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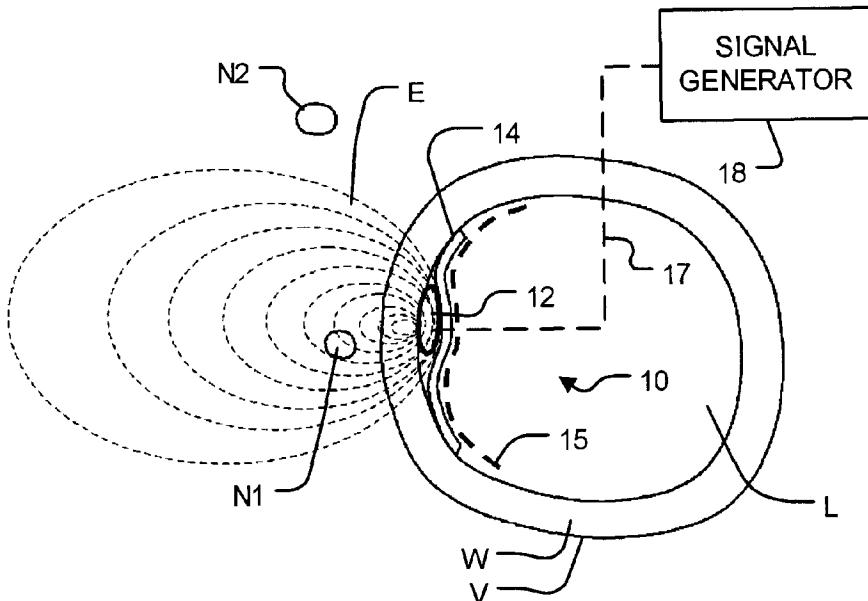
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(54) Title: TRANSVASCULAR NERVE STIMULATION APPARATUS AND METHODS



(57) Abrégé/Abstract:

(37) Abstract: Electrode structures for transvascular nerve stimulation combine electrodes with an electrically-insulating backing layer. The backing layer increases the electrical impedance of electrical paths through blood in a lumen of a blood vessel and consequently increases the flow of electrical current through surrounding tissues. The electrode structures may be applied to stimulate nerves such as the phrenic, vagus, trigeminal, obturator or other nerves.

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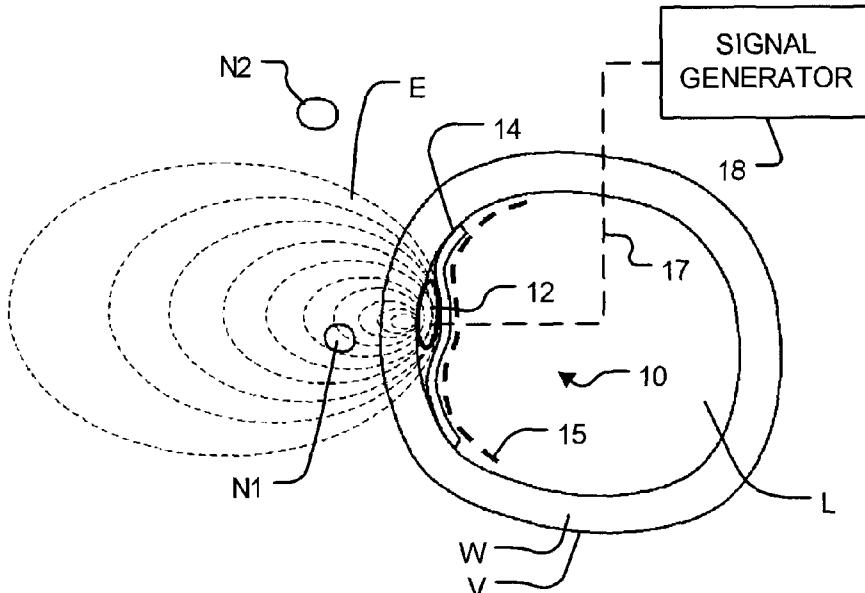


FIGURE 2

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(57) Abstract: Electrode structures for transvascular nerve stimulation combine electrodes with an electrically-insulating backing layer. The backing layer increases the electrical impedance of electrical paths through blood in a lumen of a blood vessel and consequently increases the flow of electrical current through surrounding tissues. The electrode structures may be applied to stimulate nerves such as the phrenic, vagus, trigeminal, obturator or other nerves.

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## **TRANSVASCULAR NERVE STIMULATION APPARATUS AND METHODS**

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### **Technical Field**

[0002] The invention relates to neurophysiology and in particular to apparatus and methods for stimulating nerves through the walls of blood vessels. Aspects of the 15 invention provide electrode structures that may be deployed within blood vessels to stimulate nerves passing near the blood vessels; nerve stimulation systems; and methods for nerve stimulation. Aspects of the invention may be applied for restoring breathing, treating conditions such as chronic pain, and other uses involving nerve stimulation. Aspects of the invention may be applied in the treatment of acute or 20 chronic conditions.

### **Background**

[0003] Nerve stimulation can be applied in the treatment of a range of conditions. The 25 nerve stimulation may be applied to control muscle activity or to generate sensory signals. Nerves may be stimulated by surgically implanting electrodes in, around or near the nerves and driving the electrodes from an implanted or external source of electricity.

[0004] The phrenic nerve normally causes the contractions of the diaphragm that are 30 necessary for breathing. Various conditions can prevent appropriate signals from being delivered to the phrenic nerve. These include:

- chronic or acute injury to the spinal cord or brain stem;
- Amyotrophic Lateral Sclerosis (ALS);

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- disease affecting the spinal cord or brain stem; and,
- decreased day or night ventilatory drive (e.g. central sleep apnea, Ondine's curse).

These conditions affect significant numbers of people.

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**[0005]** Mechanical ventilation may be used to help patients breathe. Some patients require chronic mechanical ventilation. Mechanical ventilation can be lifesaving but has a range of significant problems. Mechanical ventilation:

- tends to provide insufficient venting of the lungs. This can lead to accumulation of fluid in the lungs and susceptibility to infection.
- requires apparatus that is not readily portable. A patient on ventilation is tied to a ventilator. This can lead to atrophy of muscles (including breathing muscles) and an overall decline in well being.
- can adversely affect venous return because the lungs are pressurized.
- interferes with eating and speaking.
- requires costly maintenance and disposables.

**[0006]** Phrenic nerve pacing uses electrodes implanted in the chest to directly stimulate the phrenic nerve. The Mark IV Breathing Pacemaker System available from Avery Biomedical Devices, Inc. of Commack, New York USA is a diaphragmatic or phrenic nerve stimulator that consists of surgically implanted receivers and electrodes mated to an external transmitter by antennas worn over the implanted receivers. Implanting electrodes and other implantable components for phrenic nerve pacing requires significant surgery. The surgery is complicated by the fact that the phrenic nerve is small (approx. diameter 2 mm) and delicate. The surgery involves significant cost.

**[0007]** Laproscopic diaphragm pacing being developed by Case Western Reserve University bio-medical engineers and physician researchers is another technique for controlling breathing. Devices for use in Laproscopic diaphragm pacing are being developed by Synapse Biomedical, Inc. Laproscopic diaphragm pacing involves

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placing electrodes at motor points of the diaphragm. A laparoscope and a specially designed mapping procedure are used to locate the motor points.

**[0008]** References that in the field of nerve stimulation include:

- 5     •     Moffitt et al., WO 06/110338A1, entitled: TRANSVASCULAR NEURAL STIMULATION DEVICE;
- Caparso et al., US 2006/0259107, entitled: SYSTEM FOR SELECTIVE ACTIVATION OF A NERVE TRUNK USING A TRANSVASCULAR RESHAPING LEAD;
- 10    •     Dahl et al., WO 94/07564 entitled: STENT-TYPE DEFIBRILLATION ELECTRODE STRUCTURES;
- Scherlag et al., WO 99/65561 entitled: METHOD AND APPARATUS FOR TRANSVASCULAR TREATMENT OF TACHYCARDIA AND FIBRILLATION;
- 15    •     Bulkes et al., US20070288076A1 entitled: BIOLOGICAL TISSUE STIMULATOR WITH FLEXIBLE ELECTRODE CARRIER;
- Weinberg et al., EP 1304135 A2 entitled: IMPLANTABLE LEAD AND METHOD FOR STIMULATING THE VAGUS NERVE;
- Moffitt et al., US20060259107 entitled: SYSTEM FOR SELECTIVE ACTIVATION OF A NERVE TRUNK USING A TRANSVASCULAR RESHAPING LEAD;
- 20    •     Denker et al. US 6907285 entitled: IMPLANTABLE DEFIBRILLATOR WITH WIRELESS VASCULAR STENT ELECTRODES;
- Chavan et al. US20070093875 entitled IMPLANTABLE AND RECHARGEABLE NEURAL STIMULATOR;
- 25    •     Rezai, US 6885888 entitled ELECTRICAL STIMULATION OF THE SYMPATHETIC NERVE CHAIN;
- Mehra, US 5170802 entitled IMPLANTABLE ELECTRODE FOR LOCATION WITHIN A BLOOD VESSEL;
- 30    •     Mahcuk et al. US 5954761 entitled: IMPLANTABLE ENDOCARDIAL LEAD ASSEMBLY HAVING A STENT;

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- Webster Jr. et al. US 6292695 entitled: METHOD AND APPARATUS FOR TRANSVASCULAR TREATMENT OF TACHYCARDIA AND FIBRILLATION;
- Stokes, US 4643201;
- 5 • Ela Medical SA, EP 0993840A, US6385492
- WO 9407564 describes stent-type electrodes that can be inserted through a patient's vasculature.
- WO 9964105A1 describes transvascular treatment of tachycardia.
- WO 9965561A1 describes a method and apparatus for transvascular treatment 10 of tachycardia and fibrillation.
- WO02058785A1 entitled VASCULAR SLEEVE FOR INTRAVASCULAR NERVE STIMULATION AND LIQUID INFUSION describes a sleeve that includes an electrode for stimulating nerves.
- WO 06115877A1 describes vagal nerve stimulation using vascular implanted 15 devices.
- WO 07053508A1 entitled INTRAVASCULAR ELECTRONICS CARRIER AND ELECTRODE FOR A TRANSVASCULAR TISSUE STIMULATION SYSTEM and US20070106357A1 describe an intravascular mesh type electrode carrier in which the conductor of a lead is interwoven into the carrier 20 mesh.
- US 5224491 describes implantable electrodes for use in blood vessels.
- US 5954761 describes an implantable lead carrying a stent that can be inserted into the coronary sinus.
- US 6006134 describes transvenous stimulation of nerves during open heart 25 surgery.
- US 6136021 describes an expandable electrode for coronary venous leads (the electrode can be placed or retained in the vasculature of the heart).
- Spreigl et al. US 6161029 entitled: APPARATUS AND METHOD FOR FIXING ELECTRODES IN A BLOOD VESSEL describes fixing electrodes 30 in blood vessels.
- US 6438427 describes electrodes for insertion into the coronary sinus.

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- US 6584362 describes leads for pacing and/or sensing the heart from within the coronary veins.
- US 6778854 describes use of electrodes in the Jugular vein for stimulation of the Vagus nerve.
- 5 • US 6934583 discloses stimulation of the Vagus nerve with an electrode in a blood vessel.
- US 7072720 describes catheter and tube electrode devices that incorporate expanding electrodes intended to contact the interior walls of blood vessels or anatomic structures in which the electrode devices are implanted as well as methods involving stimulation of the vagus nerve.
- 10 • US 7184829 discloses transvascular stimulation of a vagal nerve.
- US 7225019 discloses intravascular nerve stimulation electrodes that may be used in the Jugular vein.
- US 7231260 describes intravascular electrodes.
- 15 • Schauerte et al., US 2002/0026228 entitled: ELECTRODE FOR INTRAVASCULAR STIMULATION, CARDIOVERSION AND/OR DEFIBRILLATION;
- Jonkman et al., US6006134
- Bonner et al., US6201994
- 20 • Brownlee et al., US 6157862
- Scheiner et al., US6584362
- Psukas, WO 01/00273
- FR 2801509, US 2002065544
- Morgan, US6295475
- 25 • Bulkes et al., US 6445953
- Rasor et al. US3835864 entitled: INTRA-CARDIAC STIMULATOR
- Denker et al. US20050187584
- Denker et al. US20060074449A1 entitled: INTRAVASCULAR STIMULATION SYSTEM WITH WIRELESS POWER SUPPLY;

- Denker et al. US20070106357A1 entitled: INTRAVASCULAR ELECTRONICS CARRIER ELECTRODE FOR A TRANSVASCULAR TISSUE STIMULATION SYSTEM;
- Boveja et al. US20050143787
- *Transvenous Parasympathetic cardiac nerve stimulation; an approach for stable sinus rate control*, Journal of Cardiovascular Electrophysiology 10(11) pp. 1517-1524 Nov. 1999
- *Transvenous Parasympathetic nerve stimulation in the inferior vena cava and atrioventricular conduction*, Journal of Cardiovascular Electrophysiology 11(1) pp. 64-69, Jan. 2000.
- Planas et al., *Diaphragmatic pressures: transvenous vs. direct phrenic nerve stimulation*, J. Appl. Physiol. 59(1): 269-273, 1985.
- Yelena Nabutovsky, M.S. et al., *Lead Design and Initial Applications of a New Lead for Long-Term Endovascular Vagal Stimulation*, PACE vol. 30, Supplement 1, January 2007 p. S215

[0009] Other references of interest include:

- Amundson, US5779732

[0010] There remains a need for surgically simpler, cost-effective and practical apparatus and methods for nerve stimulation.

#### Summary of the Invention

[0011] This invention has a range of aspects. One aspect of the invention provides a system for stimulating a left phrenic nerve and a right phrenic nerve of a patient, the system comprising:

- a signal generator to produce stimulation signals;
- a lead structure configured for insertion into (a) at least one of a left jugular vein and a left subclavian vein, (b) a left brachiocephalic vein, and (c) a vena cava of the patient, the lead

structure defining a longitudinal axis along a length of the lead structure, having an outermost surface at a position radially spaced from the longitudinal axis, and having a plurality of leads to receive stimulation signals from the signal generator;

a plurality of second pairs of electrodes longitudinally extending about the lead structure proximate a distal portion of the lead structure and configured to receive stimulation signals from at least one lead of the plurality of leads;

a plurality of first pairs of electrodes longitudinally extending about the lead structure proximal to the plurality of second pairs of electrodes, the plurality of first pairs of electrodes configured to receive stimulation signals from at least one lead of the plurality of leads, wherein the signal generator is proximal to the first pairs of electrodes; and

a control system programmed to (a) select a first stimulation pair of electrodes from the plurality of first pairs of electrodes to stimulate the left phrenic nerve, and (b) select a second stimulation pair of electrodes from the plurality of second pairs of electrodes to stimulate the right phrenic nerve,

wherein the plurality of second pairs of electrodes and the plurality of first pairs of electrodes are positioned at radial locations different from the position of the outermost surface of the lead structure.

Another aspect provides a nerve stimulation system, comprising:

a plurality of first electrodes configured to be positioned in a venous system for stimulation of a left phrenic nerve;

a plurality of second electrodes configured to be positioned in a superior vena cava for stimulation of a right phrenic nerve;

a signal generator;

at least one lead structure including an outer layer; and

a control system programmed to select a combination of electrodes from at least one of the first electrodes or the second electrodes for stimulation of the respective left phrenic nerve or right phrenic nerve, the combination having more than two electrodes;

wherein at least one of the first electrodes or one of the second electrodes is exposed through a corresponding aperture in the outer layer.

Yet another aspect provides a nerve stimulation system, comprising:

a lead structure, the lead structure including:

a plurality of first electrodes configured to be positioned in a venous system for stimulation of a left phrenic nerve; and

a plurality of second electrodes configured to be positioned in a superior vena cava for stimulation of the right phrenic nerve;

wherein at least one of the first electrodes or the second electrodes is arranged in at least two rows.

According to a preferred aspect, there is provided electrodes for transvascular stimulation of nerves. In embodiments, electrode structures comprise at least one electrode supported on an electrically-insulating backing sheet; and, a structure for holding the backing sheet against the inner wall of a blood vessel with the electrode in contact with the inner wall of the blood vessel. In some embodiments, the backing sheet is designed to unroll inside the lumen of a blood vessel to fit around the periphery of the lumen of a blood vessel. In such embodiments, the backing sheet can comprise the structure for holding the backing sheet against the inner wall of the blood vessel. In other embodiments an expandable stent or a tube is provided to hold the backing sheet and electrodes against the blood vessel wall.

**[0012]** Another preferred aspect of the invention comprises a nerve stimulation system comprising a stimulation signal generator and first and second electrode structures.

The first electrode structure comprises a first plurality of electrodes and is dimensioned to be implantable at a position along a lumen of a person's left subclavian vein that is proximate to the left phrenic nerve. The second electrode structure comprises a second plurality of electrodes and is dimensioned to be implantable at a position along a lumen of the person's superior vena cava that is proximate to the right phrenic nerve. The system comprises means such as electrical leads, a wireless system or the like for transmitting signals from the signal generator to the first and second pluralities of electrodes.

**[0013]** Another preferred aspect of the invention provides a method for regulating breathing of a person. The method comprises implanting at least one of: a first electrode structure

at a position along a lumen of the left subclavian vein that is proximate to the left phrenic nerve; and a second electrode structure at a position along a lumen of the superior vena cava that is proximate to the right phrenic nerve; and subsequently stimulating the left- and right- phrenic nerves by applying stimulation signals to electrodes of the first and second electrode structures.

**[0013a]** Another preferred aspect of the invention provides a system for stimulating a phrenic nerve of a patient, the system comprising:

    a signal generator to produce stimulation signals;

    a lead structure configured for insertion into a venous system of the patient, the lead structure having a plurality of leads to receive stimulation signals from the signal generator;

    an array of electrodes on the lead structure positionable proximate the phrenic nerve and configured to receive stimulation signals from at least one of the plurality of leads for stimulation of the phrenic nerve, wherein the array of electrodes includes more than two electrically discrete electrodes, and wherein each electrode of the array of electrodes is positioned radially inwards of an outer non-conductive portion of the lead structure and is exposed through an opening in the outer non-conductive portion; and

    a control system programmed to select a bipolar pair of electrodes from the array of electrodes, the pair of electrodes including two electrodes configured to align substantially parallel to the phrenic nerve.

