



(22) Date de dépôt/Filing Date: 2008/01/29

(41) Mise à la disp. pub./Open to Public Insp.: 2008/08/07

(45) Date de délivrance/Issue Date: 2024/04/02

(62) Demande originale/Original Application: 2 877 177

(30) Priorité/Priority: 2007/01/29 (US60/887,031)

(51) Cl.Int./Int.Cl. *A61N 1/36* (2006.01),
A61F 2/82 (2013.01), *A61F 2/92* (2013.01),
A61N 1/05 (2006.01), *A61N 1/375* (2006.01)

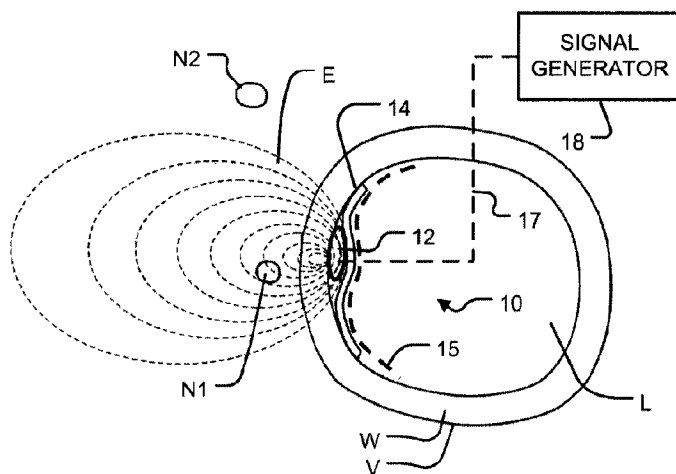
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(54) Titre : APPAREIL ET PROCEDES DE NEUROSTIMULATION TRANSVASCULAIRE

(54) Title: TRANSVASCULAR NERVE STIMULATION APPARATUS AND METHODS



(57) Abrégé/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.

Abstract of the Disclosure

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.

5 **TRANSVASCULAR NERVE STIMULATION APPARATUS AND METHODS**

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Technical Field

[0001] The invention relates to neurophysiology and in particular to apparatus and methods for stimulating nerves through the walls of blood vessels.

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[0002] Aspects of the 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 chronic conditions.

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Background

[0003] Nerve stimulation can be applied in the treatment of a range of conditions. The 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.

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

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

- 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
10 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.
- 15 • 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
20 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
25 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
30 controlling breathing. Devices for use in Laproscopic diaphragm pacing are being developed by Synapse Biomedical, Inc. Laproscopic diaphragm pacing involves

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
20 ACTIVATION OF A NERVE TRUNK USING A TRANSVASCULAR RESHAPING LEAD;
- Denker et al. US 6907285 entitled: IMPLANTABLE DEFIBRILLATOR WITH WIRELESS VASCULAR STENT ELECTRODES;
- Chavan et al. US20070093875 entitled IMPLANTABLE AND
25 RECHARGEABLE NEURAL STIMULATOR;
- Rezai, US 6885888 entitled ELECTRICAL STIMULATION OF THE SYMPATHETIC NERVE CHAIN;
- Mehra, US 5170802 entitled IMPLANTABLE ELECTRODE FOR
 LOCATION WITHIN A BLOOD VESSEL;
- 30 • Mahchek et al. US 5954761 entitled: IMPLANTABLE ENDOCARDIAL LEAD ASSEMBLY HAVING A STENT;

- 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.

- 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
10 methods involving stimulation of the vagus nerve.
- 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
- 5 • *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
- 10 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,
- 15 Supplement 1, January 2007 p. S215

[0009] Other references of interest include:

- Amundson, US5779732

20 [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

25 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

30 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 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 brachiocephalic 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 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 brachiocephalic 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 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 including a curved outer surface, 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;

a plurality of electrodes on the lead structure configured to receive stimulation signals from at least one of the plurality of leads for stimulation of the phrenic nerve, wherein the plurality of electrodes includes at least one bipolar electrode pair configured to be activated to emit an electrical field extending radially outwards from only a portion of a circumference of the lead structure including the curved outer surface;

a breathing sensor configured to sense breathing of the patient, wherein the signal generator adjusts the stimulation signals based on the sensed breathing;

a motion sensor configured to sense motion of the patient, wherein the signal generator adjusts the stimulation signals based on the sensed motion; and

a control system programmed to select the at least one bipolar electrode pair, the at least one bipolar electrode pair including two electrodes best positioned, relative to other electrodes of the plurality of electrodes, to stimulate the phrenic nerve.

