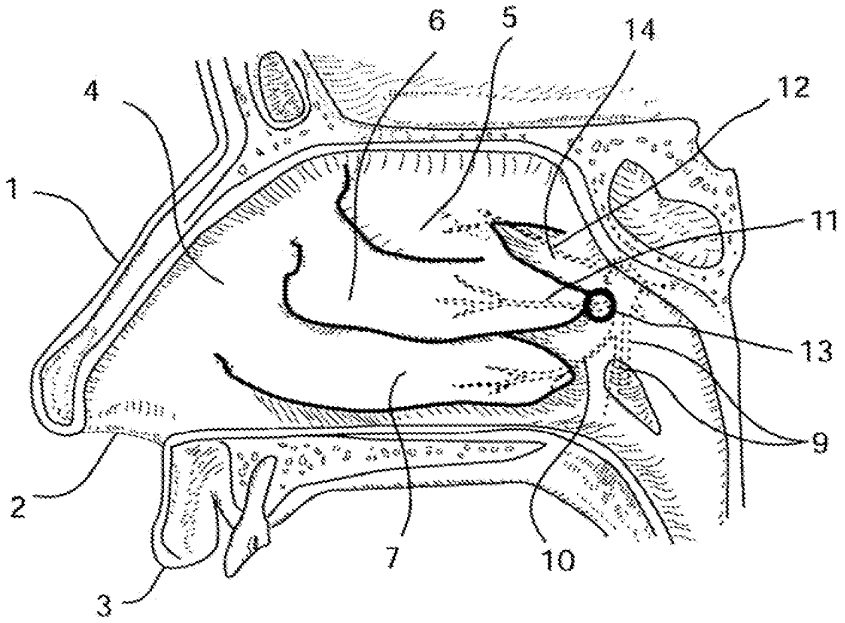


Figure 14A

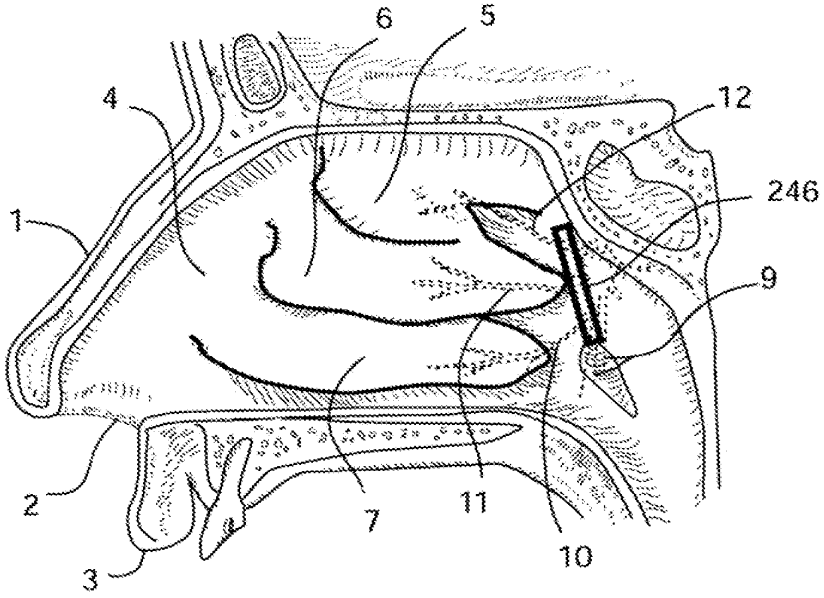


Figure 14B

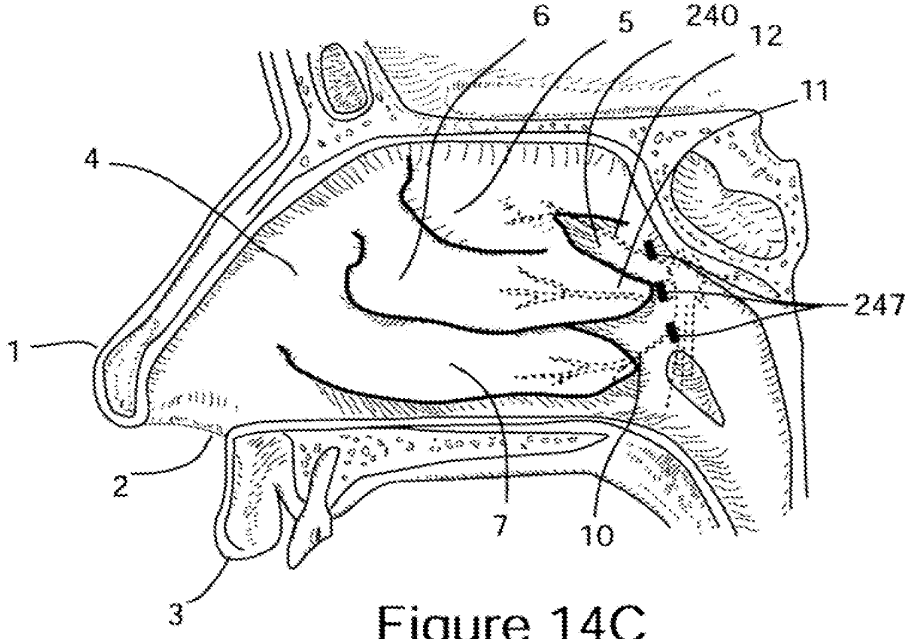


Figure 14C

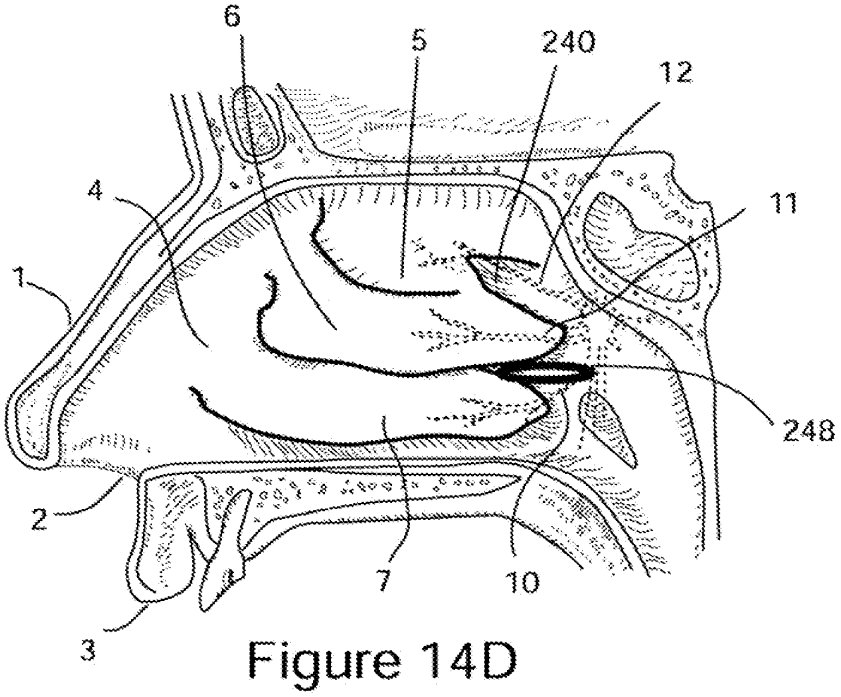


Figure 14D

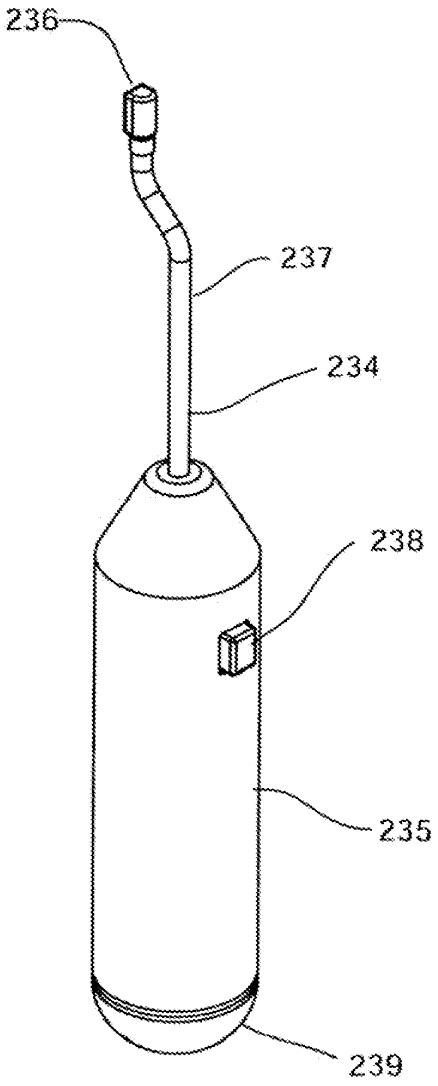


Figure 15A

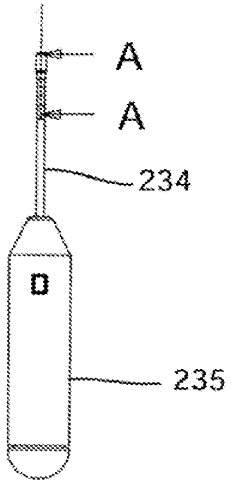
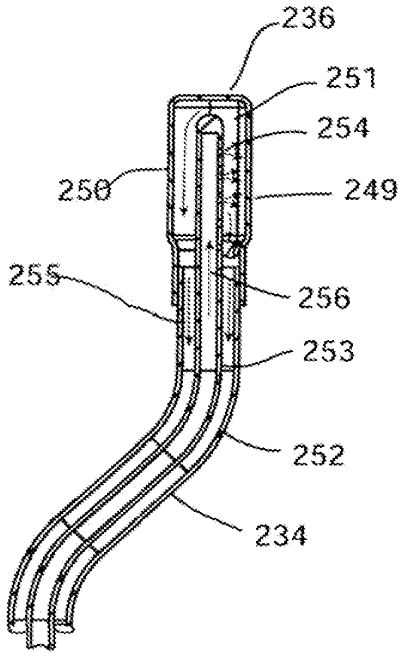