**[0013b]** Another preferred aspect of the invention provides a nerve stimulation system, comprising:

    a lead structure defining a longitudinal axis along a length of the lead structure and having an outermost surface at a position radially spaced from the longitudinal axis, the lead structure including:

        a plurality of first electrodes spaced about the longitudinal axis of the lead structure, wherein each of the first electrodes is exposed about only a portion of a circumference of the lead structure, and wherein each of the first electrodes is positioned at a radial position different from the position of the outermost surface of the lead structure; and

a plurality of second electrodes spaced about the longitudinal axis of the lead structure distal to the first electrodes, wherein each of the second electrodes is exposed about only a portion of a circumference of the lead structure;

wherein the first electrodes are configured to be positioned to stimulate a left phrenic nerve, and the second electrodes are configured to be positioned to stimulate a right phrenic nerve.

**[0013c]** Another preferred aspect of the invention provides a nerve stimulation system, comprising:

a plurality of first electrodes configured to be positioned in a venous system for stimulation of a left phrenic nerve;

a plurality of second electrodes configured to be positioned in a superior vena cava for stimulation of a right phrenic nerve;

a control system programmed to select at least one of (i) a first combination of electrodes from the plurality of first electrodes for stimulation of the left phrenic nerve, the first combination having more than two electrodes, or (ii) a second combination of electrodes from the plurality of second electrodes for stimulation of the right phrenic nerve, the second combination have more than two electrodes.

**[0013d]** Another preferred aspect of the invention provides a nerve stimulation system, comprising:

a lead structure defining a longitudinal axis along a length of the lead structure and including an outermost surface defining a plurality of apertures in the outermost surface, wherein each of the plurality of apertures extends about only a portion of a circumference of the lead structure;

a first plurality of electrodes longitudinally spaced along the lead structure proximate a distal portion of the lead structure; and

a second plurality of electrodes longitudinally spaced along the lead structure proximate a proximal portion of the lead structure,

wherein at least one of the first plurality of electrodes and the second plurality of electrodes is exposed through one of the plurality of apertures in the outermost surface.

**[0013e]** Another preferred aspect of the invention provides a system of stimulating a left phrenic nerve and a right phrenic nerve of a patient, the system comprising:

a lead structure configured for insertion into a venous system of the patient, the lead structure defining a longitudinal axis and having an outermost surface at a position radially spaced from the longitudinal axis;

a plurality of first pairs of electrodes longitudinally spaced along the lead structure proximate a distal portion of the lead structure; and

a plurality of second pairs of electrodes longitudinally spaced along the lead structure proximate a proximal portion of the lead structure,

wherein at least one of the plurality of first pairs of electrodes and the plurality of second pairs of electrodes is recessed from the outermost surface of the lead structure.

**[0013f]** Another preferred aspect of the invention provides a system for stimulating a phrenic nerve of a patient, the system comprising:

a signal generator to produce stimulation signals;

a lead structure configured for insertion into a venous system of the patient, the lead structure having a plurality of leads to receive stimulation signals from the signal generator;

an array of electrodes on the lead structure positionable proximate the phrenic nerve and configured to receive stimulation signals from at least one of the plurality of leads for stimulation of the phrenic nerve, wherein the array of electrodes includes more than two electrically discrete electrodes; and

a control system programmed to select a combination of electrodes from the array of electrodes, the combination of electrodes including exactly three electrodes.

**[0013g]** Another preferred aspect of the invention provides a system for stimulating a phrenic nerve of a patient, the system comprising:

a signal generator to produce stimulation signals, wherein the signal generator is implantable and configured to be positioned outside of the patient's vasculature;

a lead structure configured for insertion into a venous system of the patient, the lead structure having (1) a plurality of leads to receive stimulation signals from the signal generator and (2) an exterior wall;

an array of electrodes on the lead structure positionable proximate the phrenic nerve and configured to receive stimulation signals from at least one of the plurality of leads for stimulation of the phrenic nerve, wherein the array of electrodes includes more than two electrically discrete electrodes, and wherein the electrically discrete electrodes are only partially electrically exposed radially outward of the lead structure through the exterior wall of the lead structure; and

a control system programmed to select a combination of electrodes from the array of electrodes.

**[0013h]** Another preferred aspect of the invention provides a system for stimulating a phrenic nerve of a patient, the system comprising:

a signal generator to produce stimulation signals;

a lead structure configured for insertion into a venous system of the patient, the lead structure having a plurality of leads to receive stimulation signals from the signal generator;

an array of electrodes on the lead structure positionable proximate the phrenic nerve and configured to receive stimulation signals from at least one of the plurality of leads for stimulation of the phrenic nerve, wherein the array of electrodes includes more than two electrically discrete electrodes, and wherein each electrode of the array of electrodes is electrically exposed on an outer surface of the lead structure through an opening in an exterior wall of the lead structure; and

a control system programmed to select a tripolar combination of electrodes from the array of electrodes.

**[0014]** Further aspects of the invention and features of specific example embodiments of the invention are described below.

#### Brief Description of the Drawings

**[0015]** The accompanying drawings illustrate non-limiting example embodiments of the invention.

**[0016]** Figure 1 shows a number of nerves adjacent to a blood vessel.

[0017] Figure 2 is a schematic diagram of a transvascular nerve stimulation apparatus according to an example embodiment.

5 [0018] Figure 3 is a cross section through an electrode structure having multiple electrodes or rows of electrodes spaced apart around an inner wall of a blood vessel.

10 [0019] Figures 4A, 4B and 4C are partially schematic cross sectional views illustrating stages in the implanting of an electrode structure according to an example embodiment which includes an expandable stent in a blood vessel.

15 [0020] Figures 5A, 5B and 5C are partially schematic cross sectional views illustrating an electrode structure according to an embodiment having an engagement structure for holding the electrode structure expanded against an inner wall of a blood vessel.

[0021] Figures 6 and 6A are respectively perspective and cross sectional views showing an electrode structure according to another embodiment wherein electrodes are held against an inner wall of a blood vessel by a retention tube.

20 [0022] Figures 7A and 7B are perspective views showing an electrode structure having four electrodes respectively in a flat configuration and a rolled configuration. In the rolled configuration, the electrodes face radially outward.

25 [0023] Figures 7C and 7F are views showing plan views of unrolled electrode structures having electrodes that may be used in bipolar pairs (among other electrical configurations). Figures 7D and 7E show example ways for pairing the electrodes of the electrode structure of Figure 7C.

[0024] Figure 7G is a perspective view showing an electrode structure having four rows of electrodes in a rolled configuration in which the electrode structure is curled up within an apertured insertion tube.

[0025] Figure 7H is a cross section through a blood vessel within which an electrode structure according to another embodiment has been placed.

[0026] Figures 8A and 8B are schematic illustrations of the use of a structure comprising bi-polar electrodes to stimulate a nerve extending transversely to a blood vessel.

[0027] Figure 8C is a schematic illustrations of the use of a structure comprising bi-polar electrodes to stimulate a nerve extending generally parallel to a blood vessel.

[0028] Figure 9 is a cut away view of a person's neck.

[0029] Figure 9A is a cut away view illustrating a minimally invasive transvascular nerve stimulation system installed in a person according to an embodiment wherein an electrode structure is disposed in the person's internal jugular vein in the neck or upper chest region.

[0030] Figures 10A and 10B illustrate the anatomy of selected nerves and blood vessels in a person's neck and upper torso.

[0031] Figure 11 is a cut away view illustrating a minimally invasive transvascular nerve stimulation system installed in a person according to an embodiment wherein electrode structures are disposed in one or both of the person's superior vena cava and left subclavian vein.

[0032] Figure 12 is a cut away view illustrating a minimally invasive transvascular nerve stimulation system installed in a person according to an embodiment wherein

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control signals are transmitted wirelessly to cause stimulation signals to be delivered at electrode structures.

Description

5 [0033] Throughout the following description, specific details are set forth in order to provide a more thorough understanding of the invention. However, the invention may be practiced without these particulars. In other instances, well known elements have not been shown or described in detail to avoid unnecessarily obscuring the invention. Accordingly, the specification and drawings are to be regarded in an illustrative, rather  
10 than a restrictive, sense.

[0034] This invention relates to transvascular stimulation of nerves. In transvascular stimulation, suitable arrangements of one or more electrodes are positioned in a blood vessel that passes close to a nerve to be stimulated. Electrical currents pass from the  
15 electrodes through a wall of the blood vessel to stimulate the nerve.

[0035] Figure 1 shows three nerves, **N1**, **N2** and **N3** that pass nearby a blood vessel **V** having a wall **W** defining a lumen **L**. Figure 1 is illustrative and not intended to represent any specific blood vessel or nerves. Figure 1 represents any suitable one of  
20 the various places in the body where nerves pass nearby to veins or arteries. Nerves **N1** and **N2** extend roughly parallel to blood vessel **V** and nerve **N3** extends generally transversely to blood vessel **V**, at least in their parts depicted in Figure 1. Nerve **N1** is closer to blood vessel **V** than nerve **N2**.

25 [0036] Figure 2 illustrates schematically the use of an electrode structure **10** inserted into lumen **L** of blood vessel **V** to stimulate nerve **N1**. Electrode structure **10** comprises an electrode **12**, an electrically-insulating backing layer **14** and a means **15** for holding electrode **12** and backing layer **14** in place against the inner wall of blood vessel **V**. Electrode **12** may be attached to backing layer **14**. This is not mandatory,  
30 however. It is sufficient that electrode **12** can be held against or at least in close proximity to the wall **W** of the blood vessel and that backing layer **14** covers the side

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of electrode **12** facing into lumen **L**. Various example structures that may be used as means **15** are described below. Electrode structures which provide electrodes backed by electrically-insulating barriers as illustrated generally in Figure 2 may be provided in a variety of ways.

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[0037] Electrode **12** is connected to a signal generator **18** by a suitable lead **17**.

Signal generator **18** supplies electrical current to electrode **12** by way of lead **17**.

Signal generator **18** may be implanted or external to the body. Signal generator **18** may, for example, comprise an implantable pulse generator (IPG).

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[0038] In some embodiments electrode structure **10** includes a circuit (not shown) for applying signals to one or more electrodes **12** and a battery, system for receiving power wirelessly or another supply of electrical power. In such embodiments, signal generator **18** may deliver control signals which cause the circuit to apply stimulation

15 signals to electrode **12** by way of a suitable wireless link technology. The wireless link may provide communication of the control signals between a small transmitter associated with signal generator **18** and a small receiver associated with electrode structure **10**. With suitably miniature circuitry, it may be possible to provide a signal generator **18** that is co-located in a sufficiently large blood vessel with electrode structure **10**. The signal generator **18** may, for example, comprise a thin electronic circuit embedded within backing sheet **14**.

20  
25 [0039] Electrode **12** serves as a source or as a sink for electrical current. Depending upon the nature of the electrical signals generated by signal generator **18** electrode **12** may serve as a current source at some times and as a current sink at other times.

Another electrode or group of electrodes (not shown in Figure 2) in contact with the patient serves to complete an electrical circuit. The other electrode or group of electrodes may be incorporated in electrode structure **10** (as is usually preferable) or may be separate.

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[0040] Electrically-insulating backing layer **14** presents a high-impedance to the flow of electrical current and therefore reduces the amount of current flow through the blood in blood vessel **V**. It is not mandatory that layer **14** have an extremely high electrical resistance. It is sufficient if layer **14** has a resistance to the flow of electricity through layer **14** that is significantly greater than that presented by the blood in blood vessel **V**. Blood typically has a resistivity of about 120 to 190  $\Omega$ cm. In example embodiments, the blood in a blood vessel may provide an electrical resistance between closely-spaced electrical contacts that is inversely proportional to the dimensions of the lumen of the blood vessel. In large blood vessels the longitudinal electrical resistance between reasonable closely-spaced contacts can be a few tens of ohms for example. Layer **14** preferably provides an electrical resistance of at least a few hundred ohms, preferably a few kilo ohms or more to the flow of electrical current through the thickness of layer **14**. Layer **14** could have electrically conductive members such as leads and the like embedded within it or electrically-conductive on its inner surface and still be considered to be 'electrically-insulating'.

[0041] By making layer **14** of a suitable material such as silicone rubber elastomer, a biocompatible plastic, or another biocompatible insulating material it is easily possible to provide a backing layer **14** having a suitable resistance to the flow of electrical current. Figure 2 illustrates how the presence of backing layer **14** directs the electric field **E** (illustrated schematically in Figure 2 by lines of equipotential) outwardly from blood vessel **V**.

[0042] In Figure 2, the delivery of electrical stimulation to nerve **N1** is enhanced by:

- Locating electrode **12** against the internal wall of blood vessel **V** at a location close to nerve **N1**;
- Providing an electrode **12** having a relatively large contact surface that can achieve a large contact area with the inner wall of blood vessel **V**;
- Curving the contact surface of electrode **12** to roughly match the curvature of the inner face of blood vessel **V**;
- Providing electrically-insulating backing sheet **14**.

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With these features, a significantly lower stimulation intensity is required to stimulate target nerve **N1** than would be the case for wire electrodes located in lumen **L** in contact with the blood in lumen **L**. Additionally, selectivity for a nerve of interest is improved. Advantageously, electrodes **12** have active surface areas in the range of 5 about  $\frac{1}{2}$  mm<sup>2</sup> to about 5 mm<sup>2</sup>. In some embodiments, each electrode has an active surface area on the order of 2 mm<sup>2</sup>.

[0043] Electrode structure **10** may be introduced into blood vessel **V** in a minimally-invasive, safe way. Blood vessel **V** may be a relatively large blood vessel that courses 10 in the vicinity of the target nerve **N1**. In some embodiments, electrode structure **10** comprises a flexible multi-contact electrode carrier sheet (ECS) of suitable dimensions. The sheet may be tightly coiled prior to its insertion into blood vessel **V**. Once within blood vessel **V** the sheet may be allowed to unwind so as to bring electrode **12** into contact with wall **W** of blood vessel **V**.

15 [0044] An electrode structure may support multiple electrodes. Figure 3 shows an example electrode structure **20** which supports a number of electrodes including electrodes **22A**, **22B**, **22C** and **22D** (collectively electrodes **22**). Other electrodes out of the plane of Figure 3 may also be present. In the illustrated embodiment, electrodes 20 **22A**, **22B**, **22C** and **22D** are circumferentially spaced approximately equally around the perimeter of the inside wall of blood vessel **V**. Each electrode **22** is insulated from the lumen of blood vessel **V** by a thin flexible insulating sheet **24** (individually identified as **24A**, **24B**, **24C** and **24D**). Each of the insulating sheets **24** is conformally disposed against the internal wall of blood vessel **V**. In alternative embodiments, two 25 or more electrodes are disposed on a common insulating sheet. Insulating sheets **24** may be joined together or may be different parts of a continuous sheet.

[0045] **E1**, **E2**, **E3** and **E4** illustrate the areas corresponding to electrodes **24A** through **24D** in which the electrical field associated with current flow at the 30 corresponding electrode is strong enough to stimulate a nerve. Increasing the strength

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of the signal (e.g. a stimulation pulse) at an electrode increases the affected area (as indicated by the larger dotted regions).

[0046] Figure 3 shows two nerves **N4** and **N5**. It can be seen that a stimulation signal 5 from electrode **22A** can stimulate nerve **N4**. A stimulation signal from electrode **22B** can stimulate nerve **N5**. The arrangement of blood vessel **V** and nerves **N4** and **N5** is like the arrangement of the internal jugular vein and the phrenic and vagus nerves in the neck region of a person. With an arrangement as shown in Figure 3, a target phrenic nerve at the location of **N4** can be preferentially stimulated by electrode **22A** 10 due to greater proximity of electrode **22A** and also due to the shape of the area **E1** affected by electrode **22A**. The vagus nerve at location **N5** is usually approximately diametrically opposite from electrode **22A** and is not affected by signals delivered at normal levels at electrode **22A**. The vagus nerve is, however, affected by signals delivered at electrode **22C**.

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[0047] The phrenic nerve and vagus nerve in adult humans are each typically about 2 mm in diameter. The lumen of the internal jugular vein in adult humans is typically in the range of about 10 mm to 20 mm in diameter. The distance from the phrenic nerve to the internal jugular vein and the distance from the vagus nerve to the internal 20 jugular vein are each typically in the range of about 2mm to about 10 mm. Generally the phrenic nerve and vagus nerve are on opposite sides of the internal jugular vein so that they are roughly 15 mm to 30 mm apart from one another. This arrangement facilitates the ability to perform transvascular stimulation of only the vagus nerve or only the phrenic nerve without stimulating the other nerve. A system according to 25 some embodiments stimulates the phrenic nerve or vagus nerve only. A system according to other embodiments selectively stimulates either or both of the phrenic and vagus nerves from an electrode structure located in the internal jugular vein.

[0048] In many cases, nerves comprise a plurality of fascicles. For example, in the 30 example illustrated in Figure 3, the phrenic nerve **N4** is composed of three phrenic fascicles **PF1**, **PF2**, and **PF3**. These phrenic fascicles may be selectively recruited by

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progressive levels of stimulation current at electrode **22A**. At lower stimulation levels, only **PF1** is recruited. At higher levels **PF1** and **PF2** are both recruited. At still higher levels, all of **PF1**, **PF2** and **PF3** are recruited. In Figure 3, the vagus nerve **N5** is composed of two vagus fascicles **VF1**, and **VF2** that may be selectively recruited by 5 progressive levels of stimulation current at electrode **22C**. At lower stimulation levels only **VF1** is recruited. At higher stimulation levels both **VF1** and **VF2** are recruited.