[0013b] Another 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 venous system of the patient, the lead structure having a plurality of leads to receive stimulation signals from the signal generator;

second electrodes on the lead structure proximate a distal portion of the lead structure and configured to receive stimulation signals from at least one of the plurality of leads for stimulation of the right phrenic nerve;

first electrodes on the lead structure proximal of the second electrodes and configured to receive stimulation signals from at least one of the plurality of leads for stimulation of the left phrenic nerve;

a breathing sensor configured to sense breathing of the patient, wherein the signal generator adjusts the stimulation signals based on the sensed breathing; and

a control system programmed to (a) select the first electrodes from a plurality of first pairs of electrodes positioned in a first blood vessel, the first electrodes including two electrodes best positioned, relative to other electrodes of the first pairs of electrodes, to stimulate the left phrenic nerve, and (b) select the second electrodes from a plurality of second pairs of electrodes positioned in a second blood vessel, the second electrodes including two electrodes best positioned, relative to other electrodes of the second pairs of electrodes, to stimulate the right phrenic nerve.

[0013c] Another 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 configured to produce stimulation signals;

a lead structure including a curved outer surface, wherein the lead structure includes:

a plurality of first electrodes for electrical connection to the signal generator and configured to receive at least a first portion of the stimulation signals, the plurality of first electrodes being

positionable proximate to the left phrenic nerve in a lumen of at least one of a jugular vein and a left subclavian vein; and

a plurality of second electrodes for electrical connection to the signal generator and configured to receive at least a second portion of the stimulation signals, the plurality of second electrodes being positionable proximate to the right phrenic nerve in a lumen of a vena cava; and

a breathing sensor configured to sense breathing of the patient, wherein the signal generator adjusts the stimulation signals based on the sensed breathing,

wherein at least one of the plurality of first electrodes or the plurality of second electrodes includes a bipolar electrode pair configured to be activated to emit an electrical field extending radially outwards from only a portion of a circumference of the lead structure including the curved outer surface.

[0013d] Another 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 with a curved outer surface, 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;

a plurality of electrode pairs on the lead structure to receive stimulation signals from at least one of the plurality of leads for stimulation of the phrenic nerve;

a breathing sensor configured to sense breathing of the patient, wherein the signal generator adjusts the stimulation signals based on the sensed breathing; and

a control system programmed to select a pair of electrodes from the plurality of electrode pairs to stimulate the phrenic nerve, the pair of electrodes including two electrodes circumferentially spaced around a circumference of the lead structure, including the curved outer surface, the two electrodes being aligned substantially parallel to the phrenic nerve.

[0013e] Another 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 venous system of the patient, the lead structure defining a longitudinal axis along a length of the lead structure and between a proximal portion of the lead structure and a distal portion of the lead structure, and the lead structure having a plurality of leads along the longitudinal axis to receive stimulation signals from the signal generator;

a plurality of second pairs of electrodes on the lead structure proximate the distal portion of the lead structure, wherein the plurality of second pairs of electrodes includes second electrodes configured to receive stimulation signals from at least one lead of the plurality of leads for stimulation of the right phrenic nerve;

a plurality of first pairs of electrodes on the lead structure proximate the proximal portion of the lead structure wherein the plurality of first pairs of electrodes includes first electrodes configured to receive stimulation signals from at least one lead of the plurality of leads for stimulation of the left phrenic nerve, wherein the signal generator is proximal to the first electrodes;

a blood chemistry sensor for insertion into a blood vessel proximate at least one of the first electrodes and the second 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;

a motion sensor configured to sense motion of the patient, wherein the signal generator adjusts the stimulation signals based on the sensed motion; and a control system programmed to (a) select the first electrodes from the plurality of first pairs of electrodes to stimulate the left phrenic nerve, and (b) select the second electrodes from the plurality of second pairs of electrodes to stimulate the right phrenic nerve.

[0013f] Another 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 bipolar pair of electrodes from the array of electrodes, the pair of electrodes including two electrodes having a stimulation efficacy for the phrenic nerve that is greater than a stimulation efficacy of other pairs of electrodes of the array of

electrodes, wherein the two electrodes are configured to align substantially parallel to the phrenic nerve.

[0013g] Another 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.

[0013h] Another 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, and

wherein at least one entire electrode of the first electrodes or the second electrodes is positioned radially inward of the outermost surface of the lead structure.

[0013i] Another 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 to an exterior of the lead structure through one of the plurality of apertures in the outermost surface,

wherein at least two electrodes of one of the first plurality of electrodes or the second plurality of electrodes have a same longitudinal position along the length of the lead structure, and

wherein at least one entire electrode of the first plurality of electrodes or the second plurality of electrodes is radially inward from the outermost surface of the lead structure.

[0013j] Another 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 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 entire electrode of the plurality of first pairs of electrodes or the plurality of second pairs of electrodes is recessed from the outermost surface of the lead structure, and

wherein at least two electrodes of one of the plurality of first pairs of electrodes or the plurality of second pairs of electrodes have a same longitudinal position along a length of the lead structure.