Figure 15B



Section A-A

Figure 15C

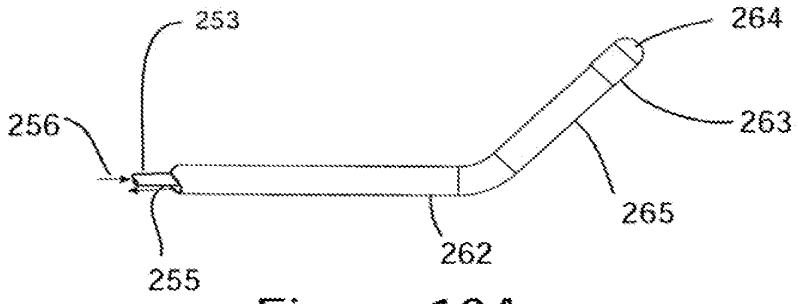


Figure 16A

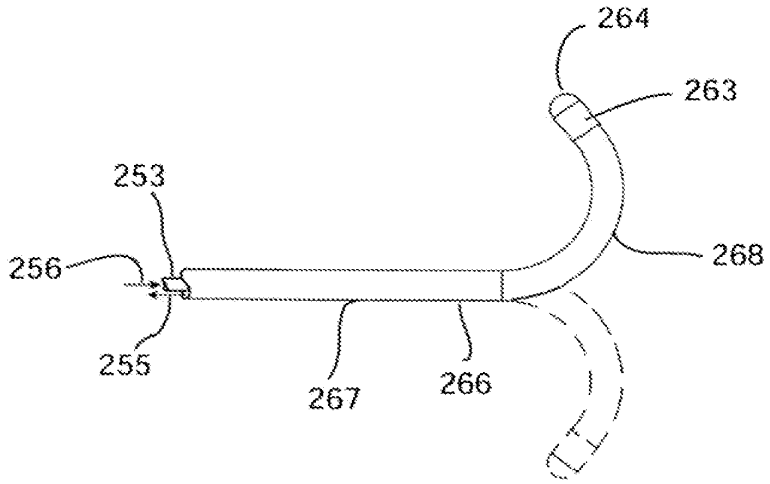


Figure 16B

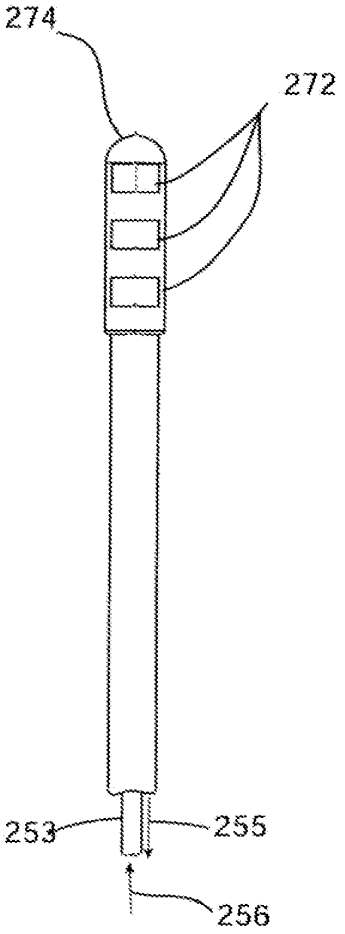


Figure 16C

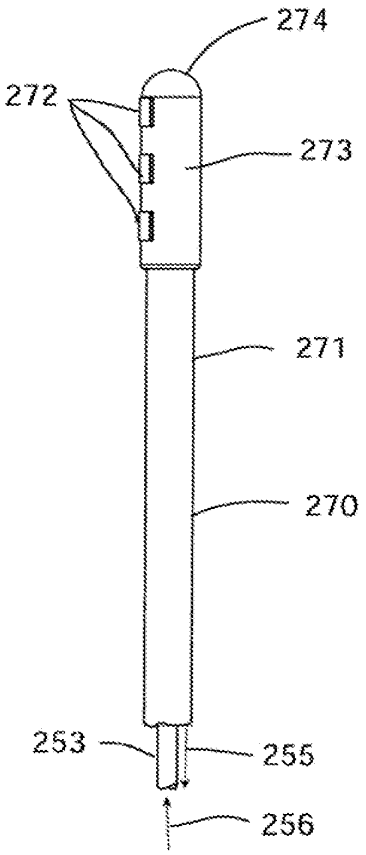


Figure 16D

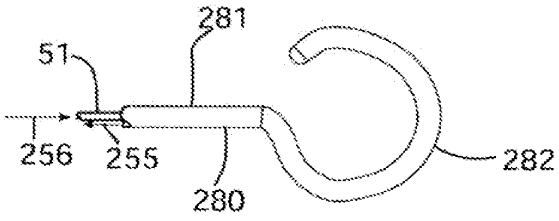


Figure 17A

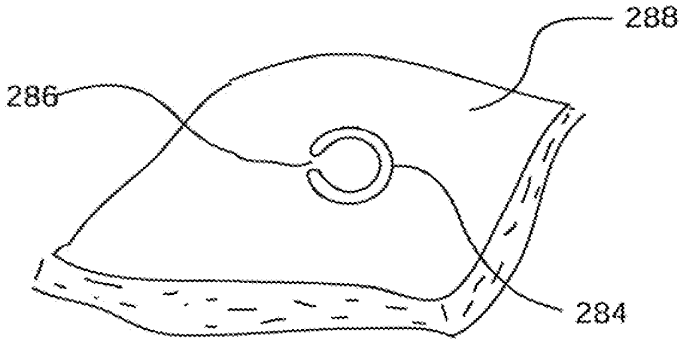


Figure 17B

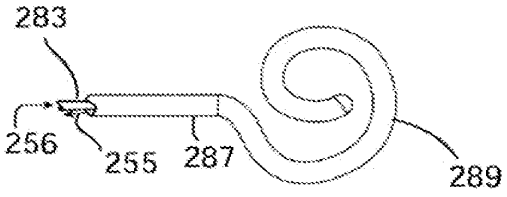