[0049] It is desirable that an electrode structure provide a minimum obstruction to the flow of blood in lumen **L** of a blood vessel **V**. Therefore, electrode structures are 10 preferably thin in comparison to the inner diameter of blood vessel **V**. In some embodiments, a structure that supports electrodes and insulating backing sheets gently urges the electrodes and insulating backing sheets radially outward in lumen **L** so as to leave an open passage for blood flow past the electrode structure. To prevent the disruption or blockage of blood flow in a blood vessel, the cross-sectional area of an 15 intravascular electrode structure should not exceed a certain fraction of the cross-sectional area of the lumen of the blood vessel. A round blood vessel with an internal diameter of 10 mm has a cross-sectional area of approximately 75 mm<sup>2</sup>. The circumference of the electrode structure when expanded in the blood vessel should preferably not be greater than about  $10 \times \pi$  mm, (approximately 30 mm). If the 20 thickness of an electrode structure is between about 0.3 and 0.5 mm then the cross-sectional area of the electrode structure will be about 10 mm<sup>2</sup> to 15 mm<sup>2</sup>, which represents less than 20% of the lumen of the vessel.

[0050] Figures 4A, 4B and 4C show an electrode structure **30** according to an 25 example embodiment. Electrode structure **30** comprises a plurality of electrodes **32** disposed on a flexible electrically-insulating sheet **34**. Electrode structure is initially introduced into a blood vessel **V** tightly curled up around an expandable stent **35** inside an introducer tube **36**. Stent **35** may, for example, comprise an expandable wire stent. A variety of suitable expandable wire stents is available from medical devices 30 manufacturers.

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[0051] Electrode structure 30 is guided to a desired location in a blood vessel V inside introducer tube 36. At the desired location, introducer tube 36 is retracted to allow electrically-insulating sheet 34 to begin to unroll as shown in Figure 4B. Stent 35 is then expanded in order to further unroll electrically-insulating sheet 34 and to urge 5 electrically insulating sheet 34 and the electrodes 32 carried on electrically-insulating sheet 34 against the inner wall of blood vessel V as shown in Figure 4C.

[0052] In the illustrated embodiment, stent 35 is attached to sheet 34 at a point, row of points or line 37. Stent 35 is left in place to retain electrodes 32 and sheet 34.

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[0053] Stent 35 may comprise any suitable type of expandable stent. A wide range of such stents are known. Stent 35 is expanded in a manner appropriate to the stent. For example, in some embodiments a balloon is placed inside the stent and the stent is expanded by inflating the balloon. The balloon may be withdrawn after the stent has 15 been expanded.

[0054] Figures 5A, 5B and 5C illustrate an electrode structure 40 which is similar to electrode structure 30 except that it has electrodes 42 supported on a flexible sheet 44 and an engagement mechanism 47 which allows opposed edges portions 44A and 44B 20 of flexible sheet 44 to be locked together when flexible sheet 44 has been opened within the lumen L of blood vessel V. The locking together of edge portions 44A and 44B holds flexible sheet 44 in an expanded configuration with electrodes 42 contacting the inner surface of wall W. Electrode structure 40 does not have a stent 25 inside flexible sheet 44 (although a stent could optionally be added to provide further support for sheet 44). Sheet 44 may be made so that it has a tendency to unroll toward a configuration that is less tightly-rolled than shown in either of Figures 5A or 5B. This tendency will bias sheet 44 to open into the configuration of Figure 5B when removed from insertion tube 46 and will help to hold sheet 44 in place inside blood vessel V.

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[0055] In the illustrated embodiment, mechanism 47 comprises mating sets of ridges 47A and 47B that extend longitudinally respectively along edge portions 44A and 44B. Ridges 47A and 47B are on opposing major surfaces of sheet 44 so that they can contact one another when sheet 44 is sufficiently unrolled. As shown in Figure 5B, 5 ridges 47A and 47B interlock when sheet 44 is unrolled as fully as the dimension of blood vessel V will permit. Mechanism 47 thus serves to retain sheet 44 and electrodes 42 snugly against the inside of wall W and prevent sheet 44 from curling inwardly or moving away from the wall W.

10 [0056] In preferred embodiments, mechanism 47 permits engagement of edge portions 44A and 44B in a range of degrees of overlap. Thus, mechanism 47 allows engagement of edge portions 44A and 44B when sheet 44 has been expanded against the inner wall of blood vessels having sizes within a given range of different sizes.

15 [0057] Alternative engagement mechanisms 47 are possible. For example, in some embodiments, a biocompatible adhesive is introduced between edge portions 44A and 44B. In other embodiments, ridges or other interlocking features and a biocompatible glue are both used.

20 [0058] An electrode structure 40 may be placed in a desired location by: introducing and sliding the electrode structure along a blood vessel to a desired location; at the desired location, sliding electrode structure 40 out of tube 46; if electrode structure 40 is partially or entirely self-unwinding, allowing electrode structure 40 to unwind; and, if necessary, inflating a balloon 49 to fully expand electrode structure 40 and/or 25 engage engagement mechanism 47. Introducing the electrode structure may comprise cannulating the blood vessel and introducing the electrode structure at the cannulation site.

[0059] Figure 5C illustrates a method for removing or relocating an electrode structure 40. Electrode structure 40 comprises a tab 48 or other projection that is attached to sheet 44 near or at an inside edge thereof and is graspable from within 30

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lumen **L**. A tool **50** is inserted into lumen **L** and has jaws **51** operable to grasp tab **48**. At position **50A** jaws **51** of tool **50** are opened to receive tab **48**. At position **50B**, jaws **51** have been operated to grasp tab **48**. At position **50C** tool **50** has been moved toward the center of lumen **L** and tool **50** has thereby peeled the inner edge of sheet **44**

5 away from wall **W**. Tool **50** may be rotated about its axis to roll electrode structure **40** into a smaller configuration. Electrode structure **40** may then be moved along blood vessel **44** to a new position; or pulled into an insertion tube for safe removal from blood vessel **V**.

10 [0060] Figures 6 and 6A show an electrode structure **70** that includes a rolled, flexible electrically-insulating sheet **74** carrying electrodes **72**. Sheet **74** may be opened by partial unrolling within a blood vessel **V**. A tubular retainer **73** may then be inserted to retain sheet **74** and electrodes **72** in place against a wall of the blood vessel. In cases where electrode structure **70** is to be inserted into the blood vessel through an incision

15 that is smaller than the lumen of the blood vessel then tubular retainer **73** may be expandable so that it can be introduced through the opening and then expanded to a size suitable for retaining sheet **74** and electrodes **72**.

[0061] Retainer **73** has a diameter selected such that, when placed inside sheet **74**, it

20 will retain sheet **74** and electrodes **72** in close apposition to the inside wall of the blood vessel for as long as required. The outside diameter of retainer **73** is chosen to closely match the inner diameter of the blood vessel **V** minus twice the thickness of sheet **74**. For example, for a blood vessel with an inside diameter of 10 mm and an electrode structure **70** with sheet thickness of  $\frac{1}{2}$  mm, the outside diameter of retainer

25 **73** should be approximately  $10 \text{ mm} - 2 \times \frac{1}{2} \text{ mm} = 9 \text{ mm}$ . Retainers **73** in a range of diameters may be provided to allow a surgeon to select and insert the best size. In typical blood vessels having inner diameters of 10 mm or more, the length of retainer **73** should be at least about twice its diameter to ensure that retainer **73** will not tilt inside the blood vessel. The wall thickness of retainer **73** may be fairly small, for

30 example, up to about 0.3 mm or so. Retainer **73** may be made of a suitable material

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such as a biocompatible metal (e.g. stainless steel or titanium) or a high-strength biocompatible polymer.

[0062] Wires 75 carry signals from a signal generator to electrodes 72. In an 5 alternative embodiment, a signal generator is integrated with electrode structure 70. Such as signal generator may be controlled to issue stimulation pulses in response to control signals provided by way of a suitable wireless link.

[0063] Figures 7A to 7G show examples of electrode structures. Electrode structure 10 80 of Figure 7A has four electrodes 82 (individually 82A to 82D) supported on a major face 81 of a flexible insulating sheet 84. Insulated leads 85 connect electrodes 82 to a signal generator (not shown in Figure 7A). Sheet 84 may comprise a flexible layer of silicone for example. Electrodes 82 and electrode leads 85 may be of any suitable shape and material; e.g., stainless steel or platinum-iridium multi-stranded 15 wire electrodes with Teflon<sup>TM</sup> coated wire leads.

[0064] An electrode structure 80 may be fabricated, for example, by connecting suitable electrodes to coated wire leads and then embedding the electrodes and leads in a layer of silicone such that the electrodes are exposed on one major face of the 20 silicone layer but not the other.

[0065] Electrode structure 80 may be used to stimulate nerves by inserting electrode structure 80 into a blood vessel with electrodes 82 facing outwardly; and connecting any one electrode to the negative output of a standard constant-current (preferably) or 25 constant-voltage nerve stimulator (cathodic stimulation) with respect to a remote reference electrode. Alternatively, any two electrodes 82 can be selected as anode and cathode.

[0066] Electrode structure 80 is similar to a nerve cuff but 'inside out'. Each electrode 30 preferentially stimulates a sector of tissue that radiates outwardly from a blood vessel V and spans a limited angle. For example, in an electrode structure having four

electrodes disposed approximately every 90 degrees around the circumference of a blood vessel, the volume of tissue affected by each electrode may span approximately 90 degrees (see Figure 3 for example).

[ 0067] A further improvement in angular selectivity may be obtained by providing longitudinal ridges on the outer major surface of electrode structure 80. The ridges enhance the electrical separation between circumferentially-adjacent electrodes 82. The ridges may be similar to the ridges described in Hoffer et al. US Patent 5,824,027 entitled NERVE CUFF HAVING ONE OR MORE ISOLATED CHAMBERS. Ridges 86 are shown schematically in Figure 7A.

[ 0068] Optionally, sheet 84 may include geometrical complexities such as holes or protuberances to provide a better substrate for connective tissue adhesion and so increase the long-term mechanical stability and immobility of structure 80 inside a blood vessel.

[ 0069] Figure 7B shows an electrode structure like electrode structure 80 wrapped into a tight spiral with electrodes facing out in preparation for insertion into a blood vessel.

[ 0070] Figure 7C shows an electrode structure 90 according to another embodiment. Electrode structure 90 comprises a flexible sheet 94 that supports four pairs of electrodes 92. Sheet 94 may comprise a thin flexible silicone sheet, for example. Electrical leads 93 are provided to connect corresponding electrodes 92 to a signal source. Electrodes and electrode leads may be of any suitable shape and material; e.g., stainless steel or platinum-iridium multi-stranded wire with Teflon<sup>TM</sup> coated leads. In the illustrated embodiment, electrode contact surfaces are exposed through electrode windows in which insulation of the leads is not present. Electrodes 92A and 92E; 92B and 92F; 92C and 92G; and 92D and 92H may be paired, for example, as shown in

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Figure 7D. As another example, electrodes **92A** and **92B**; **92C** and **92D**; **92E** and **92F**; and **92G** and **92H** may be paired as shown in Figure 7E.

[0071] Electrode structure **90** may be applied to stimulate a nerve or nerves by 5 inserting electrode structure **90** into a blood vessel with electrodes **92** facing outwardly; and connecting any two electrodes **92** to the negative and positive outputs of a standard constant-current or constant-voltage nerve stimulator. An effective mode of stimulation is to select a pair of electrodes that are aligned along a line that is generally parallel to the target nerve, such that the greatest potential difference during 10 stimulation will be generated along the nerve axons in the target nerve. Since the target nerve and target blood vessel may not be strictly parallel to one another, it is useful to have multiple electrodes in an electrode structure from which the pair of electrodes that provide the greatest stimulation selectivity for a target nerve can be identified by trial and error.

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[0072] Figure 7F shows an electrode structure **90A** that is like electrode structure **90** except that it includes ridges **91** of electrically-insulating material that extend between groups of electrodes **92**.

20 [0073] Figure 7G shows an electrode structure like electrode structure **90** prepared for insertion into a blood vessel. Electrode structure **90** is rolled up into a spiral and held by an outside retainer **95**. Outside retainer **95** has relatively thin walls. For example, the wall thickness may be about  $\frac{1}{2}$  mm or less in some embodiments. Apertures **96** penetrate the wall of outside retainer **95** and allow flow of electrical currents.

25 Apertures **96** could optionally be filled with electrically-conducting plugs.

[0074] At least one electrode **92** of electrode structure **90** is electrically exposed to the surroundings through an aperture **96**. As the electrode structure is being advanced toward an intravascular target location (the target location may be determined in 30 advance from an imaging survey study for each patient, and monitored with fluoroscopy during the ECS implant procedure), electrodes **92** are energized. Since at

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least some electrodes 92 are exposed by way of apertures 96 the target nerve will be stimulated when electrode structure 90 is close enough to the target nerve. An effect of stimulation of the target nerve can be watched for in order to determine when electrode structure has reached the vicinity of the target nerve. The response may be

5 monitored to fine tune the position of electrode structure 90 in a blood vessel. Outside retainer 95 may be removed when electrode structure 90 is at the target location. Outside retainer 95 is tethered by a tether 97 so that it can be recovered after deployment of structure 90.

10 [0075] Figure 7H shows structure 90 at its intended location in blood vessel V. Outer retainer 96 has been removed and the structure 90 has been allowed to unwind and deploy against the inside wall of blood vessel V. The width (circumferential dimension) of structure 90 is chosen to closely match the inside perimeter of blood vessel V at the target location. The inside dimension of the blood vessel V may have

15 been previously determined from ultrasound imaging, balloon catheter, magnetic resonance imaging or other non-invasive or minimally-invasive imaging technique.

[0076] When electrode structure 90 is at its desired position for optimal stimulation of the target nerve, the outer retainer 95 is gently removed and withdrawn from the

20 patient's body while structure 90 is kept in place, if needed, by means of a semi-rigid rod-like tool (not shown) that is temporarily used to stabilize structure 90 and prevent it from moving while outer retainer 95 is withdrawn. As the outer retainer 95 is withdrawn, structure 90 will naturally and rapidly unwrap toward its preferred enlarged-cylindrical (or near-planar in some embodiments) configuration and will

25 stretch out against the inside wall of the blood vessel with electrodes 92 disposed outwardly in close contact to the blood vessel wall.

[0077] As noted above, the choice of electrodes to use to stimulate a target nerve can depend on the orientation of the target nerve relative to the blood vessel in which an

30 electrode structure is deployed. Where a target nerve passes more or less at right angles to a blood vessel, it can be most efficient to stimulate the target nerve by

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passing electric current between two electrodes that are spaced apart circumferentially around the wall of the blood vessel. In such cases it may be desirable to provide elongated electrodes that extend generally parallel to the blood vessel (e.g. generally parallel to an axis of curvature of the electrode structure). Such elongated electrodes 5 may be emulated by a row of smaller electrodes that are electrically connected together.

[0078] Figures 8A and 8B show a nerve **N** extending transversely to a blood vessel **V**. In the illustrated embodiment, the nerve extends generally at right angles to the blood 10 vessel. An electrode structure **54** comprising first and second electrodes **55A** and **55B** (collectively electrodes **55**) is located in lumen **L** of blood vessel **V**. Electrodes **55** are each close to or pressed against the inner face of wall **W** of blood vessel **V**. Electrode structure **54** may have additional electrodes as well as other features such as a structure for holding electrodes **54** in place however these are not shown in Figure 8A 15 or 8B for clarity. Electrodes **55A** and **55B** are spaced apart from one another in a circumferential direction around the periphery of blood vessel **V**. Electrodes **55** are ideally disposed in a plane in which nerve **N** lies and which intersects blood vessel **V** perpendicularly. Precise placement of the electrodes in such a configuration is not mandatory. Electrodes **55** are spaced apart in a direction that is generally along an 20 axis of nerve **N**.

[0079] Each electrode **55** is protected against electrical contact with the blood in lumen **L** of blood vessel **V** by an insulating backing member **56**. In the illustrated embodiment, backing members **56** comprise hollow insulating caps that may, for 25 example, have the form of hollow hemispheres. An edge of each insulating cap contacts wall **W** of blood vessel **V** around the periphery of the corresponding electrode **55**.

[0080] In this embodiment, electrodes **55** are connected in a bi-polar arrangement 30 such that one electrode acts as a current source and the other acts as a current sink. It is not mandatory that the polarities of electrodes **55** always stay the same. For

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example, in some stimulation modes the polarities could be switched. In the illustrated embodiment, electrode **55A** is connected as a cathode (negative) electrode while electrode **55B** is connected as an anode (positive) electrode to a signal source (not shown in Figure 8A or 8B). When a stimulation signal is applied between electrodes 5 55 an electric field is created. The electric field causes small electrical currents to flow between electrodes **55** by way of the surrounding tissues.

[0081] Since electrodes **55** are insulated from the lumen of blood vessel **V**, electric current flows out of the current source electrode **55A** through wall **W** and surrounding 10 tissues and returns to the current sink electrode **55B**. The stimulation current flows longitudinally through the nerve **N** in the direction shown by arrows **F**. For stimulation pulses of sufficient duration and intensity, the nerve axons in target nerve **N** will generate action potentials that will be conducted along the stimulated axons in nerve **N**.

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[0082] Where a target nerve extends generally parallel to a blood vessel it can be efficient to stimulate the target nerve by passing electric current between two electrodes that are spaced apart longitudinally along the wall of the blood vessel.

20 [0083] Figure 8C shows a nerve **N** extending parallel to a blood vessel **V**. An electrode structure **88** having first and second electrodes **89A** and **89B** (collectively electrodes **89**) is located inside blood vessel **V** with electrodes **89A** and **89B** close to, preferably against the inside of the wall **W** of blood vessel **V**. Electrode structure **88** may have additional electrodes as well as other features such as a structure for holding 25 electrodes **89** in place however these are not shown in Figure 8C for clarity. Electrodes **89A** and **89B** are spaced apart from one another in a longitudinal direction along blood vessel **V**. The electrodes are ideally disposed on a line extending parallel to an axis of the blood vessel although precise placement of the electrodes in such a configuration is not mandatory.