[0013k] Another 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 for stimulation of a left phrenic nerve and more than two electrically discrete electrodes for stimulation of a right phrenic nerve, and wherein a first electrode and a second electrode of the array of electrodes are positioned on or about a same longitudinal axis of the lead structure when the first electrode is positioned by the left phrenic nerve for stimulation of the left phrenic nerve and the second electrode is positioned by the right phrenic nerve for stimulation of the right phrenic nerve; and

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

[0013l] Another 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 for stimulation of a left phrenic nerve and more than two electrically discrete electrodes for stimulation of a right phrenic nerve, 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 wherein a first electrode and a second electrode of the array of electrodes are positioned on or about a same longitudinal axis of the lead structure when the first electrode is positioned by the left phrenic nerve for stimulation of the left phrenic nerve and the second electrode is positioned by the right phrenic nerve for stimulation of the right phrenic nerve; and

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

[0013m] Another 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 for stimulation of a left phrenic nerve and more than two electrically discrete electrodes for stimulation of a right phrenic nerve, 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 wherein a first electrode and a second electrode of the array of electrodes are positioned on or about a same longitudinal axis of the lead structure when the first electrode is positioned by the left phrenic nerve for stimulation of the left phrenic nerve and the second electrode is positioned by the right phrenic nerve for stimulation of the right phrenic nerve; and

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

[0013n] Another aspect of the invention provides a system for stimulating a nerve in a patient, comprising:

an electrode structure supported on a flexible electrically insulating sheet, the electrode structure comprising a plurality of electrodes, wherein the plurality of electrodes comprise a first electrode and a second electrode, and wherein the first electrode is positionable proximate a left phrenic nerve, and the second electrode is positionable proximate a right phrenic nerve, and the first electrode is configured to stimulate the left phrenic nerve and the second electrode is configured to stimulate the right phrenic nerve; and

a tube configured for intravascular insertion, wherein the electrode structure and at least a first portion of the electrically insulating sheet are spirally arranged on the tube, and the plurality of the electrodes comprise an array of electrodes aligned longitudinally with respect to the tube;

wherein the flexible electrically insulating sheet includes:

a proximal end in contact with the tube;

a distal end in contact with the tube; and

a segment that supports an electrode of the plurality of electrodes, wherein the segment is between the proximal end of the flexible electrically insulating sheet and the distal end of the flexible electrically insulating sheet, and is in contact with the tube when the system delivers stimulation.

[0013o] Another aspect of the invention provides a system for stimulating a nerve in a patient, comprising:

- an electrode structure supported on a flexible electrically insulating sheet, wherein the electrode structure comprises a plurality of electrodes, and at least one electrode of the plurality of electrodes is configured to stimulate the nerve; and

- a tube configured for intravascular insertion, wherein the electrode structure is spirally arranged on the tube so that a first electrode of the plurality of electrodes is longitudinally and circumferentially spaced from a second electrode of the plurality of electrodes;

- wherein the flexible electrically insulating sheet includes:

- a proximal end in contact with the tube;

- a distal end in contact with the tube; and

- a segment that supports at least two electrodes of the plurality of electrodes, wherein the segment is between the proximal end of the flexible electrically insulating sheet and the distal end of the flexible electrically insulating sheet, and is in contact with the tube when the system delivers stimulation, and

- when the system delivers stimulation, the flexible electrically insulating sheet is spirally arranged so that each of the plurality of electrodes faces radially outward.

[0013p] Another aspect of the invention provides a system for stimulating a nerve in a patient, comprising:

- a plurality of electrodes supported on a flexible electrically insulating sheet, wherein at least one electrode of the plurality of electrodes is configured to stimulate the nerve; and

- a plurality of leads arranged longitudinally along the electrically insulating sheet, each of the plurality of leads being configured to provide a stimulation signal to a corresponding one of the plurality of electrodes,

- wherein the electrically insulating sheet is spirally arranged on the tube so that each of the plurality of electrodes faces radially outward and not radially inward, and wherein the plurality of electrodes comprise an array of longitudinally and circumferentially spaced electrodes; and

- wherein the flexible electrically insulating sheet includes:

- a proximal end in contact with the tube;

- a distal end in contact with the tube; and

- a segment that supports at least two electrodes of the plurality of electrodes, wherein the segment is between the proximal end of the flexible electrically insulating sheet and the distal end of the flexible electrically insulating sheet, and is in contact with the tube when the system delivers stimulation, and

when the system delivers stimulation, the flexible electrically insulating sheet is spirally arranged so that each of the plurality of electrodes faces radially outward.

[0013q] Another aspect of the invention provides an apparatus comprising:

- one or more sensors suitable for detecting when a subject is breathing;
- a device configured to deliver a stimulus to the subject's thorax or abdomen during at least part of a phase of the subject's breathing in response to a signal generated by the one or more sensors; and

- a flexible insulating sheet including one or more electrodes;

wherein the device is configured to deliver the stimulus via the one or more electrodes configured to be positioned within a blood vessel, and is effective to cause a contraction in a muscle of the subject.