Figure 17C

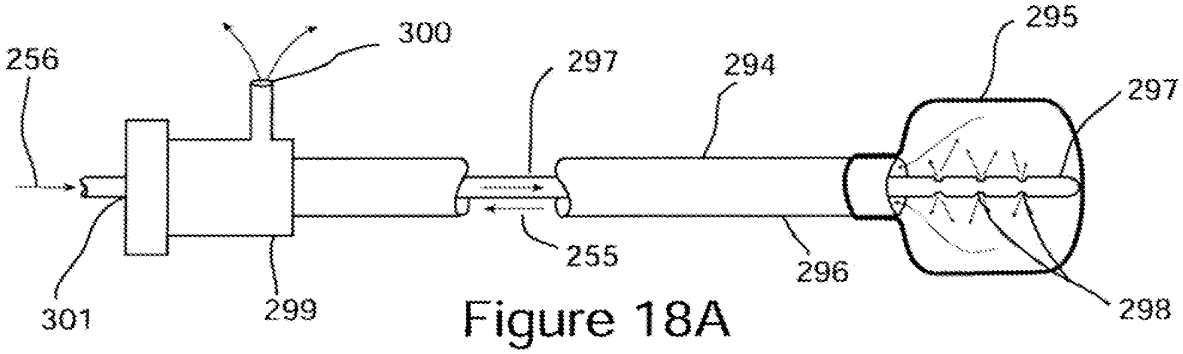


Figure 18A

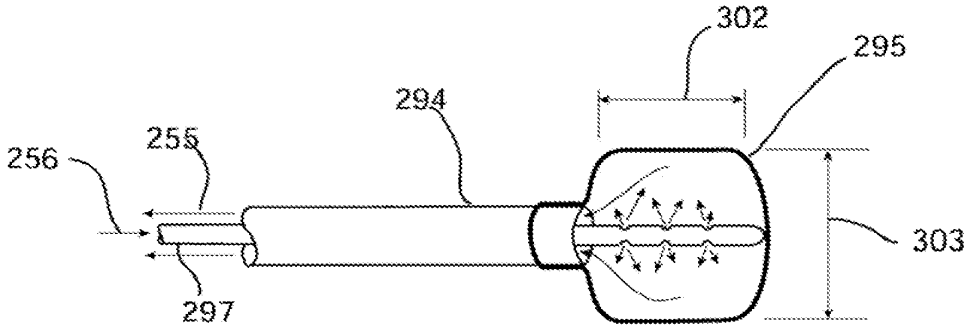


Figure 18B

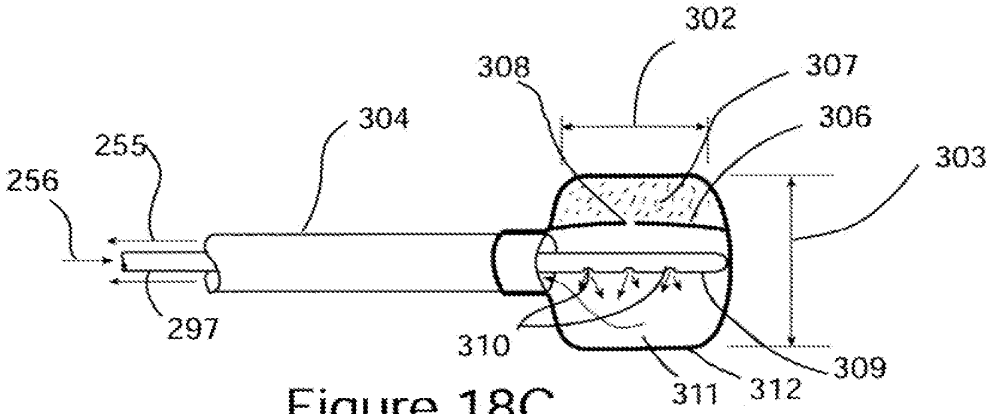


Figure 18C

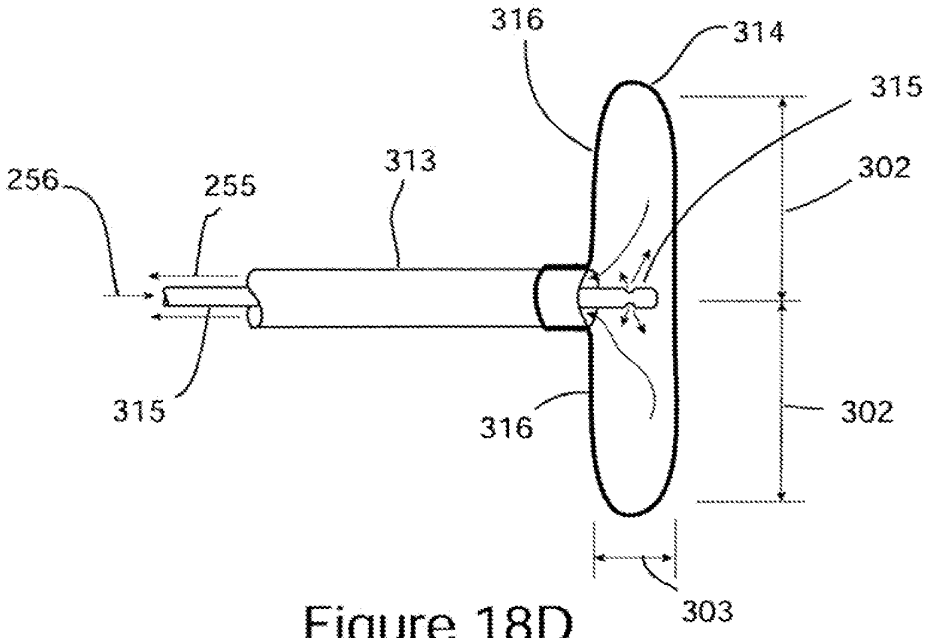


Figure 18D

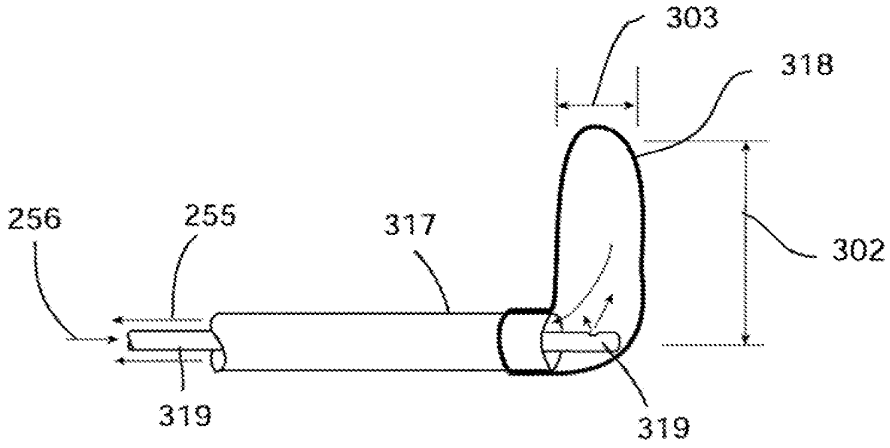


Figure 18E

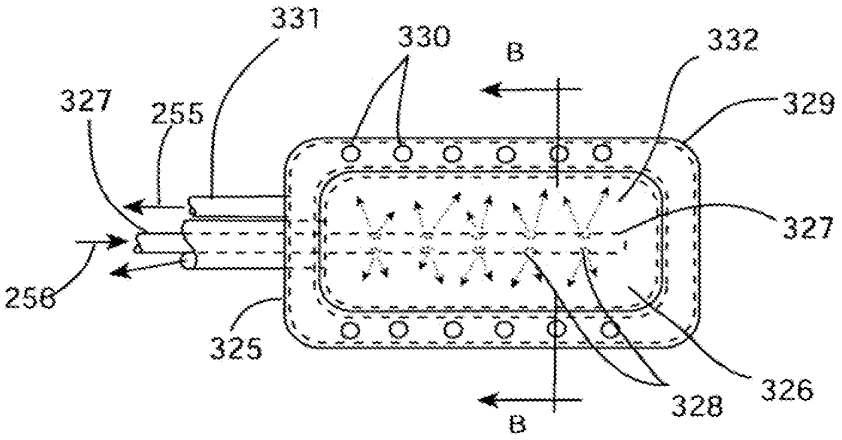
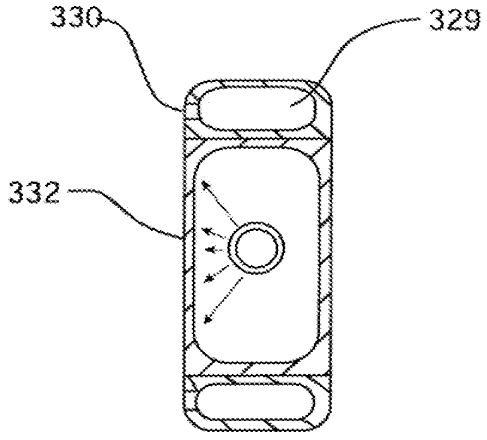