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[0084] In this embodiment, electrodes **89A** and **89B** are connected in a bi-polar arrangement such that one electrode acts as a current source and the other acts as a current sink. It is not mandatory that the polarities of electrodes **89A** and **89B** always stay the same. For example, in some stimulation modes the polarities could be  
5 switched.

[0085] In the illustrated embodiment, electrode **89A** is connected as a cathode (negative) electrode while electrode **89B** is connected as an anode (positive) electrode to a signal source (not shown in Figure 8C). Each electrode **89** is protected against  
10 electrical contact with the blood in lumen **L** of blood vessel **V** by an insulating backing member **87**. In the illustrated embodiment, the backing members comprise hollow insulating caps that may, for example, have the form of hollow hemispheres. An edge of each insulating cap contacts the wall of blood vessel **V** around the periphery of the corresponding electrode **89**.

15 [0086] Since electrodes **89** are electrically insulated from the blood in lumen **L** of blood vessel **V**, electric current flows out of the current source (e.g. cathode **89A**), through wall **W** and eventually returns to the current sink (e.g. anode electrode **89B**). This results in a stimulation current that flows longitudinally through nerve **N** in the  
20 direction shown by arrows **F**. For stimulation pulses of sufficient duration and intensity, the nerve axons in the target nerve will generate action potentials that will be conducted along the stimulated axons in nerve **N**.

[0087] Stimulating the phrenic nerves to regulate or cause breathing is an example  
25 application of electrode structures as described herein. The present invention provides a surgically simple, lower risk response to the need of stimulating the phrenic nerves to control the movement of the diaphragm and restore normal breathing rate in people who have lost control of diaphragm due to a central neurological lesion such as a high cervical spinal cord injury or disease, including quadriplegia; central alveolar  
30 hypoventilation; decreased day or night ventilatory drive (e.g. central sleep apnea,

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Ondine's Curse) or brain stem injury or disease. Phrenic nerves may be stimulated on an acute care or chronic basis.

5 [0088] The phrenic nerves provide the major nerve supply to the diaphragm. Each phrenic nerve contributes predominantly motor fibres solely to its hemidiaphragm.

The passage taken by the right and left phrenic nerves through the thorax is different. This is largely due to the disposition of great vessels within the mediastinum. Occasionally, the phrenic nerve may be joined by an accessory phrenic nerve.

10 [0089] The phrenic nerve on both sides originates from the ventral rami of the third to fifth cervical nerves. The phrenic nerve passes inferiorly down the neck to the lateral border of scalenus anterior. Then, it passes medially across the border of scalenus anterior parallel to the internal jugular vein which lies inferomedially. At this point the phrenic nerve is deep to the prevertebral fascia, the transverse cervical artery and the 15 suprascapular artery.

[0090] At the anterior, inferomedial margin of scalenus anterior and hence superficial to the second part of the right subclavian artery, the right phrenic nerve passes medially to cross the pleural cupola deep to the subclavian vein. More medially, it 20 crosses the internal thoracic artery at approximately the level of the first costochondral junction.

[0091] Within the thorax the right phrenic nerve is in contact with mediastinal pleura laterally and medially, in succession from superior to inferior, the following venous 25 structures: right brachiocephalic vein, superior vena cava, pericardium of the right atrium, inferior vena cava. From the level of the superior vena cava it is joined by the pericardiophrenic artery and both run inferiorly anterior to the lung root. The right phrenic nerve pierces the diaphragm in its tendinous portion just slightly lateral to the inferior vena caval foramen. It then forms three branches on the inferior surface of the 30 diaphragm: anterior, lateral and posterior. These ramify out in a radial manner from the point of perforation to supply all but the periphery of the muscle.

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[0092] At the anteroinferior medial margin of scalenus anterior, the left phrenic nerve crosses the first part of the left subclavian artery and then the internal thoracic artery sited slightly inferiorly. Passing inferiorly with the internal thoracic artery laterally, it 5 lies deep to the left brachiocephalic vein and the left first costochondral joint. It receives a pericardiophrenic branch of the internal thoracic artery which stays with its distal course.

[0093] Within the thorax, the left phrenic nerve continues inferiorly and slightly 10 laterally on the anterolateral aspect of the arch of the aorta, separated from the posterior right vagus nerve by the left superior intercostal vein. Then it descends anterior to the root of the left lung intermediate to fibrous pericardium medially and parietal pleura laterally. Finally, it curves inferiorly and anteriorly to reach the surface of the diaphragm which it pierces anterior to the central tendon and lateral to the 15 pericardium. It then forms three branches on the inferior surface of the diaphragm: anterior, lateral and posterior. These ramify out in a radial manner from the point of perforation to supply all but the periphery of the muscle.

[0094] The accessory phrenic nerve on each side occurs in roughly 15-25% of people. 20 It originates as a branch of the fifth cervical nerve which would otherwise pass to the subclavius. The accessory phrenic nerve begins lateral to the phrenic nerve in the neck and obliquely traverses the anterior surface of scalenus anterior as it descends. It joins the phrenic nerve at the root of the neck to descend to the diaphragm.

25 [0095] Figure 9 shows the anatomy of the neck and, in particular, the relative locations of phrenic nerve (PhN), vagus nerve (VN) and internal jugular vein (IJV). Note that the IJV courses between the PhN and VN. The PhN merges with the IJV and the three structures run together distally at level of the clavicle (indicated by circle 99).

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[0096] In one example embodiment illustrated in Figure 9A, a minimally invasive nerve stimulation system ('MINS') 100 comprising a flexible intravascular electrode array 101, for example, an electrode structure of one of the embodiments described above is permanently placed inside a target blood vessel V (in this example the left 5 Internal Jugular Vein, IJV) in close proximity to a target nerve (in this example the left phrenic nerve PhN). One or more electrodes of the electrode array is disposed for selective stimulation of the PhN. Other electrodes are optionally disposed for selective stimulation of a second target nerve, in this example the left vagus nerve VN.

10 [0097] The electrode leads 104 from electrode array 101 emerge from the cannulated BV at the original venous penetration site, C, and then course subcutaneously to connectors 105 that connect to the header of an implanted pulse generator 102 that is surgically placed in a standard subcutaneous pocket. The pocket may be in the upper chest wall for example. Figure 9 shows only one electrode array 101 on the left side of 15 the neck.

[0098] In this embodiment, the implanted MINS 100 stimulates the left PhN to assist breathing by causing rhythmic inspiratory movements of the diaphragm muscle (not shown in Figure 9). Another electrode array may additionally be implanted in a blood 20 vessel on the right side of the patient's body. For example, another electrode array 101 may be implanted in the right internal jugular vein for selective stimulation of the right PhN and, optionally, also the right VN, if so desired. The additional electrode array may be connected to internal pulse generator 102 or to a second internal pulse generator (not shown in Figure 9).

25 [0099] MINS 100 may be installed percutaneously using standard procedures for the installation of deep catheters, cannulas, leads or other intravascular device. Such procedures are described in the medical literature. Once an electrode array has been introduced to a location near the target location in the internal jugular vein then the 30 position of the electrode array may be fine-tuned by applying low-current stimulation

signals to one or more of the electrodes in electrode array **101** and observing the patient's breathing.

**[0100]** Figures 10A and 10B illustrate the anatomy of the neck and chest and, in particular, the relative locations of the left and right phrenic nerves (PhN), vagus nerves (VN), internal jugular veins (IJV), brachiocephalic veins (BCV), subclavian veins (SCV) and superior vena cava (SVC). The PhNs run approximately perpendicular to and close to the BCVs in areas **107R** and **107L** near the IJV/BCV junctions.

**[0101]** Each PhN may have more than one branch. The branches may join together at variable locations ranging from the neck region to the chest region below the IJV/BCV junctions. In the latter case, branches of the PhN on either side of the body may course on opposite sides of the BCVs. Two branches of the right PhN are labeled **PhN-1** and **PhN-2** in Figure 10B. The right PhN may include branches that course on either side of the SVC. The left and right PhN extend respectively to left and right hemi-diaphragms (HD).

**[0102]** Figure 11 shows a MINS **110** having electrode structures **111L** and **111R** (collectively **111**) located respectively in a patient's left SCV and SVC vessels near the left- and right-PhN respectively. Leads **112L** and **112R** (collectively **112**) respectively connect the electrodes of left- and right- electrode structures **111L** and **111R** to a signal generator. In the illustrated embodiment, the signal generator comprises an implantable pulse generator (IPG) **115**. Alternatively, as described above, some or all functions of pulse generator **115** may be provided by circuitry that is co-located with or integrated with one or both of electrode structures **111**. In some embodiments, pulse generator **115** generates control signals that are transmitted by way of a wireless communication link to cause circuitry that is local to electrode structures **111** to apply stimulation pulses by way of electrodes on electrode structures **111**.

[0103] The implantable pulse generator may be configured to deliver electrical pulses to electrodes of the left- and right electrode structures 111 more-or-less simultaneously so that the left- and right- hemidiaphragms are induced to undergo breathing motions in a synchronized manner. IPG 115 may, for example, apply bursts of stimulus pulses at a rate of about 12 or 13 bursts per minute. Each burst may, for example, comprise 20-40 current pulses delivered at a rate of 20 Hz or so and last roughly 1 to 2 seconds. Each burst induces signals in the phrenic nerve that cause the diaphragm to move to provide inspiration. Expiration occurs between bursts.

[0104] MINS 110 can be readily installed as shown in Figure 11. Electrode structures 111R and 111L may both be introduced through the same intravascular insertion point C1 in the left SCV. In some embodiments, electrode structure 111L is installed first. In such embodiments, electrode structure 111L can be passed through the left SCV past electrode structure 111L (e.g. through a bore of electrode structure 111L) to its target location in the SVC. Flexible leadout cable 112R passes through electrode structure 111L. Both leadout cables 112 emerge from the SCV and course subcutaneously to a subcutaneous pocket area in the upper chest where the leadout cable connectors are connected to IPG 115.

[0105] Locating initial target positions for electrode structures 111 is facilitated because the SVC, heart and BCV can be readily visualized using available imaging techniques. It is known that the phrenic nerves pass tightly past the heart on each side. Therefore, target locations in the blood vessels within  $\pm 1$  to 2 cm of the optimum positions for stimulating the phrenic nerves can be determined readily from images of the upper chest and lower neck.

[0106] The arrangement shown in Figure 11 has the advantage that the distance from electrode structures 111 to the target nerves in these locations may be smaller, more uniform and more reproducible than for similar electrodes implanted in more proximal locations in the IJVs where the target PhNs run parallel to the IJVs, but at more variable distances (see Figure 9, for example).

[0107] MINS 110 may be varied by leaving out one of electrode structures 111 and its associated cable 112. Such embodiments may be useful in acute care environments where it is necessary to provide breathing assistance using a simple quick procedure.

5 Such embodiments may also be useful in chronic situations where stimulation of one hemi-diaphragm is sufficient. Where only one electrode structure 111 is implanted, the electrode structure may be at either the location of electrode structure 111R or the location of electrode structure 111L.

10 [0108] Figure 12 shows a minimally-invasive nerve stimulation system 120 that is like MINS 110 of Figure 11 but provides a wireless connection between an implantable pulse generator and circuits which deliver stimulation signals to electrodes. System 120 has two sets of intravascular electrodes 121A and 121B. In some embodiments, each set of electrodes comprises an electrode structure as described herein. Each set of electrodes 121A and 121B is connected by short flexible lead wires 123 to an associated RF receiver unit 124. RF receiver units receive wireless stimulation commands 125 from an implanted pulse generator 126 having an associated transmitter (which is built into implantable pulse generator 126 in the illustrated embodiment).

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20 [0109] Each receiver unit 124 may comprise a hermetic package containing an antenna and circuitry to decode command signals and deliver stimulation pulses to the electrodes of the corresponding electrode array 121. Each receiver unit may be attached to an autonomous stent-like structure for safe, permanent and stable installation in a blood vessel near the associated electrode array 121. The receiver units may be powered by the RF signal received from implantable pulse generator 126. In such cases, the receiver units do not require internal batteries.

25 [0110] Implantable pulse generator 126 may contain batteries or another source of 30 electrical energy, control circuitry and transmitter antennas to communicate with

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receiver units 124 and with an external programmer (not shown) that allows a therapist to program the implanted system.

[0111] In some embodiments, an implantable pulse generator or other signal source 5 may have a primary battery or a rechargeable battery that can be periodically recharged through the patient's skin. In either case, it is desirable that the battery or other source of electrical power have an expected life span such that it will not require replacement for a reasonable period such as at least about 3 to 5 years.

10 [0112] Methods of stimulating the phrenic nerves, as described herein can have the advantages that:

- electrodes do not come into contact with the delicate phrenic nerves;
- there is no implanted structure that interferes with movement of the diaphragm;

15 • the system may be implanted and self-contained such that no wires cross the skin;

- access to both the right and left phrenic nerves can be provided through a single point of entry;
- a control system, such as an implantable pulse generator may be placed in 20 reasonably close proximity to an electrode structure so as to facilitate wireless control over the delivery of stimulation pulses at the electrode structure by the implantable pulse generator.

[0113] The applications of the apparatus and methods described herein are not limited 25 to phrenic and vagus nerves. The apparatus and methods described herein may be applied to provide surgically simple, low risk solutions for stimulating a wide range of peripheral or cranial nerves. For example, the methods and apparatus may be applied to stimulate the obturator nerve in the hip/groin area or the trigeminal nerve in the head.

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[0114] The apparatus and methods may be applied to treatment of a wide variety of disorders such as pain of peripheral or craniofacial origin, sensory deficits, paralysis or paresis of central origin, autonomic disorders, and generally any medical condition that can be treated or alleviated using neuromodulation by electrical stimulation of a 5 nerve that is in close proximity to a larger blood vessel into which a flexible multi-channel electrode array can be deployed.

[0115] Advantageously, implantation of electrode structures in blood vessels is reversible and does not require surgical intervention directly involving the target 10 nerves.

[0116] In some embodiments, signal generator 115 has sensors that sense a condition of the patient and adjust stimulation of the phrenic nerve based on input from the sensors. The sensors may detect things such as one or more of:

15     •     whether the patient is speaking or preparing to speak;  
   •     whether the patient is lying down or sitting or standing;  
   •     whether the patient is awake or asleep;  
   •     blood oxygen concentration;  
   •     blood CO<sub>2</sub> concentration;  
20     •     etc.

In response to the sensor signals, the signal generator may adapt the pattern or rate of breathing. For example:

•     Breathing could be automatically suppressed when a sensor signal indicates that the patient is attempting to speak.

25     •     A breathing rate could be increased during periods of increased physical activity or low blood oxygen concentration.

   •     A breathing rate could be decreased or regularized during periods of relaxation or sleep.

   •     On-demand breathing stimulation could be provided in response to the 30 detection of the onset of irregular breathing during sleep.

[0117] The sensors may be built into the signal generator. For example, the signal generator may include:

- accelerometers and processor logic configured to determine from outputs of the accelerometers whether the patient's motions indicate that the patient is awake or asleep;
- an inclinometer or accelerometer and processor logic configured to determine from one or more outputs of the inclinometer or accelerometer whether the patient is lying or upright.

10 [0118] Other sensors may be implanted. For example, in some embodiments, a blood chemistry sensor such as a blood oxygen sensor and/or a blood CO<sub>2</sub> sensor is implanted at a suitable location in the patient. The blood oxygen monitor may be mounted on an electrode structure 111 for example. Other sensors may sense signals in the patient's nerves.

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[0119] Where a component (e.g. an electrode, signal generator, lead, stent, assembly, device, antenna, circuit, etc.) is referred to above, unless otherwise indicated, reference to that component (including a reference to a "means") should be interpreted as including as equivalents of that component any component which performs the function of the described component (i.e., that is functionally equivalent), including components which are not structurally equivalent to the disclosed structure which performs the function in the illustrated exemplary embodiments of the invention.

25 [0120] As will be apparent to those skilled in the art in the light of the foregoing disclosure, many alterations and modifications are possible in the practice of this invention without departing from the spirit or scope thereof. For example, electrodes on an electrode structure may be arranged to provide unipolar, bipolar, tripolar or balanced tripolar electrode arrangements or combinations thereof. The example embodiments described herein include various features such as different geometries 30 for insulating backing sheets, different arrangements of electrodes, different control arrangements, and the like. These features may be mixed and matched (i.e. combined

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on additional combinations) in other embodiments of the invention. Accordingly, the scope of the invention is to be construed in accordance with the substance defined by the following claims.

**WHAT IS CLAIMED IS:**

1. A system for stimulating a left phrenic nerve and a right phrenic nerve of a patient, the system comprising:

    a signal generator to produce stimulation signals;

    a lead structure configured for insertion into (a) at least one of a left jugular vein and a left subclavian vein, (b) a left brachiocephalic vein, and (c) a vena cava of the patient, the lead structure defining a longitudinal axis along a length of the lead structure, having an outermost surface at a position radially spaced from the longitudinal axis, and having a plurality of leads to receive stimulation signals from the signal generator;

    a plurality of second pairs of electrodes longitudinally extending about the lead structure proximate a distal portion of the lead structure and configured to receive stimulation signals from at least one lead of the plurality of leads;

    a plurality of first pairs of electrodes longitudinally extending about the lead structure proximal to the plurality of second pairs of electrodes, the plurality of first pairs of electrodes configured to receive stimulation signals from at least one lead of the plurality of leads, wherein the signal generator is proximal to the first pairs of electrodes; and

    a control system programmed to (a) select a first stimulation pair of electrodes from the plurality of first pairs of electrodes to stimulate the left phrenic nerve, and (b) select a second stimulation pair of electrodes from the plurality of second pairs of electrodes to stimulate the right phrenic nerve,

    wherein the plurality of second pairs of electrodes and the plurality of first pairs of electrodes are positioned at radial locations different from the position of the outermost surface of the lead structure.