[0013r] Another aspect of the invention provides a system for controlling delivery of energy to an electrode, the system comprising:

- a processor configured to:

- cause a generator to deliver an amount of energy to an electrode disposed on a medical device;

- receive a measurement signal from a sensor, wherein the measurement signal is indicative of a motion of a body of a patient in which the electrode is in contact with;
 - and

- generate a control signal based on the measurement signal meeting a determined condition; wherein the control signal is configured to cause the generator to vary the amount of energy.

[0013s] Another aspect of the invention provides a system for controlling delivery of energy to an electrode, the system comprising:

- a generator configured to deliver an amount of energy to an electrode disposed on a medical device;

- a sensor configured to receive a measurement signal, wherein the measurement signal is indicative of a motion of a body of a patient in which the electrode is in contact with; and

- control circuitry configured to generate a control signal based on the received measurement signal;

- wherein, after the control signal is generated, the generator varies the amount of energy delivered.

[0013t] Another aspect of the invention provides a system for controlling delivery of energy to an electrode, the system comprising:

a control system configured to:

cause a generator to deliver an amount of energy to an electrode disposed on a medical device;

receive a measurement signal indicative of a respiratory motion of a patient in which the electrode is in contact with;

generate a control signal based on the measurement signal; and

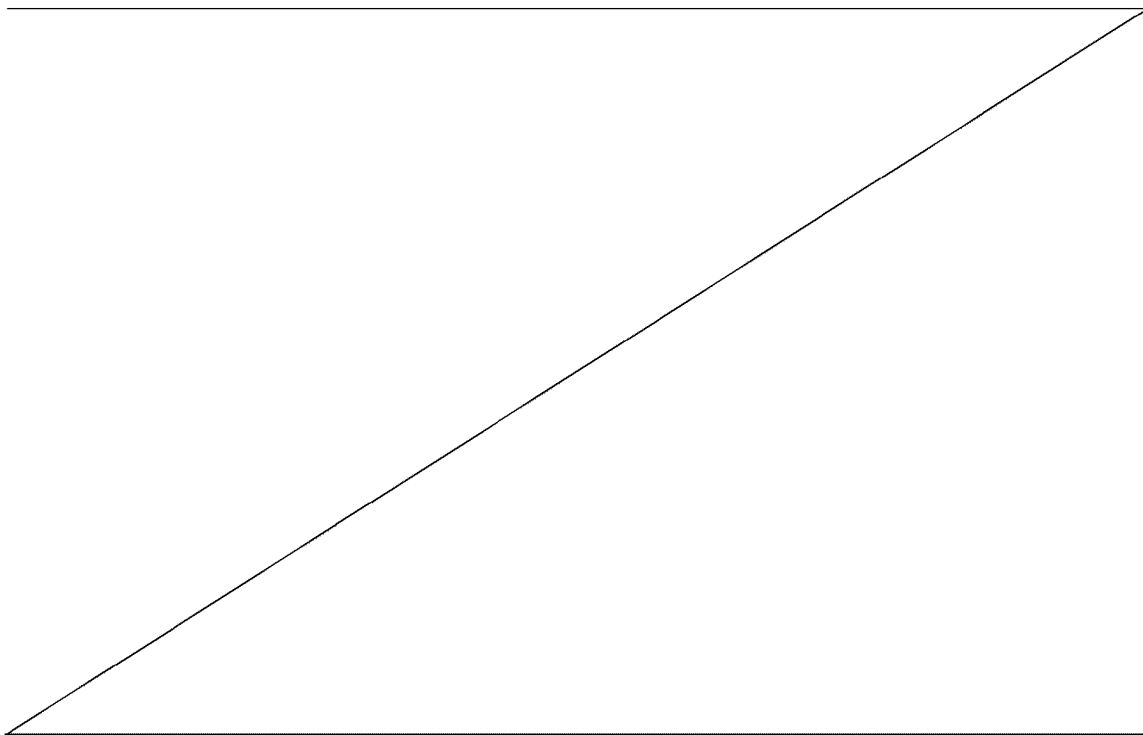
send the control signal to the generator, the control signal being configured to cause the generator to vary the amount of energy.

[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.

[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
10 embodiment which includes an expandable stent in a blood vessel.

[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
15 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.

5 **[0025]** Figure 7H is a cross section through a blood vessel within which an electrode structure according to another embodiment has been placed.

10 **[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.

15 **[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.

20 **[0028]** Figure 9 is a cut away view of a person's neck.

25 **[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.

30 **[0030]** Figures 10A and 10B illustrate the anatomy of selected nerves and blood vessels in a person's neck and upper torso.

35 **[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 brachiocephalic vein.

40 **[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

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

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.

5

[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).

10

[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 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

[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.

25

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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 Ωcm . 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**.

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 about $\frac{1}{2}$ mm² to about 5 mm². In some embodiments, each electrode has an active surface area on the order of 2 mm².

[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 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**.

[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 **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 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 corresponding electrode is strong enough to stimulate a nerve. Increasing the strength

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 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** 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**.

[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 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 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 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

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 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 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 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 mm². 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 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 mm² to 15 mm², 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 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 manufacturers.