Figure 19A



Section B-B

Figure 19B

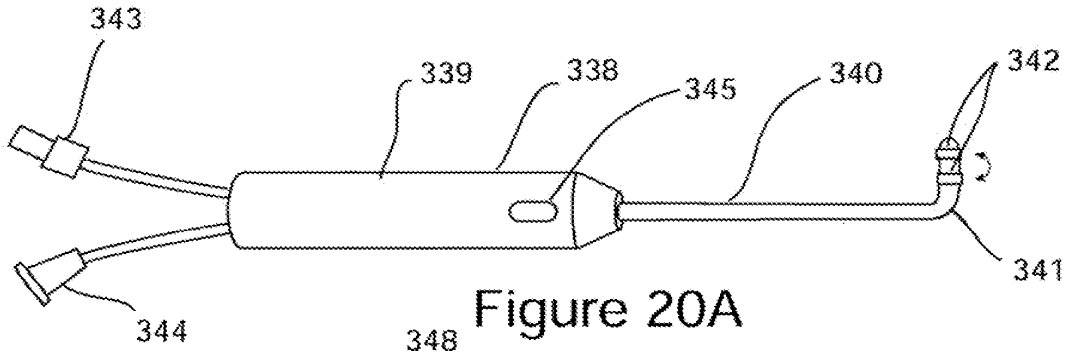


Figure 20A

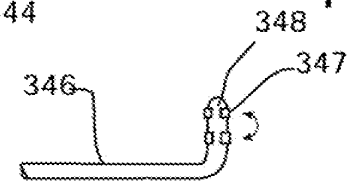


Figure 20B

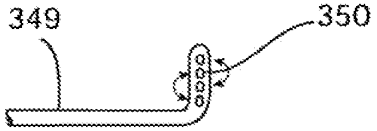


Figure 20C

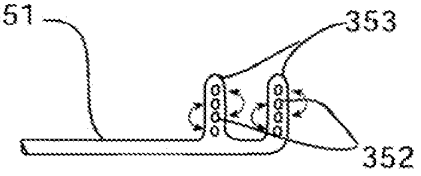


Figure 20D

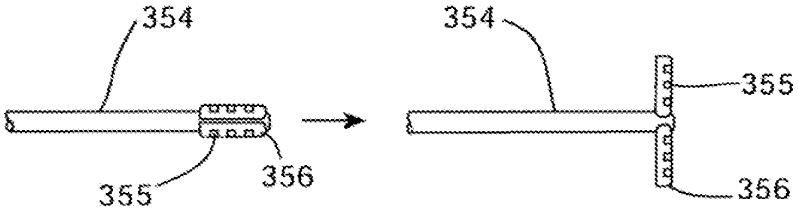