2. The system according to claim 1, wherein the plurality of second pairs of electrodes comprises at least two pairs of electrodes.

3. The system according to claim 2, wherein the second stimulation pair of electrodes is one of the at least two pairs of electrodes, and the control system is

programmed to select the second stimulation pair of electrodes from the at least two pairs of electrodes.

4. The system according to claim 3, wherein the control system is programmed to select the second stimulation pair of electrodes by determining that the second stimulation pair of electrodes has a stimulation efficacy for the right phrenic nerve that is greater than a stimulation efficacy of any of the other pairs of electrodes of the at least two pairs of electrodes.

5. The system according to any one of claims 1 to 4, wherein the first stimulation pair of electrodes includes a first electrode and a second electrode, and the first electrode and the second electrode are configured to be aligned along a line substantially parallel to the left phrenic nerve, and wherein the second stimulation pair of electrodes includes a third electrode and a fourth electrode, and the third electrode and the fourth electrode are configured to be aligned along a line substantially parallel to the right phrenic nerve.

6. The system according to any one of claims 1 to 5, wherein the control system is programmed to cause the signal generator to produce stimulation signals for delivery to the first and second stimulation pair of electrodes approximately simultaneously.

7. The system according to any one of claims 1 to 6, wherein the signal generator is configured to be implantable in the patient.

8. The system according to any one of claims 1 to 7, wherein the distal portion of the lead structure has a first configuration for insertion of the lead structure through an insertion point of a blood vessel and a second configuration, different than the first configuration, for urging the plurality of second pairs of electrodes toward an inner wall of the superior vena cava.

9. The system according to claim 8, wherein the distal portion of the lead structure expands from the first configuration to the second configuration.

10. The system according to claim 8, wherein the distal portion of the lead structure is biased to the second configuration.
11. The system according to any one of claims 8 to 10, wherein, when the lead structure is in the second configuration, the plurality of second pairs of electrodes are configured to be proximate to multiple circumferentially spaced points of the inner wall of the superior vena cava.
12. The system according to any one of claims 1 to 11, further comprising:
  - a blood chemistry sensor for insertion in a blood vessel proximate at least one of the plurality of first pairs of electrodes and the plurality of second pairs of electrodes, the blood chemistry sensor configured to sense a condition of blood of the patient, wherein the signal generator adjusts the stimulation signals based on the sensed condition of blood; and
  - a motion sensor configured to sense motion of the patient, wherein the signal generator adjusts the stimulation signals based on the sensed motion.
13. The system according to claim 12, wherein the blood chemistry sensor is at least one of a blood oxygen concentration sensor and a blood CO<sub>2</sub> concentration sensor, and the signal generator changes an intensity of the stimulation signals when the blood chemistry sensor senses at least one of a low blood oxygen concentration and a high blood CO<sub>2</sub> concentration.
14. The system according to claim 12 or 13, wherein the motion sensor is one of an accelerometer or an inclinometer, and the signal generator changes an intensity of the stimulation signals when the motion sensor senses a change in motion of the patient.
15. The system according to any one of claims 1 to 14, wherein the first stimulation pair of electrodes includes a source electrode and a sink electrode.
16. The system according to any one of claims 1 to 15, wherein the plurality of leads connect the plurality of first pairs of electrodes and the plurality of second pairs of electrodes to the signal generator.

17. A nerve stimulation system, comprising:

a plurality of first electrodes configured to be positioned in a venous system for stimulation of a left phrenic nerve;

a plurality of second electrodes configured to be positioned in a superior vena cava for stimulation of a right phrenic nerve;

a signal generator;

at least one lead structure including an outer layer; and

a control system programmed to select a combination of electrodes from at least one of the first electrodes or the second electrodes for stimulation of the respective left phrenic nerve or right phrenic nerve, the combination having more than two electrodes,

wherein at least one of the first electrodes or one of the second electrodes is exposed through a corresponding aperture in the outer layer.

18. The nerve stimulation system of claim 17, wherein the combination includes a tripolar electrode combination.

19. The nerve stimulation system of any one of claim 17 or 18, wherein the first electrodes are configured to be positioned in a left subclavian vein.

20. The nerve stimulation system of claim 17, wherein the combination includes at least two electrodes configured to be aligned generally parallel to the left phrenic nerve or the right phrenic nerve.

21. The nerve stimulation system of any one of claims 17 to 20, where each first electrode is coupled to a corresponding lead in a one-to-one relationship, and each second electrode is coupled to a corresponding lead in a one-to-one relationship.

22. The nerve stimulation system of any one of claims 17 to 21, wherein each of the first electrodes and each of the second electrodes extends only partially around a longitudinal axis of the lead structure.

23. The nerve stimulation system of claims 17 to 21, wherein the first and second electrodes are positioned about a longitudinal axis of the lead structure,

and wherein the signal generator is positioned about the longitudinal axis proximal to the first electrodes.

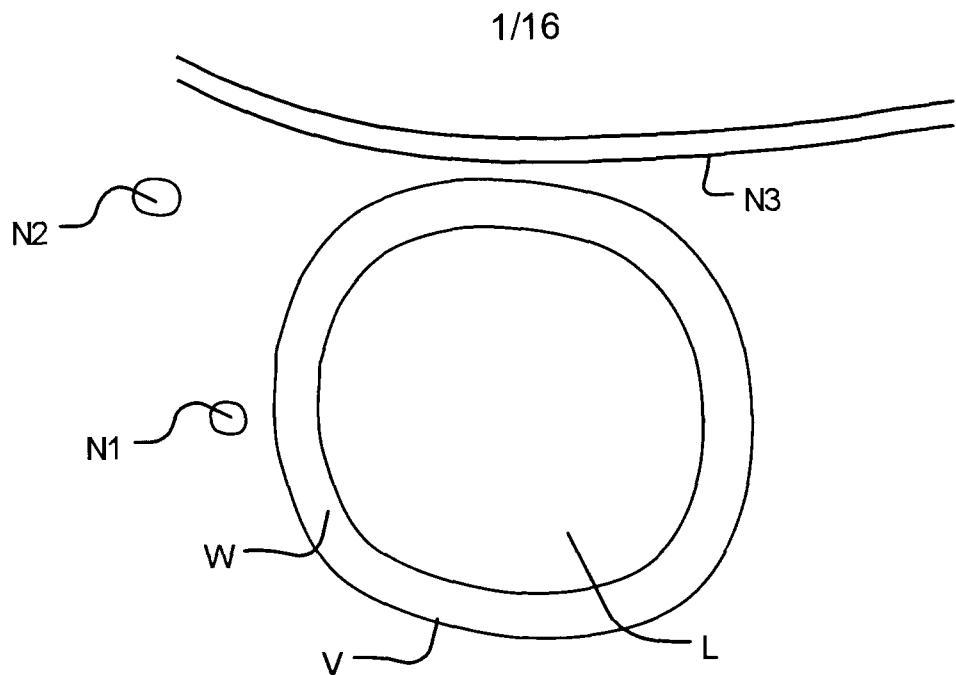
24. The nerve stimulation system of any one of claims 17 to 23, wherein each of the first electrodes and each of the second electrodes is electrically exposed through an opening in an outer non-conductive exterior wall portion of the lead structure.

25. The nerve stimulation system of any one of claims 17 to 24, wherein the combination of electrodes is configured to emit an electrical current extending from only a portion of a circumference of the lead structure.

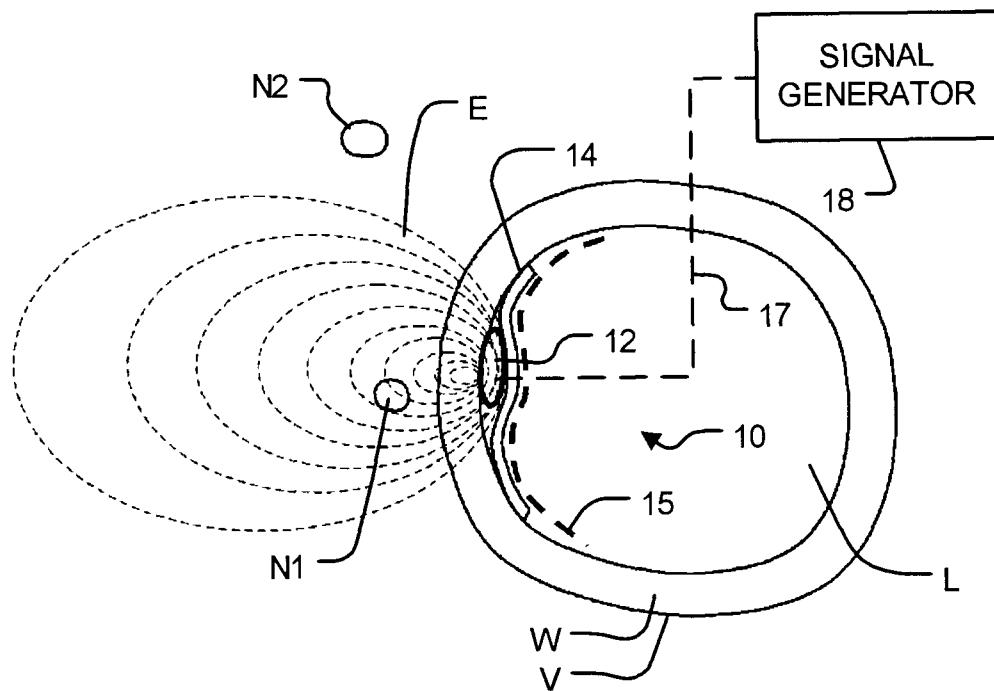
26. The nerve stimulation system of any one of claims 17 to 25, further comprising an accelerometer.

27. The nerve stimulation system of any one of claims 17 to 26, wherein at least one of the first electrodes or the second electrodes is arranged in at least two rows.

28. The nerve stimulation system of any one of claims 17 to 27, further comprising a breathing sensor to sense breathing of a patient.



## FIGURE 1 - PRIOR ART



## FIGURE 2

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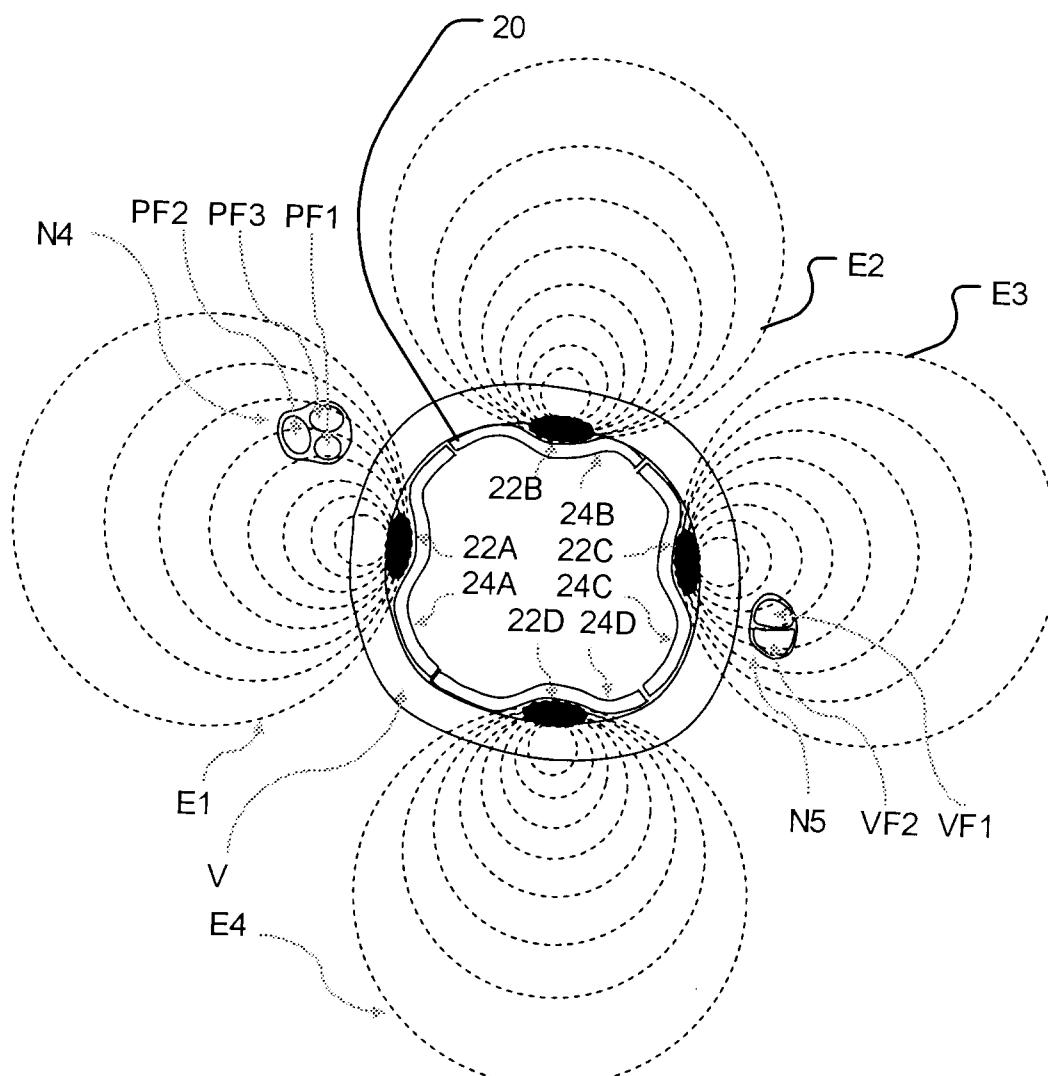