[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 inside flexible sheet **44** (although a stent could optionally be added to provide further
25 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**.

[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, 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
30 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

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** 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

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

5 [0062] Wires 75 carry signals from a signal generator to electrodes 72. In an 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.

10 [0063] Figures 7A to 7G show examples of electrode structures. Electrode structure 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™ 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).

5 **[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
10 **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
15 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.

20 **[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.,
25 stainless steel or platinum-iridium multi-stranded wire with Teflon™ 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

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.

15

[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 ½ 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

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

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

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 **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 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**.

[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.

[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 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.

[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,

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.

[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).

30

[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 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.

5 **[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) 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.

10 **[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
15 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 BCV and SVC vessels near
20 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
25 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**.

30

[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.

10 [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 BCV. In some embodiments, electrode structure **111L** is installed first. In such embodiments, electrode structure **111L** can be passed through the left BVC past electrode structure **111L** (e.g. through a bore of electrode structure **111L**) to its target location in the SVC. Flexible leadout cables **112R** passes through electrode structure **111L**. Both leadout cables **112** emerge from the BCV and course subcutaneously to a subcutaneous pocket area in the upper chest where the leadout cable connectors are connected to IPG **115**.

20 [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 ± 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

15 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).

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

25 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.

[0110] Implantable pulse generator 126 may contain batteries or another source of

30 electrical energy, control circuitry and transmitter antennas to communicate with

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

5 **[0111]** In some embodiments, an implantable pulse generator or other signal source 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.

25 **[0113]** The applications of the apparatus and methods described herein are not limited 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.

30

[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 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 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:

- 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 CO₂ concentration;
- 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.
- 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 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.

[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 CO₂ 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.

[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.

[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 for insulating backing sheets, different arrangements of electrodes, different control arrangements, and the like. These features may be mixed and matched (i.e. combined

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. An apparatus comprising:

one or more sensors suitable for detecting when a subject is breathing;

a device configured to deliver a stimulus to the subject's thorax or abdomen during at least part of a phase of the subject's breathing in response to a signal generated by the one or more sensors; and

a flexible insulating sheet including one or more electrodes;

wherein the device is configured to deliver the stimulus via the one or more electrodes configured to be positioned within a blood vessel, and is effective to cause a contraction in a muscle of the subject.

2. The apparatus of claim 1, wherein the one or more sensors include an accelerometer configured to determine a movement of the subject.

3. The apparatus of claim 1, wherein the one or more sensors are suitable for detecting when a subject is inhaling or exhaling.

4. The apparatus of claim 1, wherein the phase of breathing is an inspiration phase.

5. The apparatus of claim 1, wherein being configured to deliver stimulus to the subject's thorax or abdomen includes being configured to deliver stimulus to a diaphragm.

6. The apparatus of claim 5, wherein being configured to deliver stimulus to the diaphragm includes being configured to deliver electrical stimulus to the diaphragm or a nerve.

7. The apparatus of claim 1, wherein the contraction of a breathing muscle includes a contraction of a diaphragm.

8. The apparatus of claim 1, wherein the device is configured to deliver stimulus during an inspiration phase of the subject's breathing.

9. The apparatus of claim 1, wherein being configured to deliver the stimulus includes being configured to deliver an electrical signal via an electrode pair of the one or more electrodes.

10. The apparatus of claim 1, wherein the apparatus is at least in part implantable in the subject's thorax or abdomen.

11. The apparatus of claim 1, wherein the one or more electrodes are first electrodes, the stimulus is a first stimulus, and the apparatus further includes one or more second electrodes;

wherein the first electrodes are configured to deliver the first stimulus to a first region of the subject's thorax or abdomen;

the second electrodes are configured to deliver a second stimulus to a second region of the subject's thorax or abdomen; and

the first stimulus causes contraction of a first portion of a respiratory muscle, and the second stimulus causes contraction of a second portion of the respiratory muscle.

12. The apparatus of claim 1, wherein the flexible insulating sheet includes a lead connecting the one or more electrodes to the device; and

wherein the stimulus delivered via the one or more electrodes includes an electrical field emitted from one surface of the flexible insulating sheet.

13. The apparatus of claim 1, wherein the flexible insulating sheet is configured to conform to a portion of a subject's anatomy.