Figure 20E

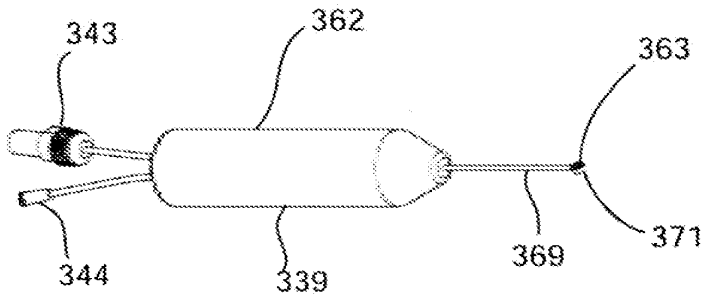


Figure 21A

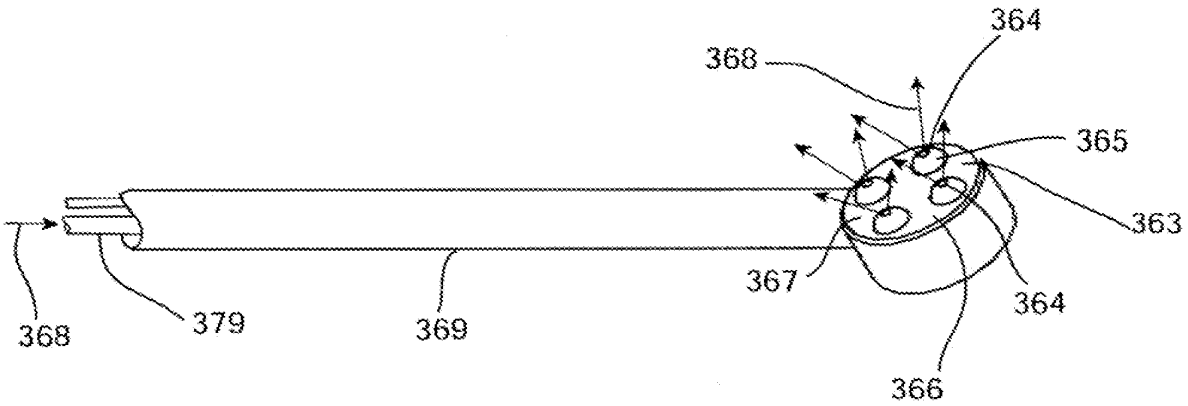


Figure 21B

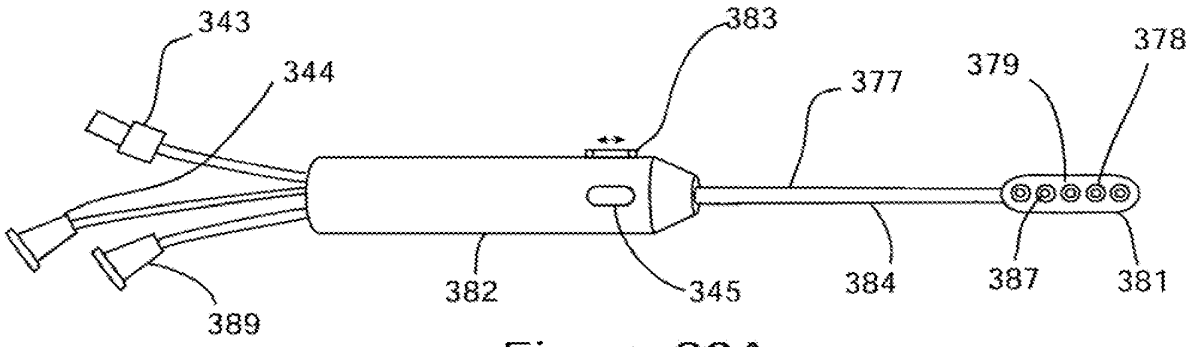


Figure 22A

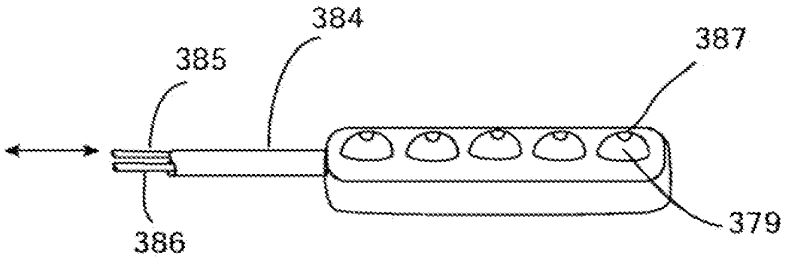


Figure 22B

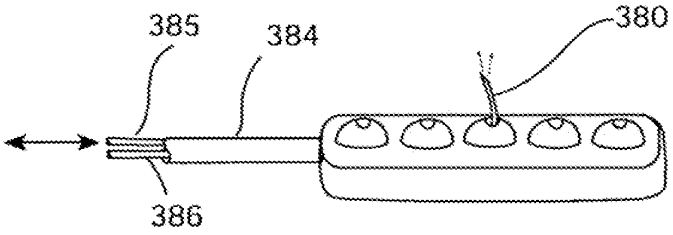


Figure 22C