FIGURE 3

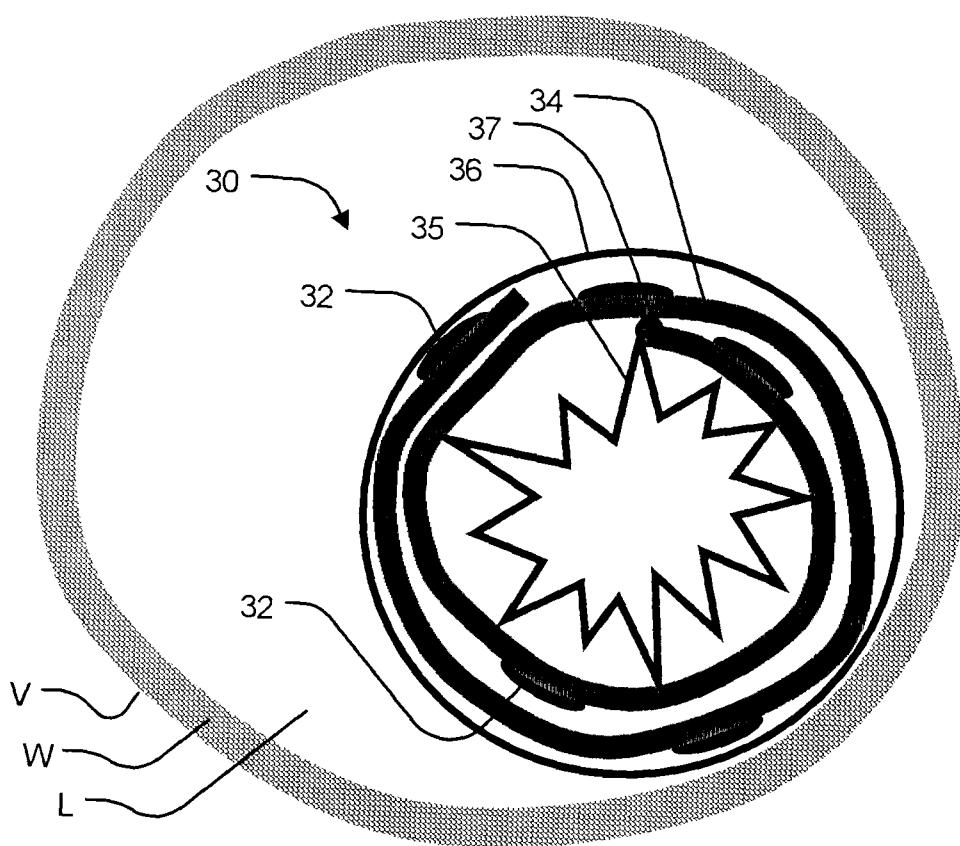


FIGURE 4A

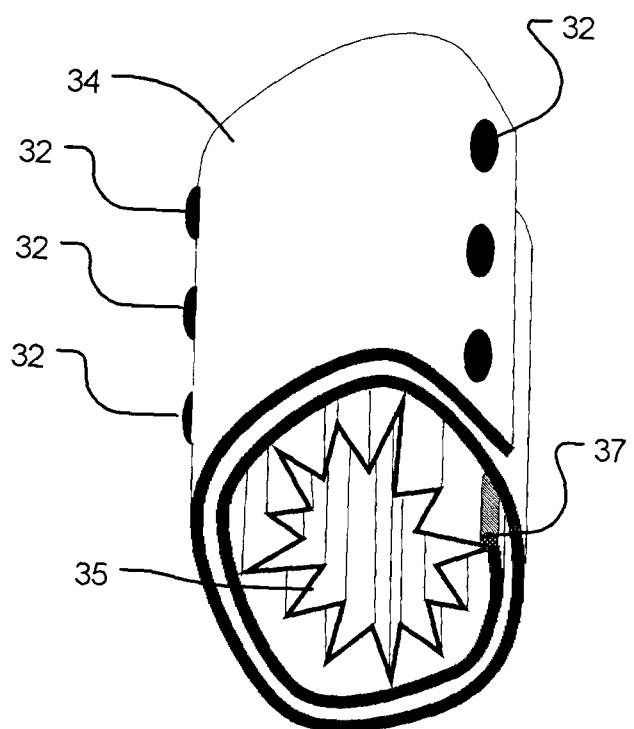


FIGURE 4B

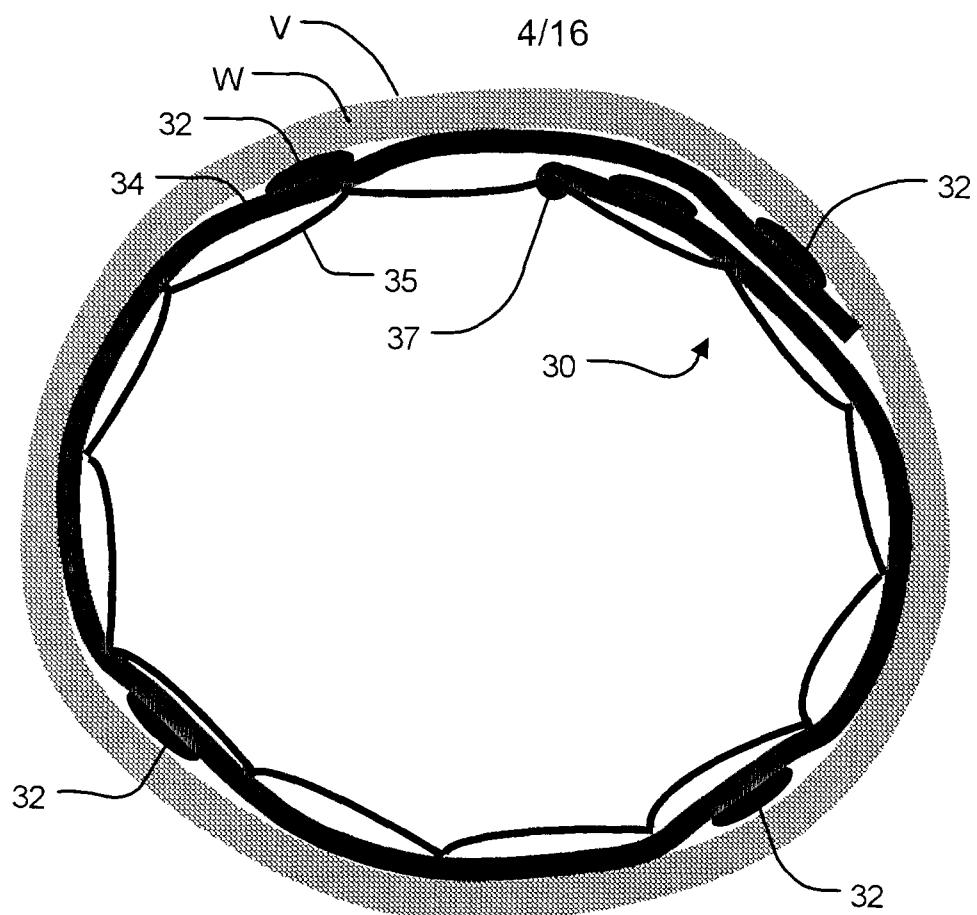


FIGURE 4C

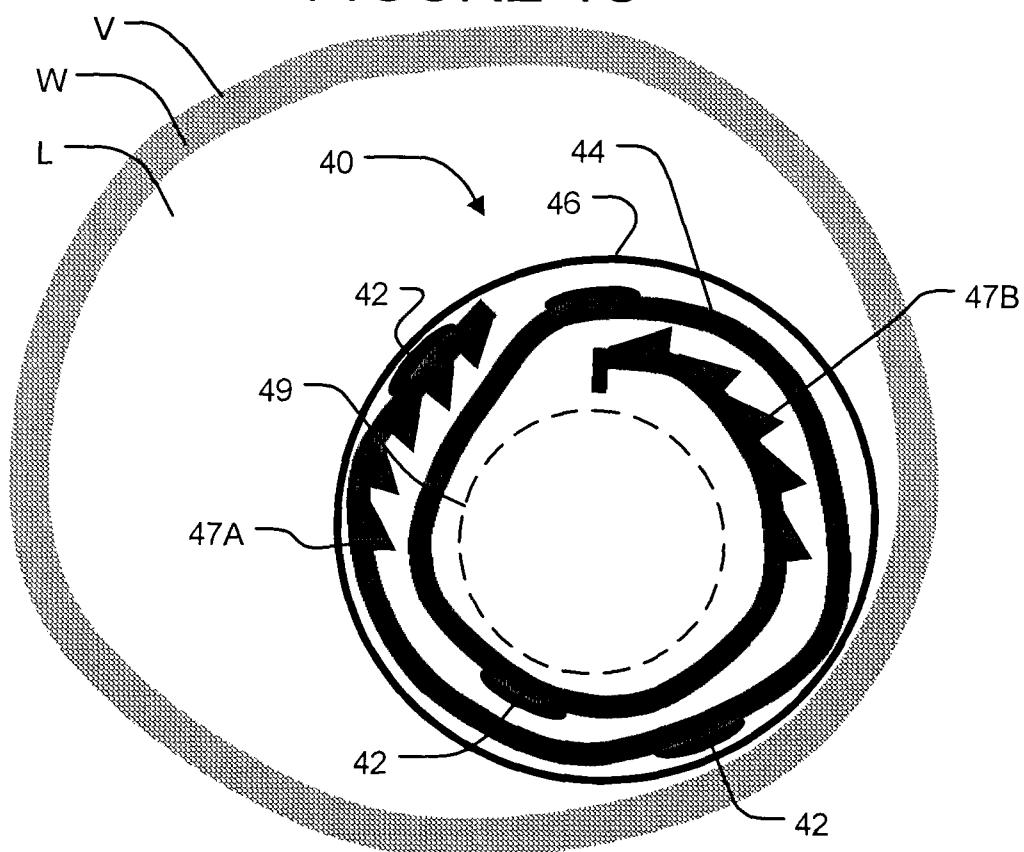


FIGURE 5A

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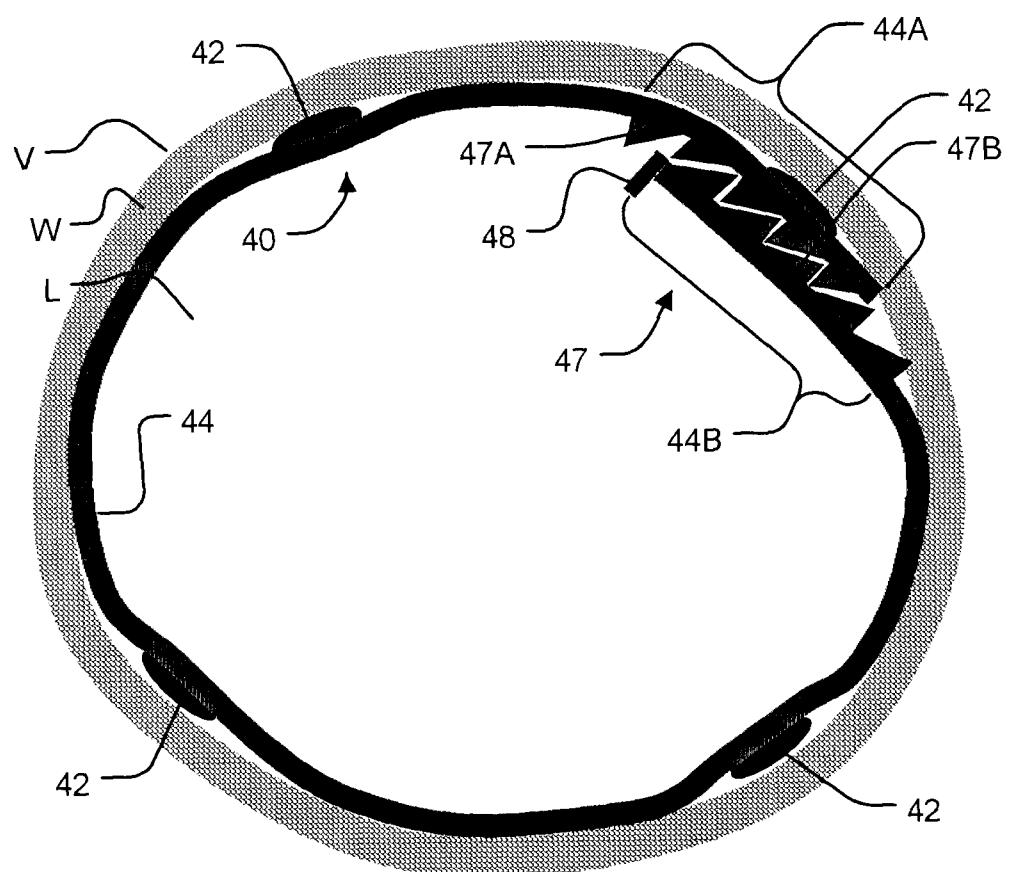


FIGURE 5B

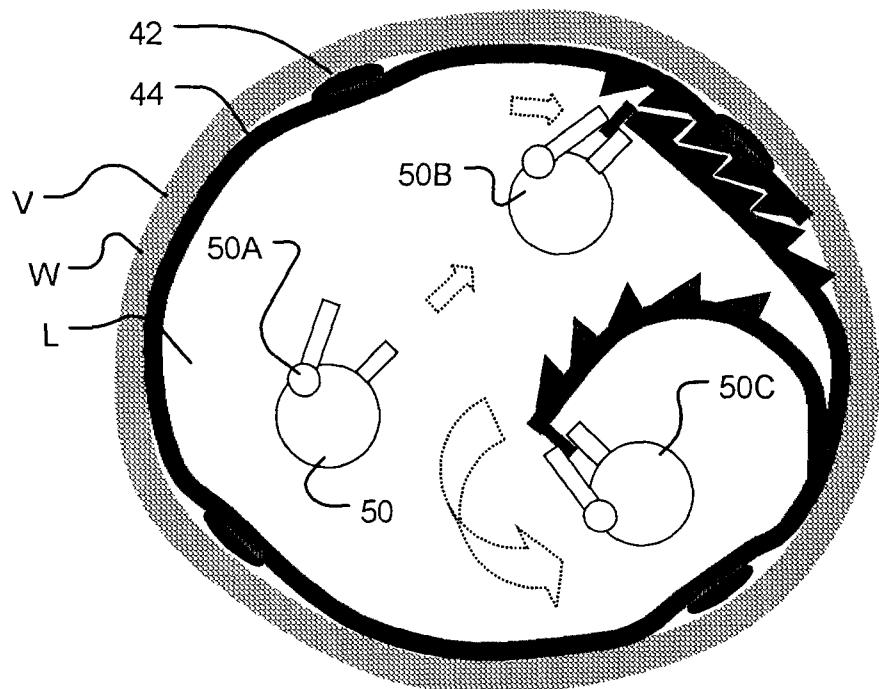
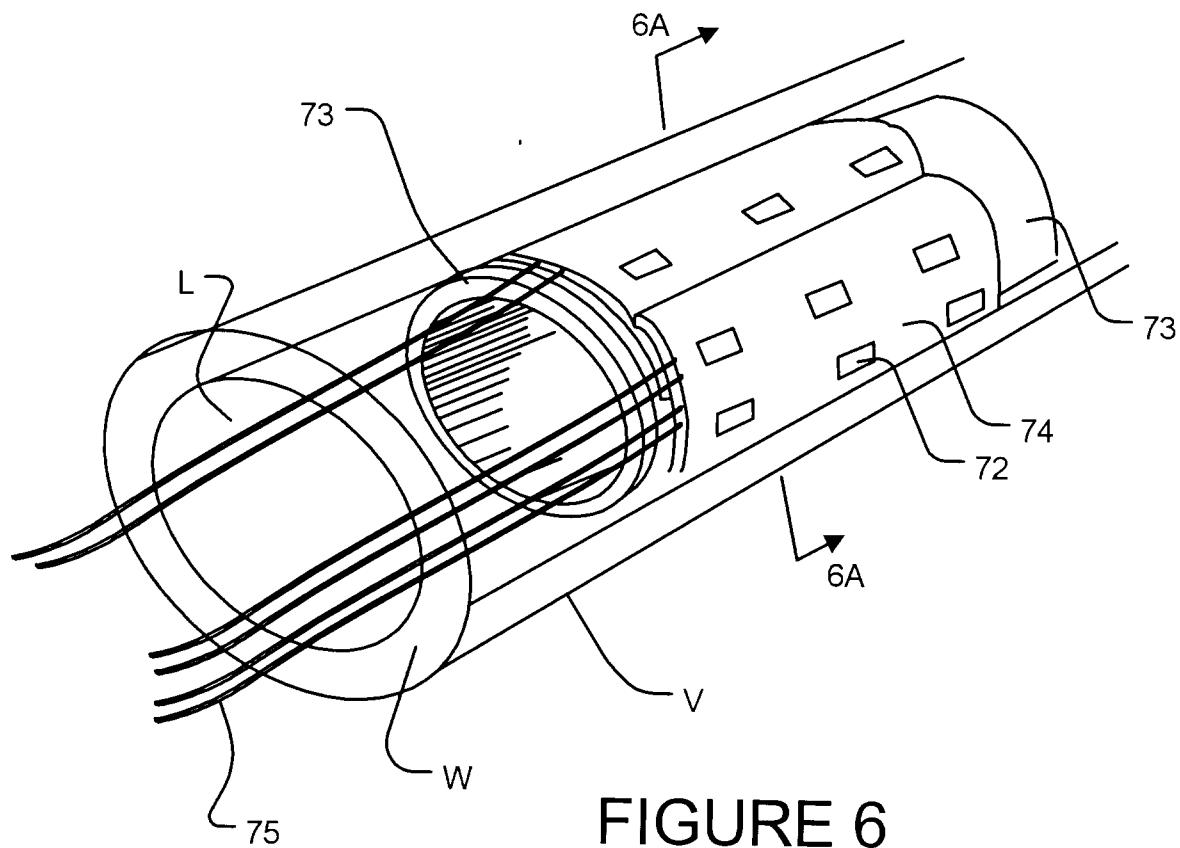
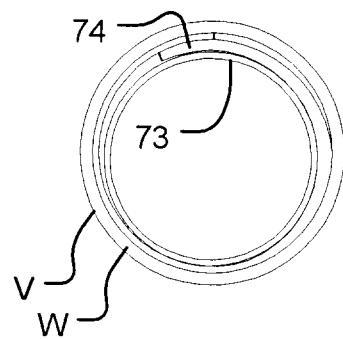


FIGURE 5C

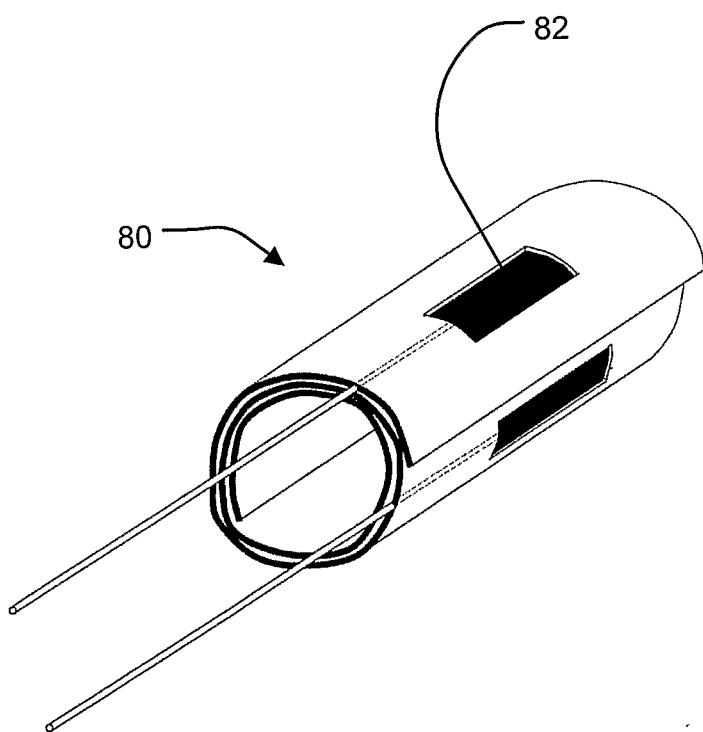
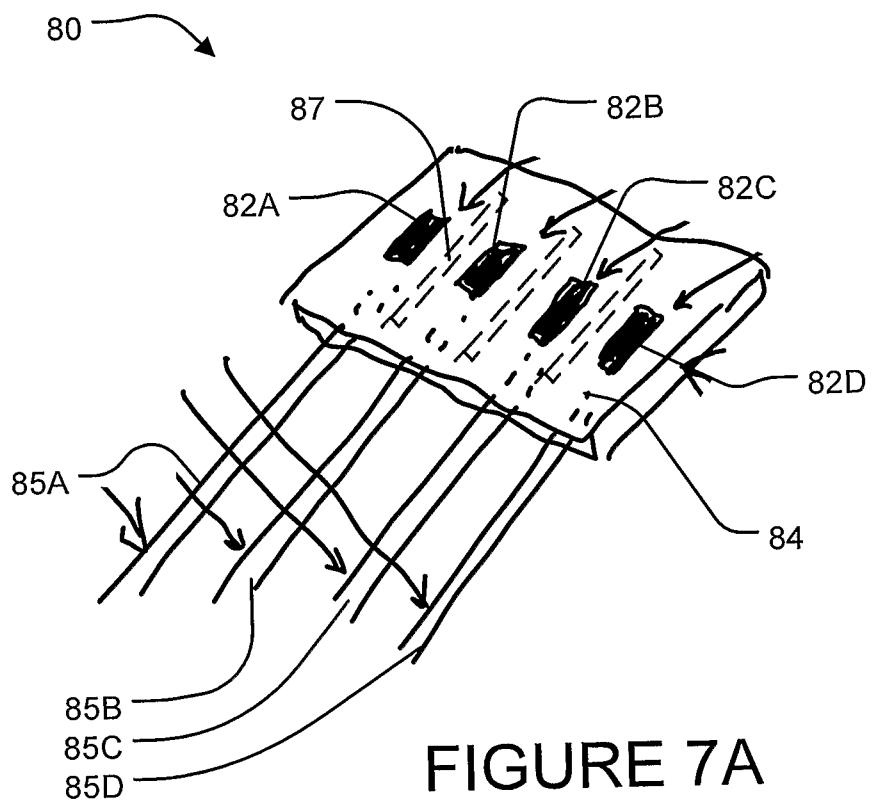
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## FIGURE 6