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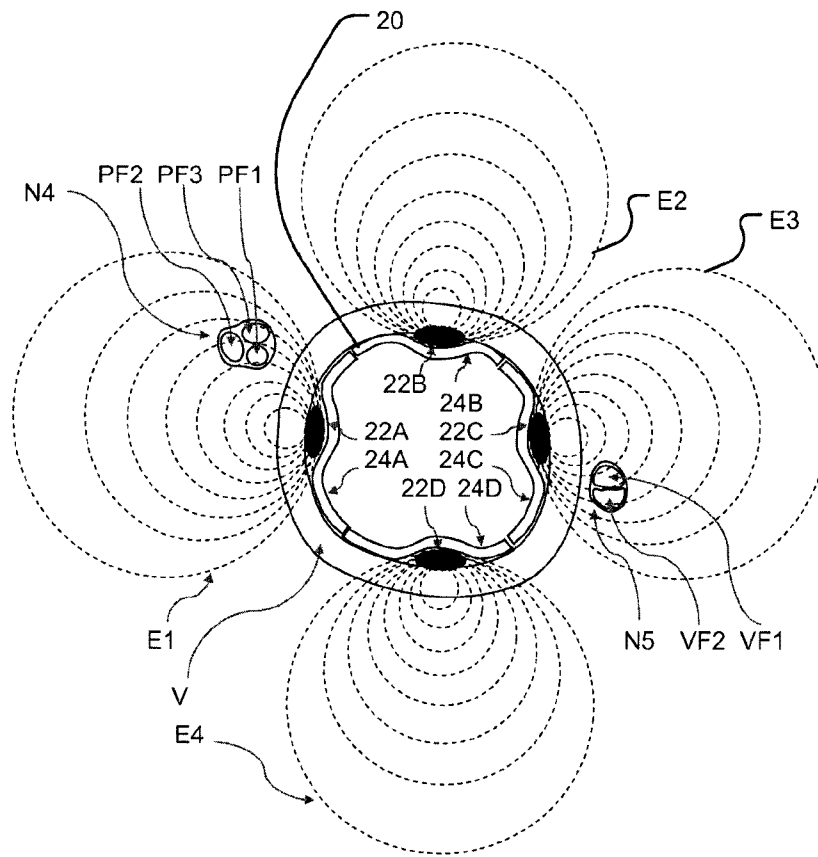