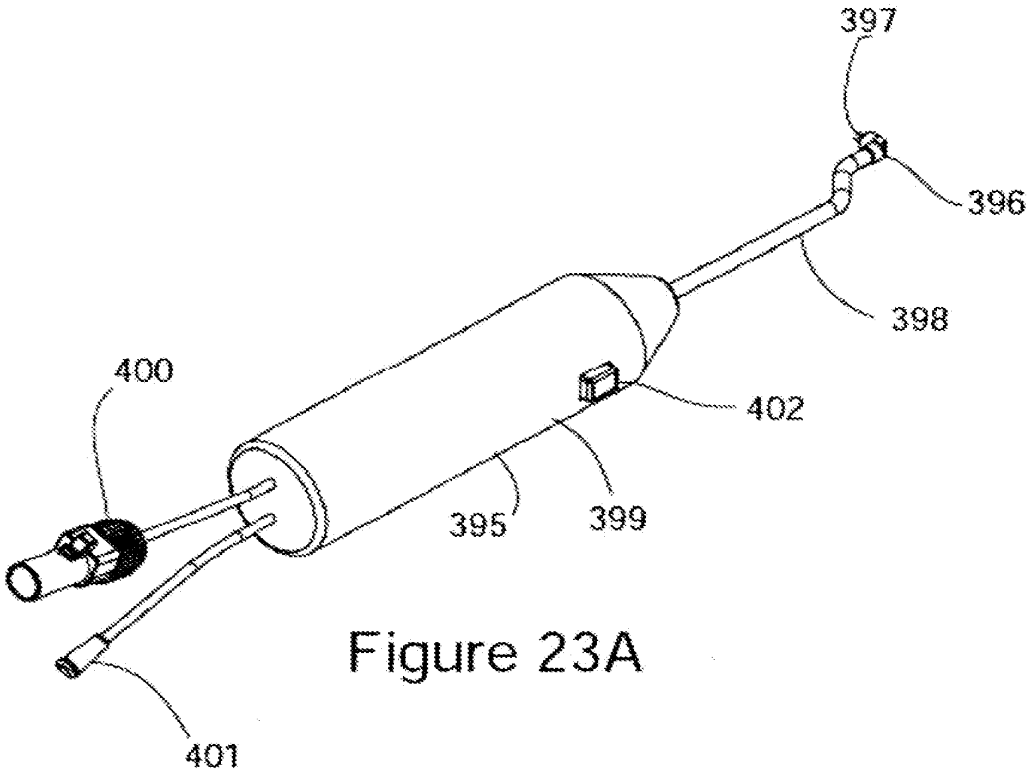


Figure 23A

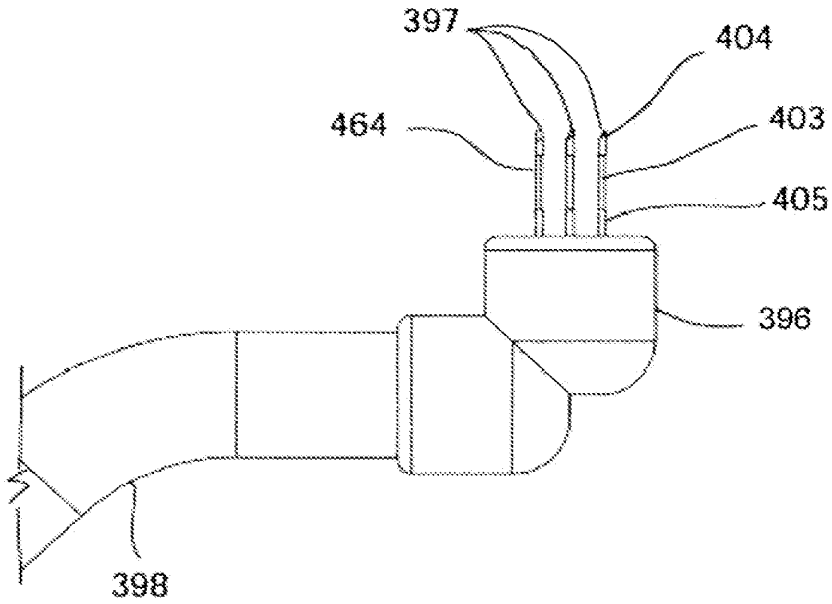


Figure 23B

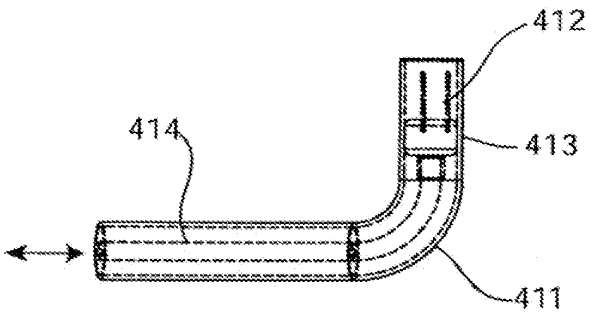


Figure 24A

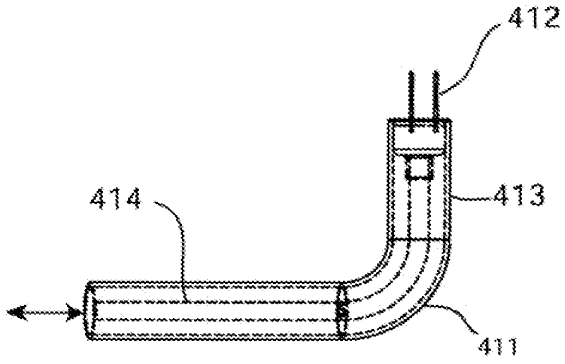


Figure 24B

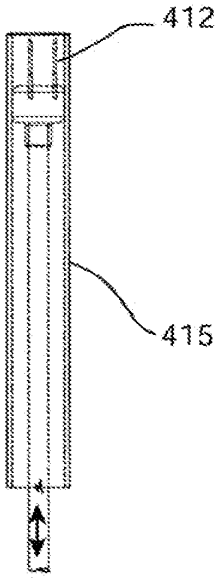


Figure 24C

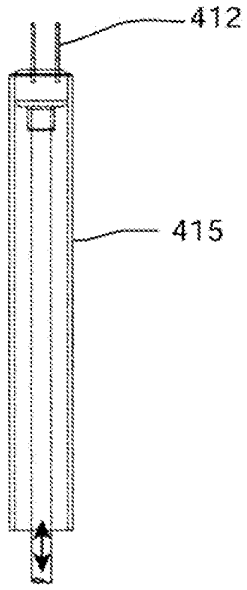