## FIGURE 6A



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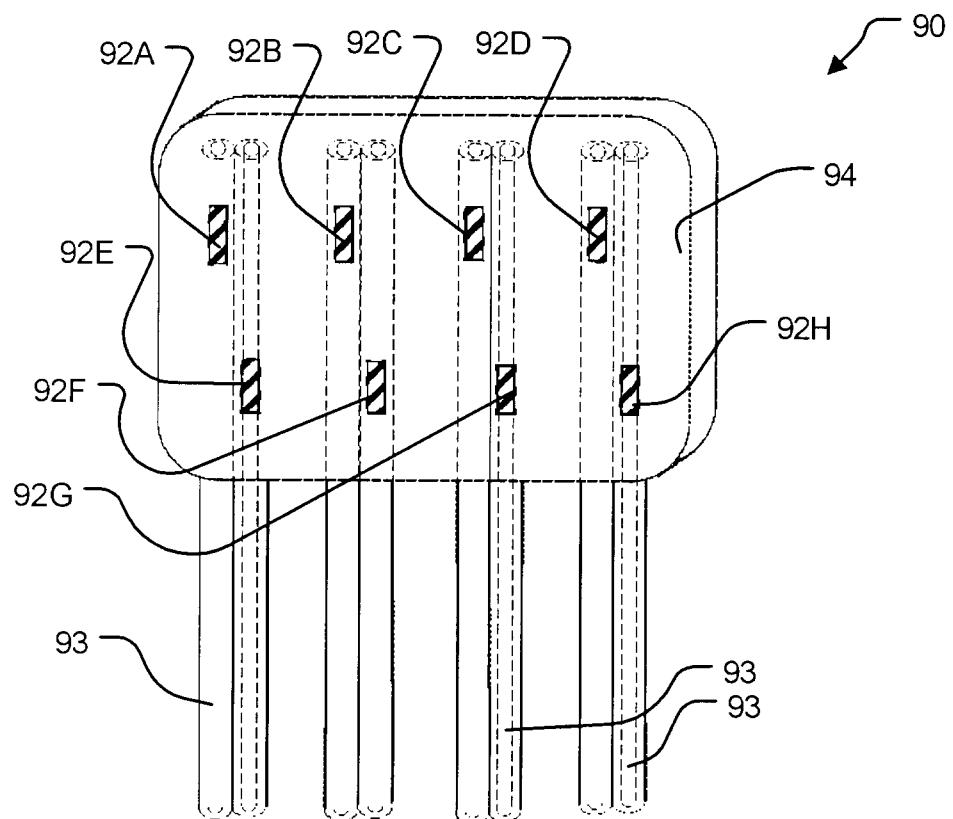


FIGURE 7C

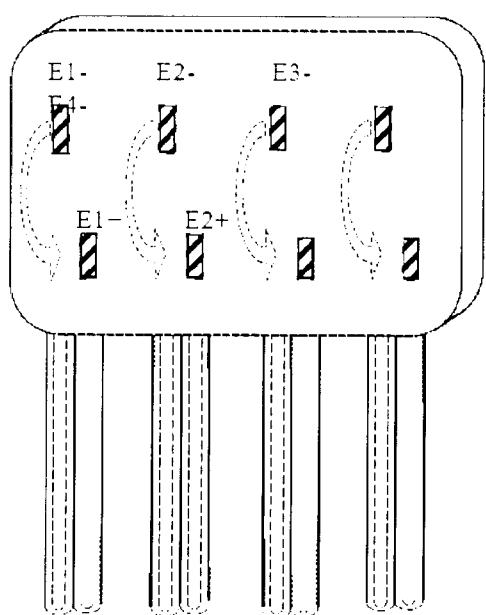


FIGURE 7D

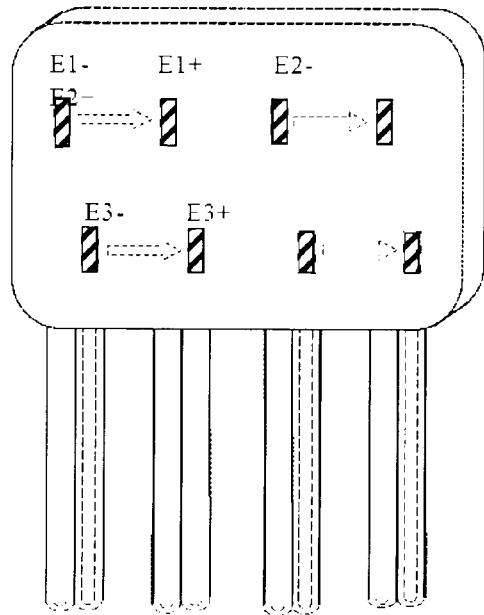


FIGURE 7E

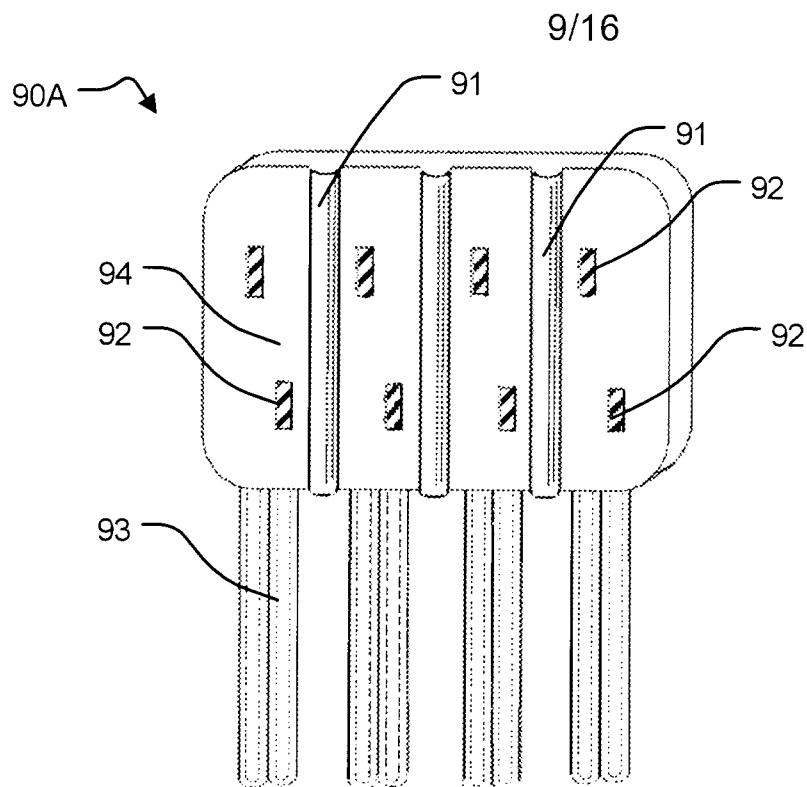


FIGURE 7F

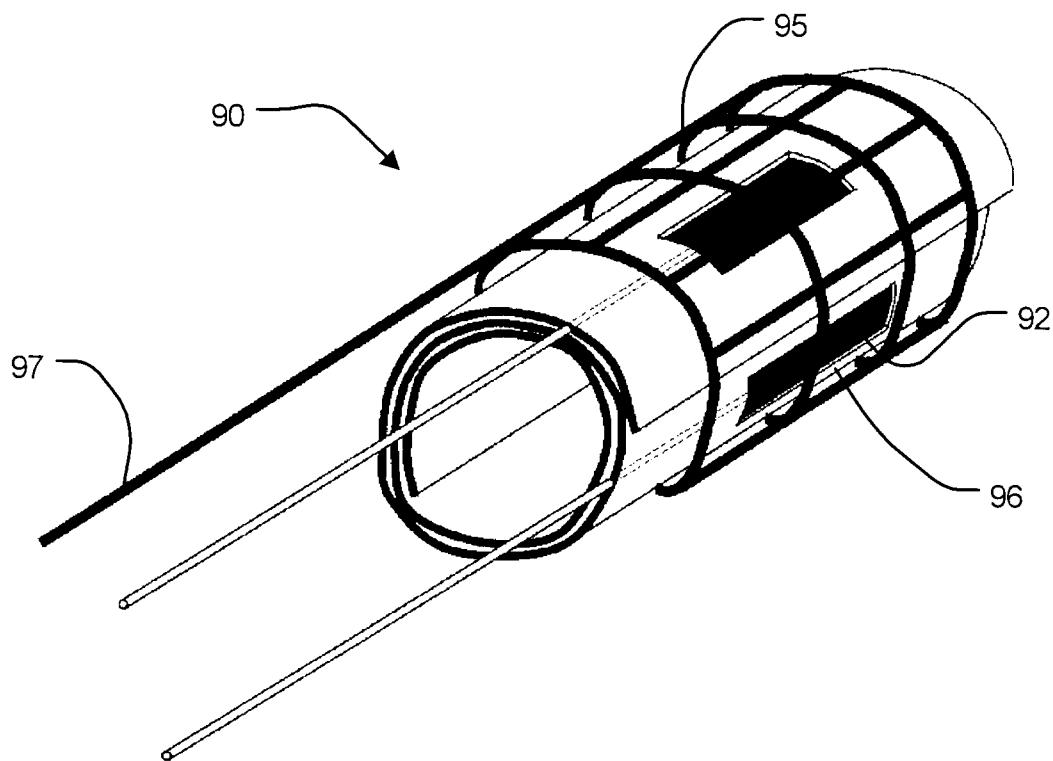
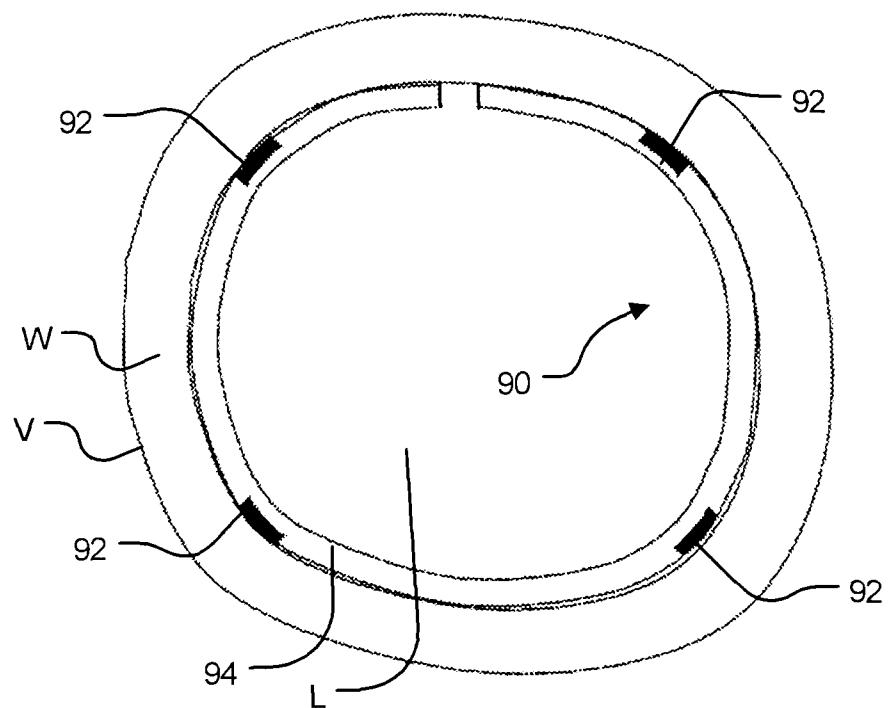
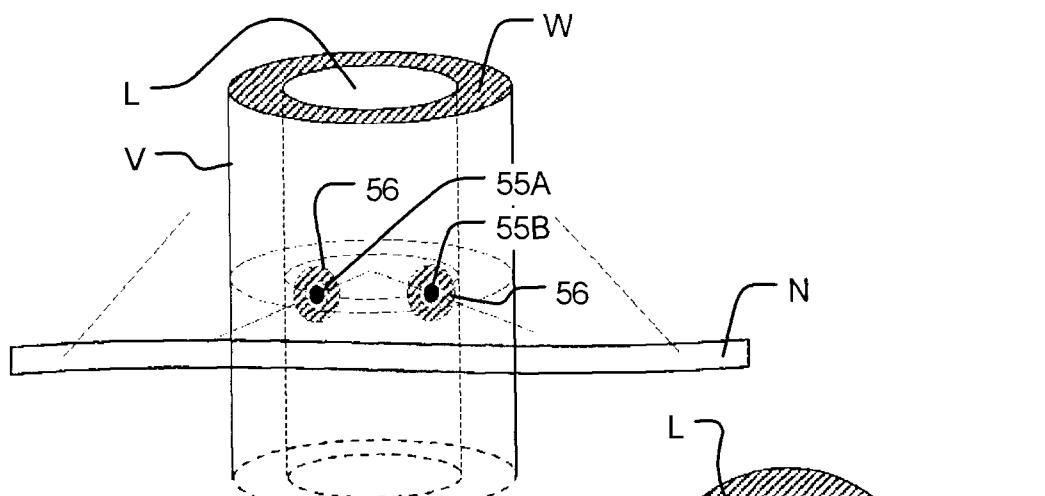
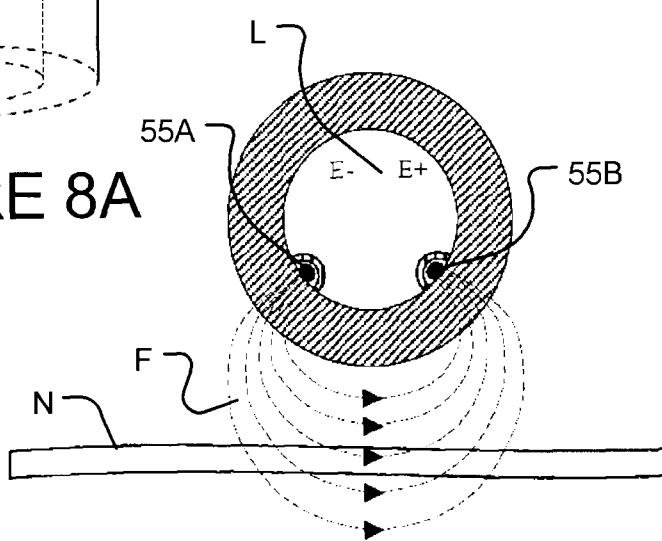


FIGURE 7G

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**FIGURE 7H****FIGURE 8A****FIGURE 8B**