FIGURE 3

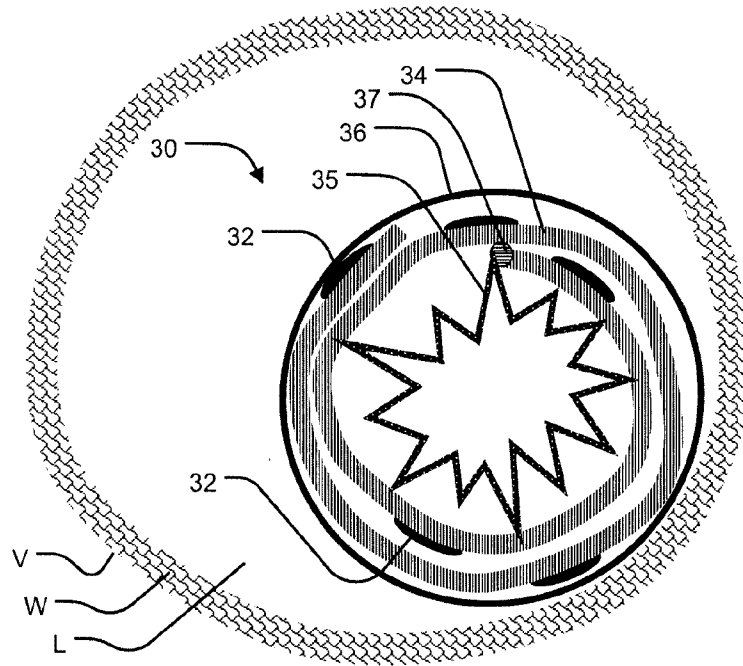


FIGURE 4A

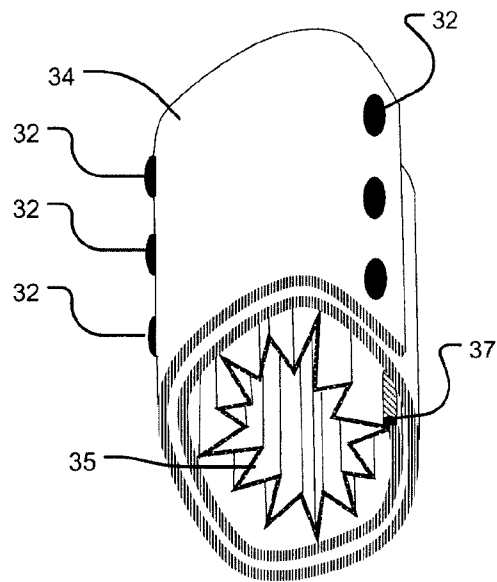


FIGURE 4B

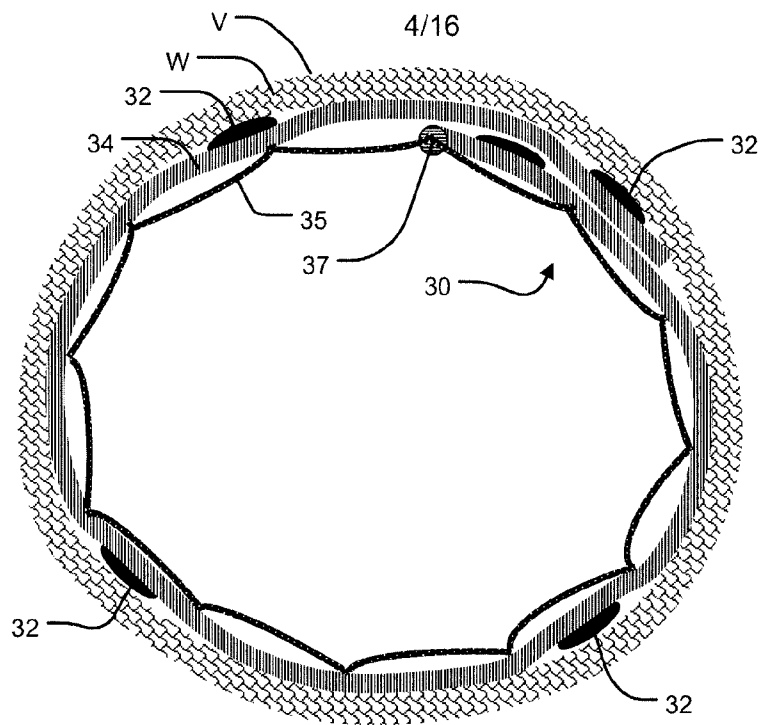


FIGURE 4C

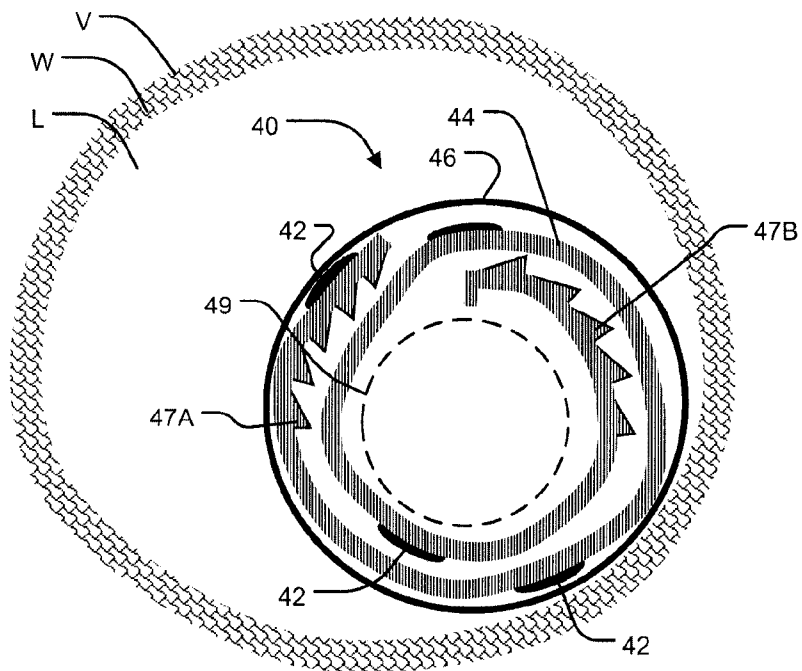


FIGURE 5A