Figure 24D

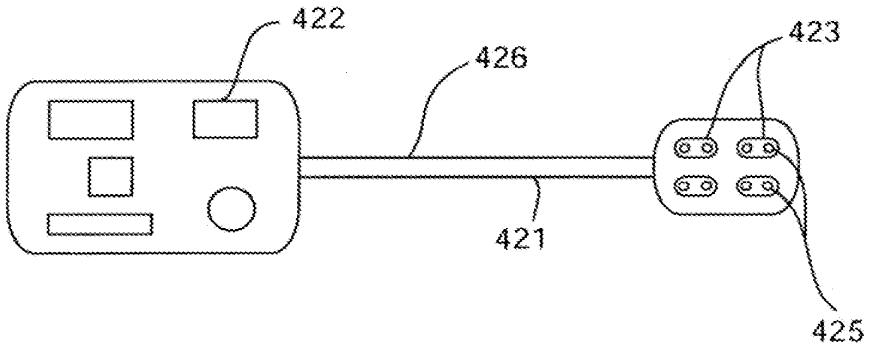


Figure 25A

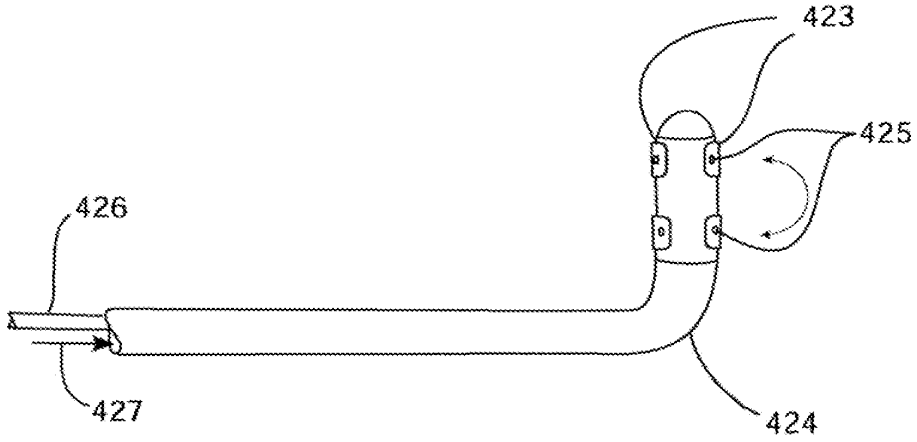


Figure 25B

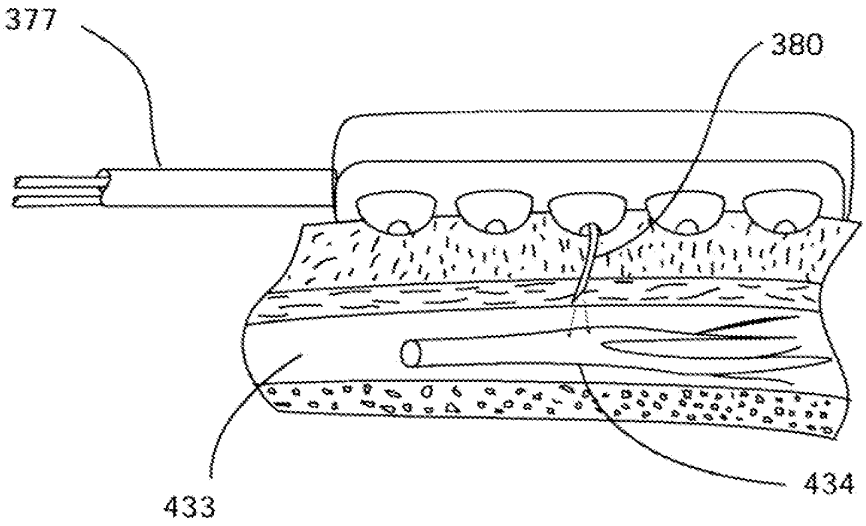


Figure 26A

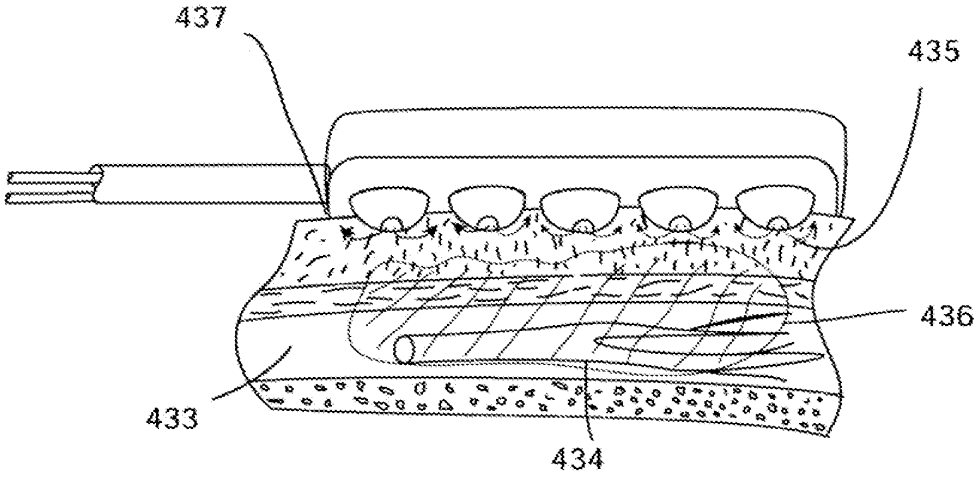


Figure 26B

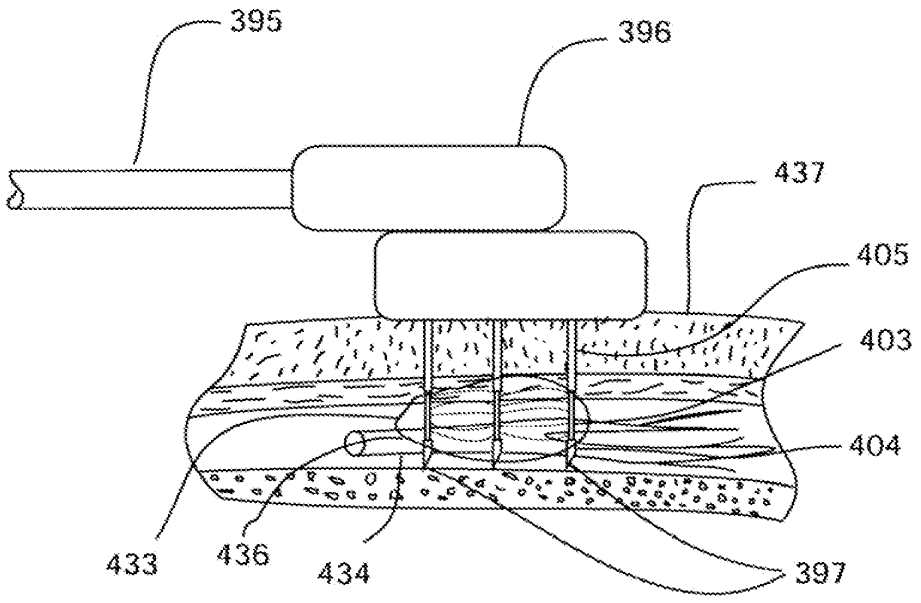


Figure 27