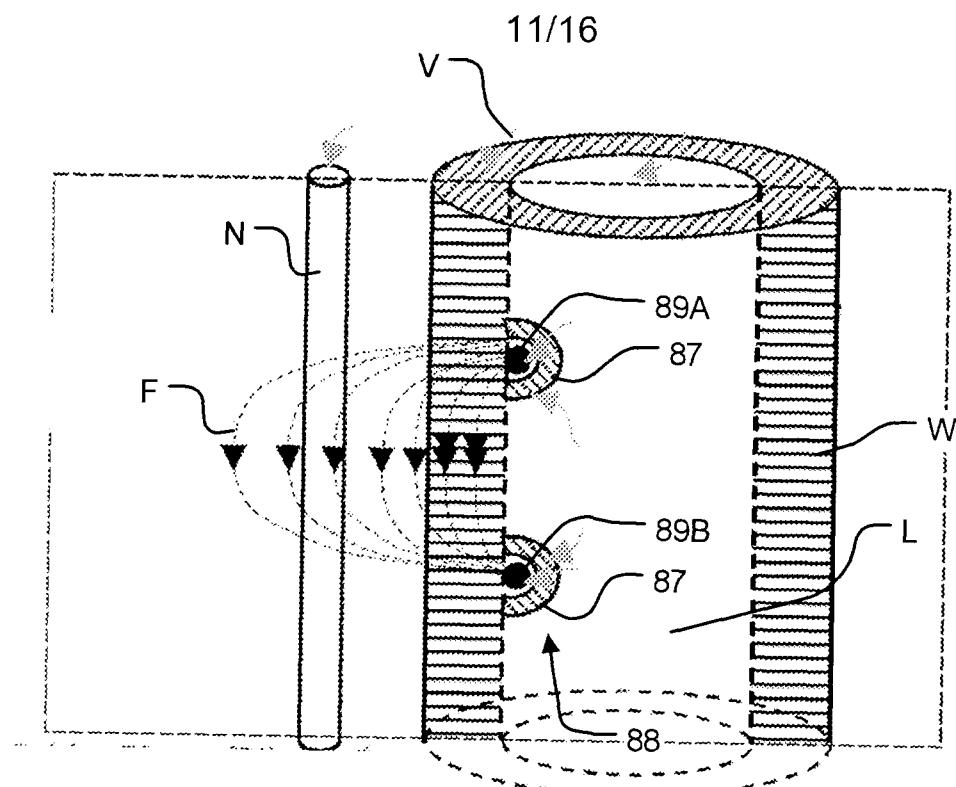


FIGURE 8C

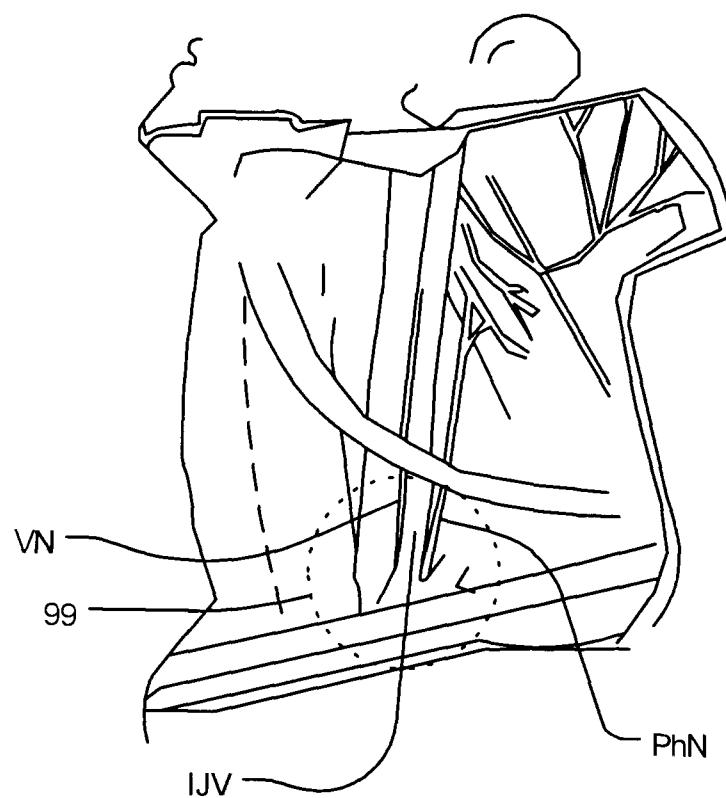


FIGURE 9  
PRIOR ART

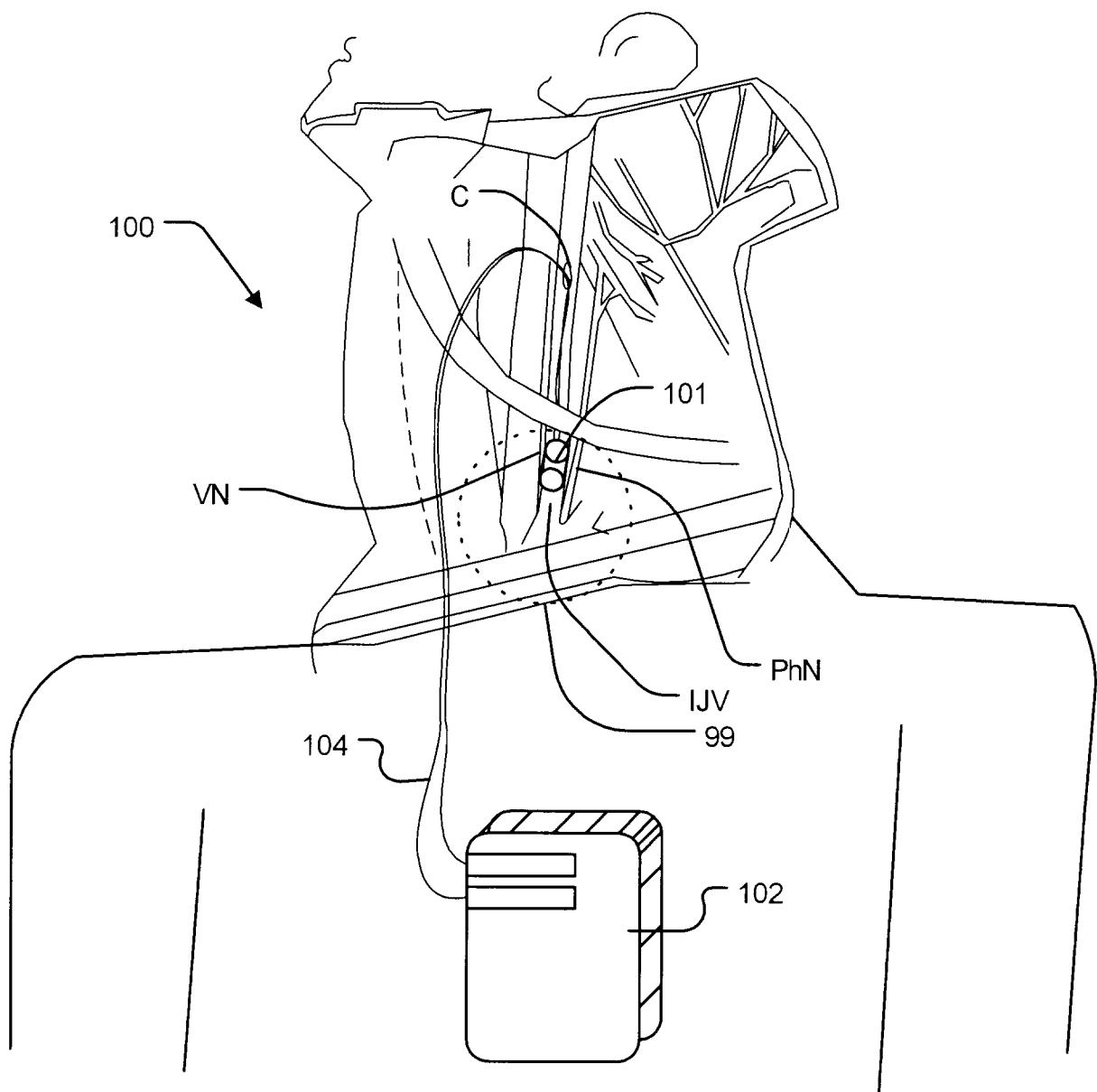
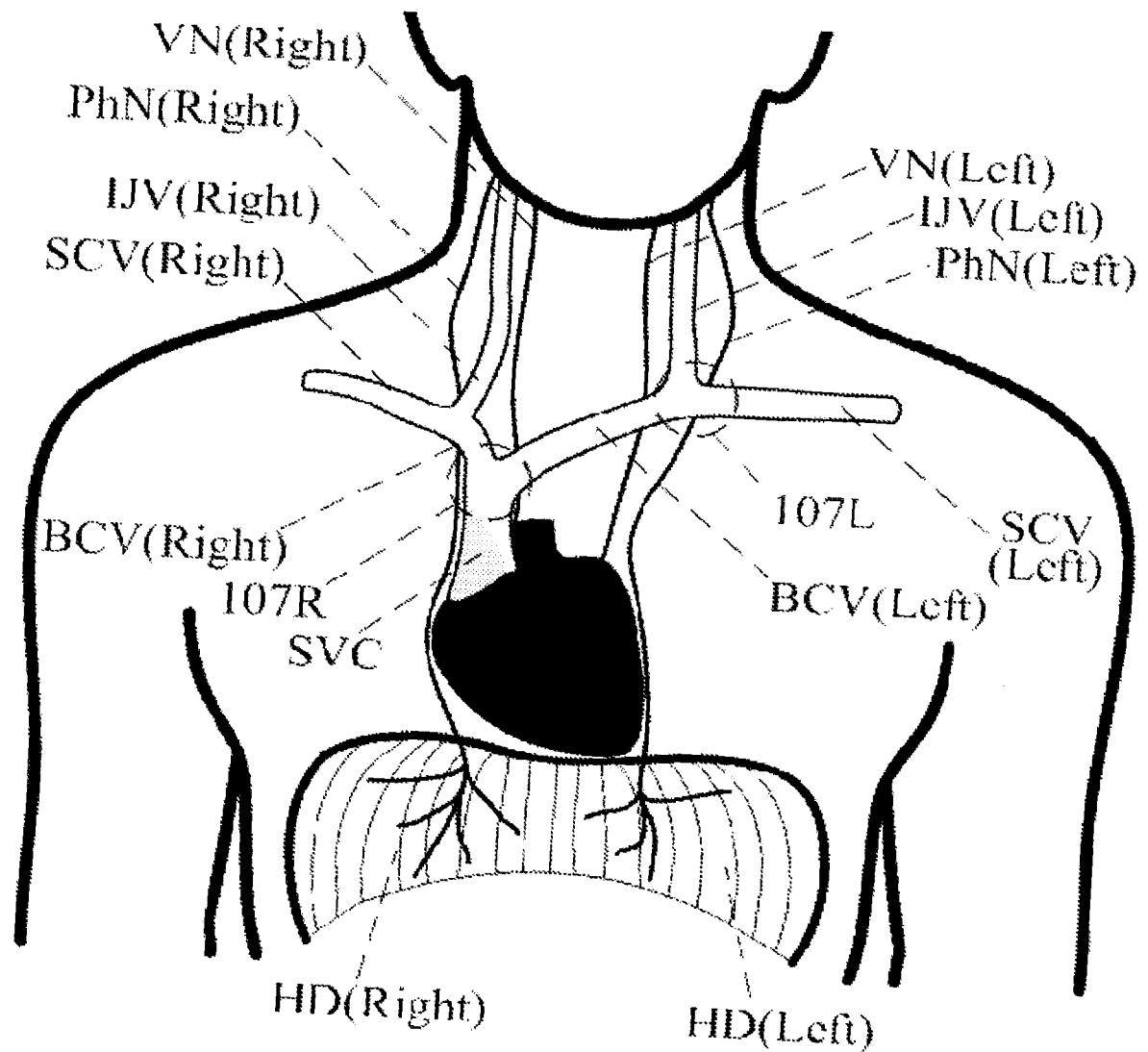


FIGURE 9A

## Replacement Sheet

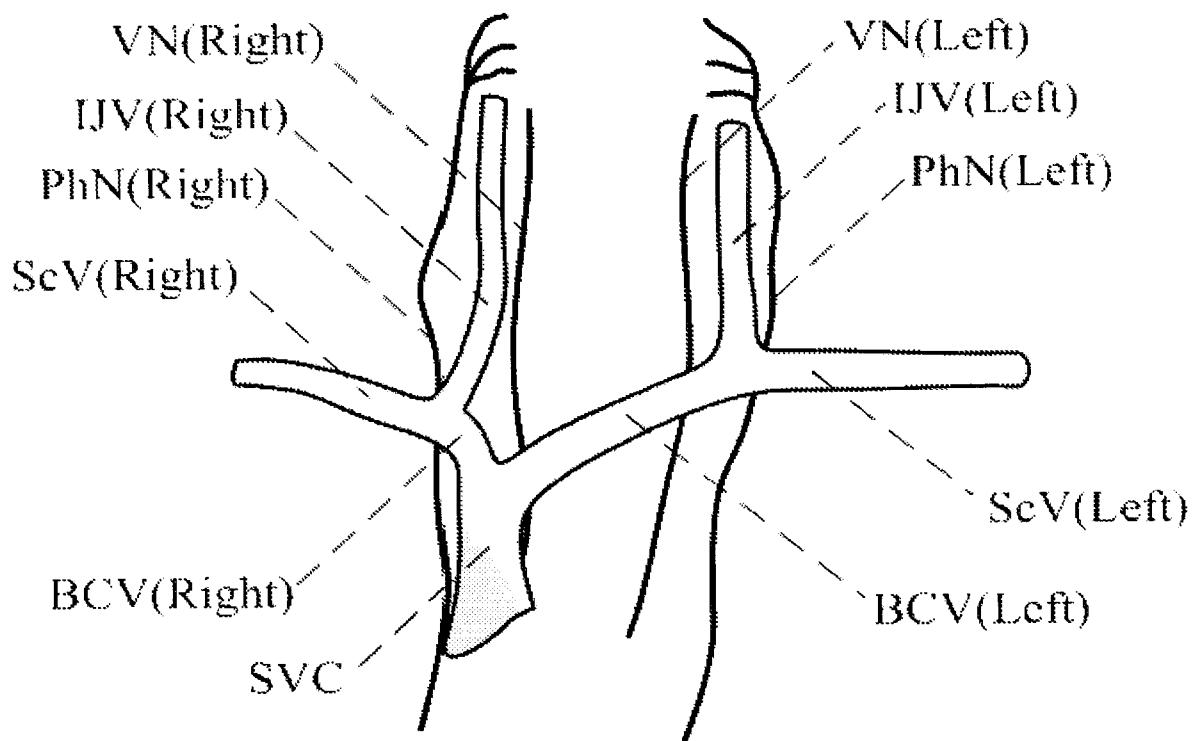
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**FIGURE 10A**  
**PRIOR ART**

## Replacement Sheet

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**FIGURE 10B**  
**PRIOR ART**

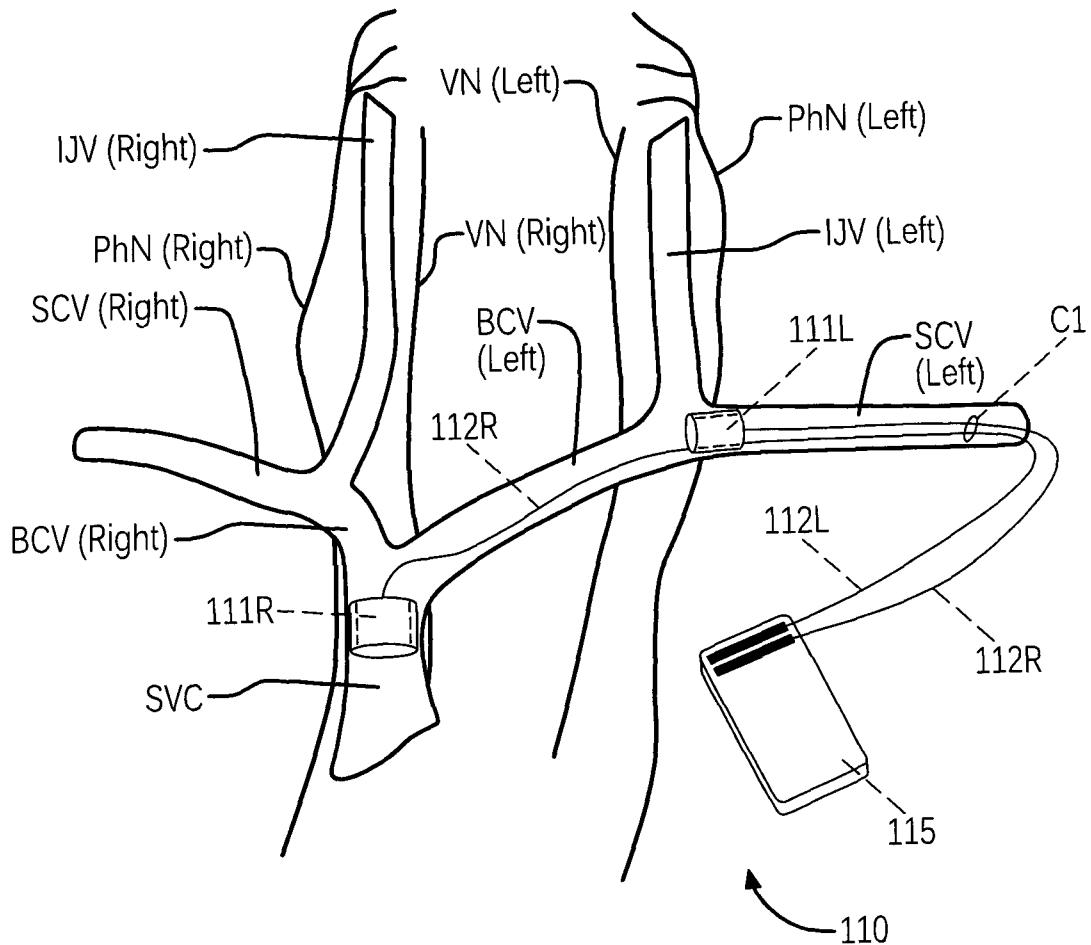
REPLACEMENT SHEET  
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FIGURE 11

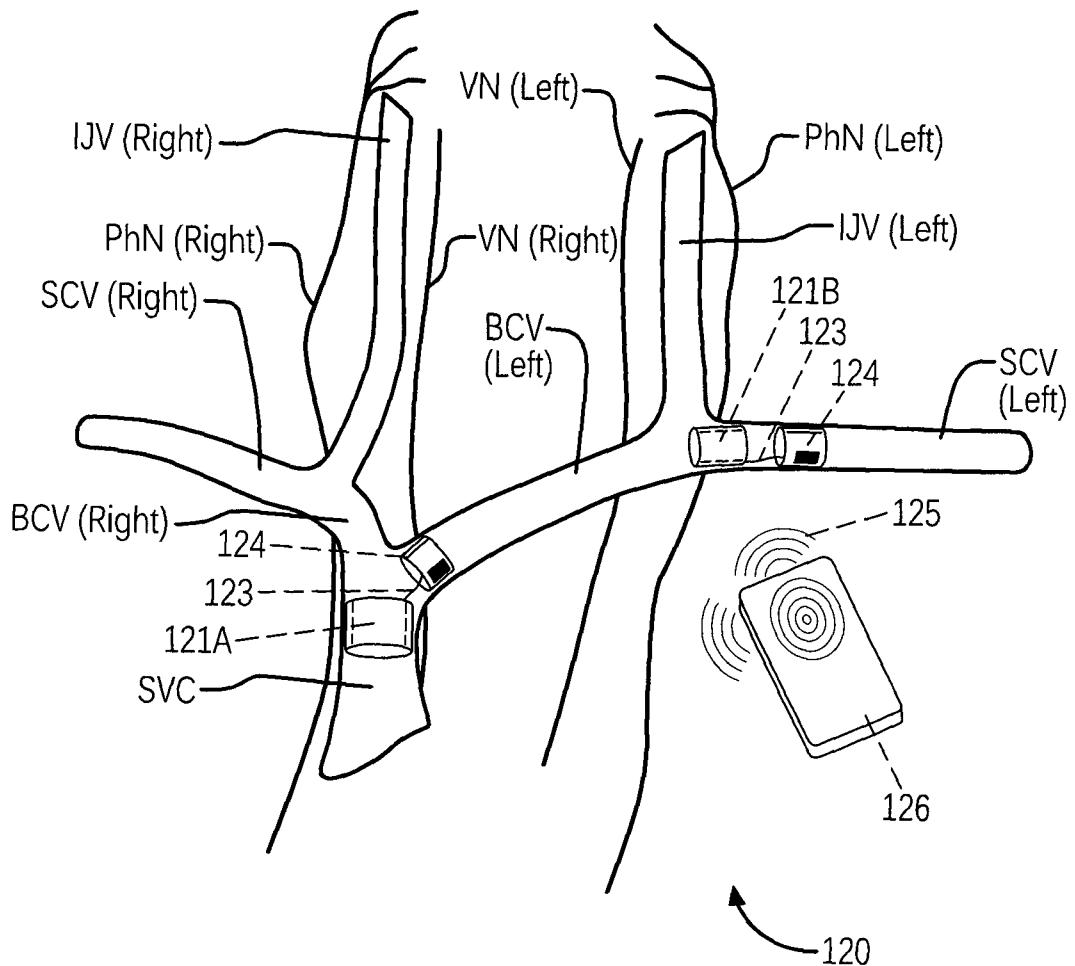
REPLACEMENT SHEET  
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FIGURE 12