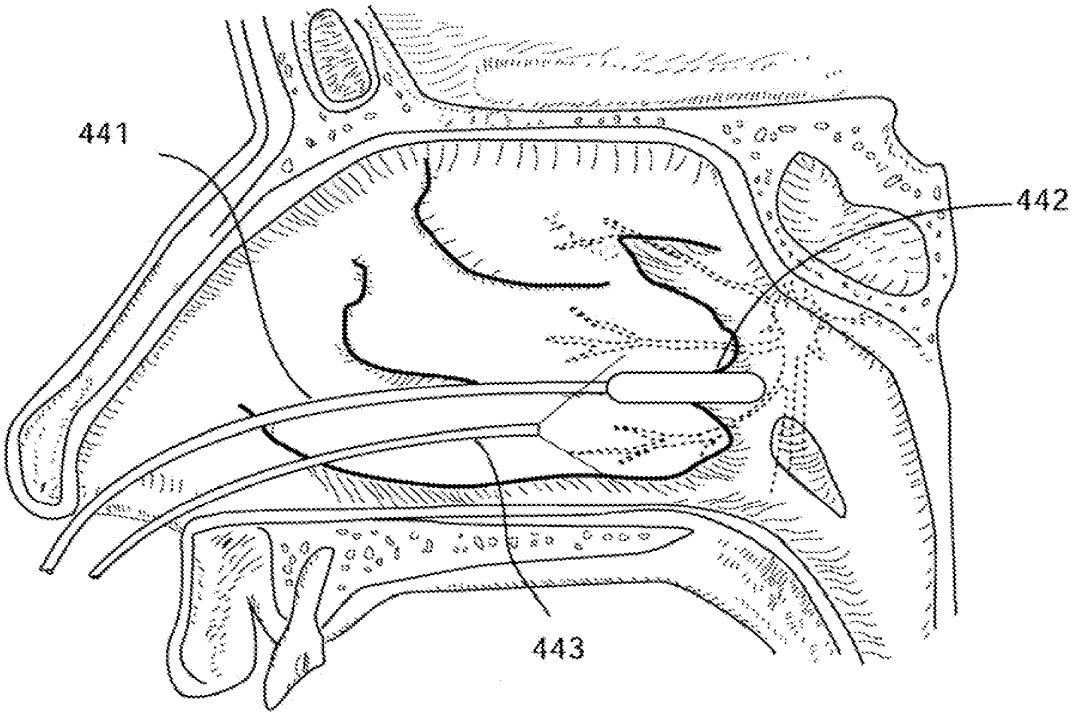


Figure 28

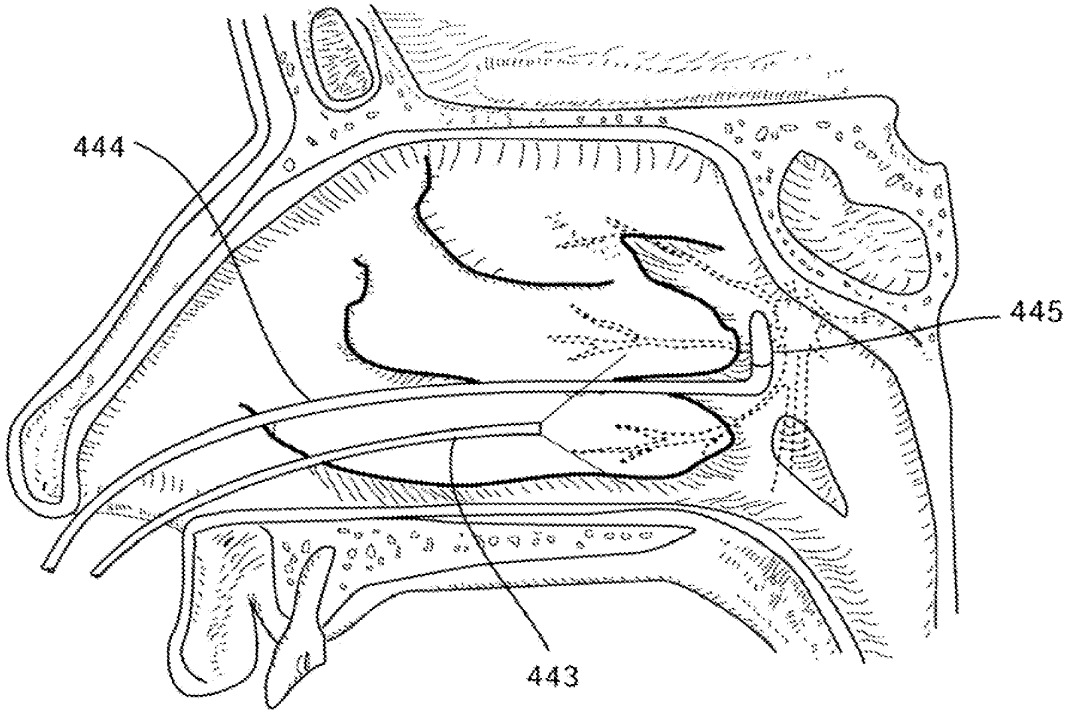


Figure 29

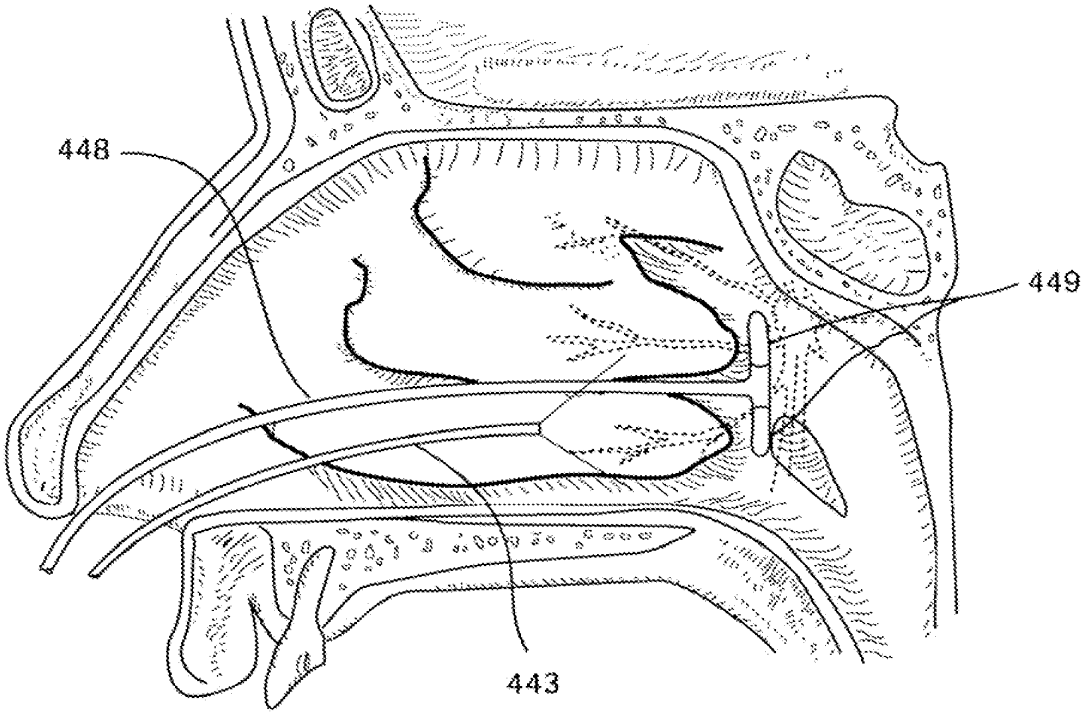


Figure 30

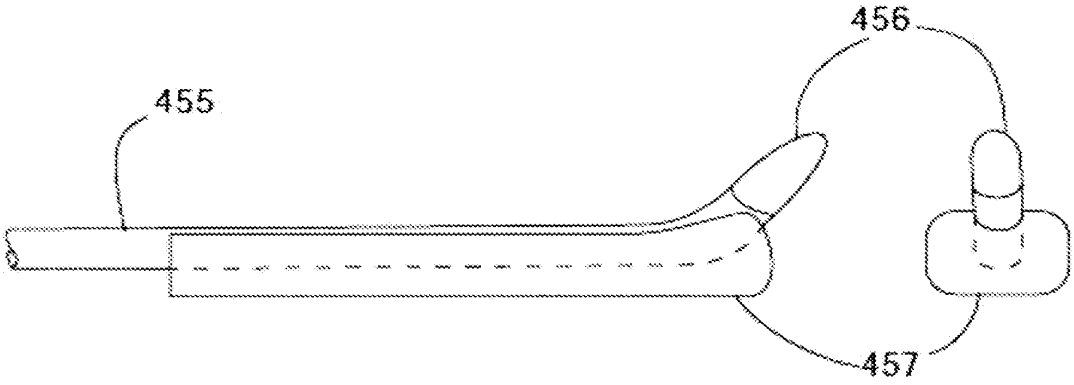


Figure 31A

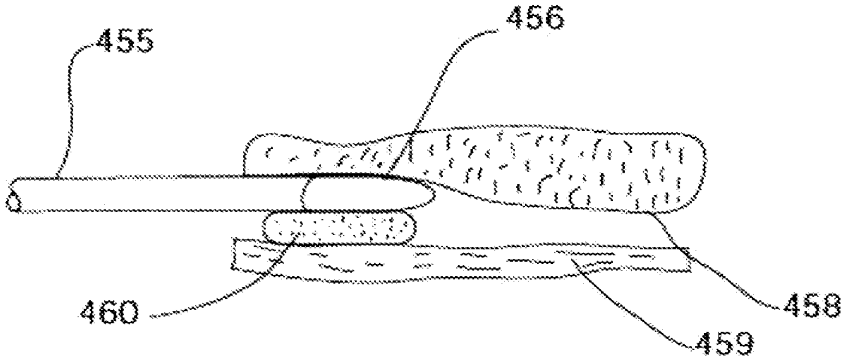


Figure 31B

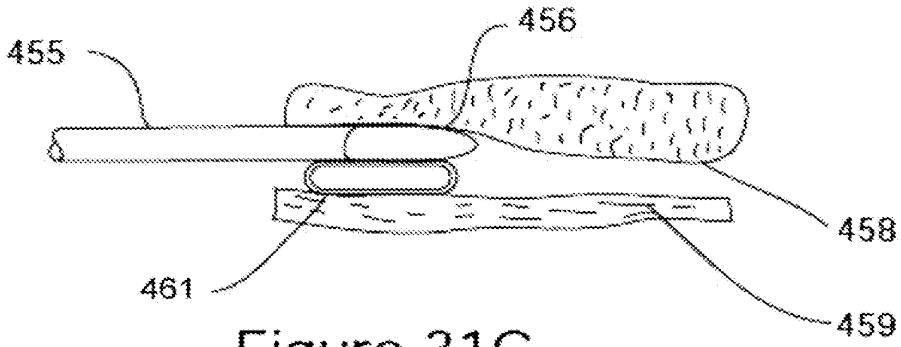


Figure 31C