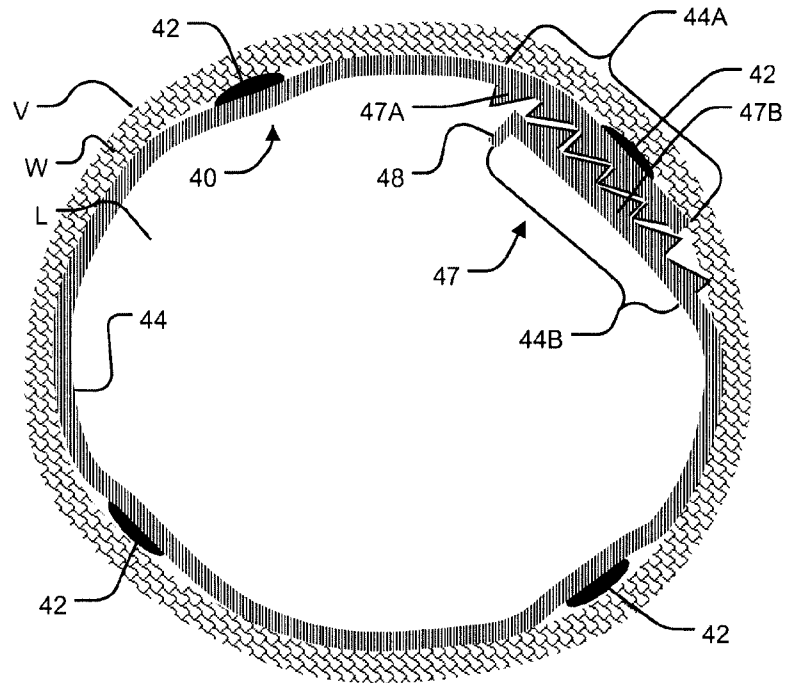


FIGURE 5B

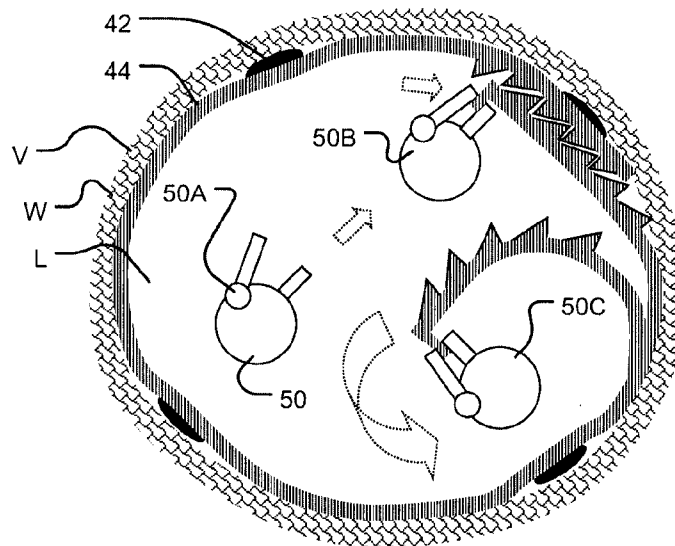
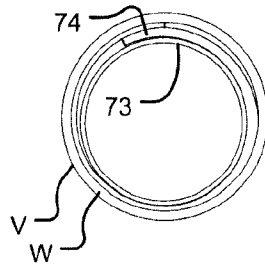
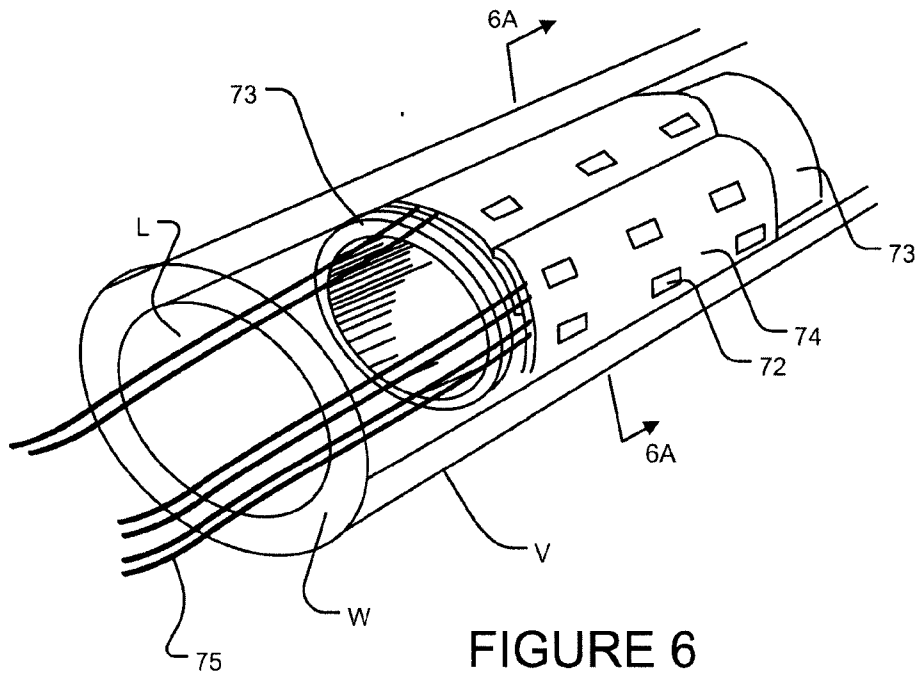
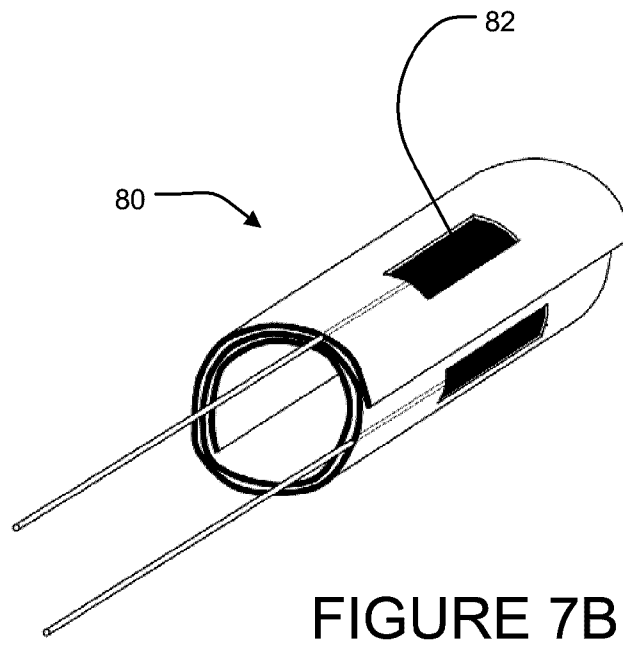
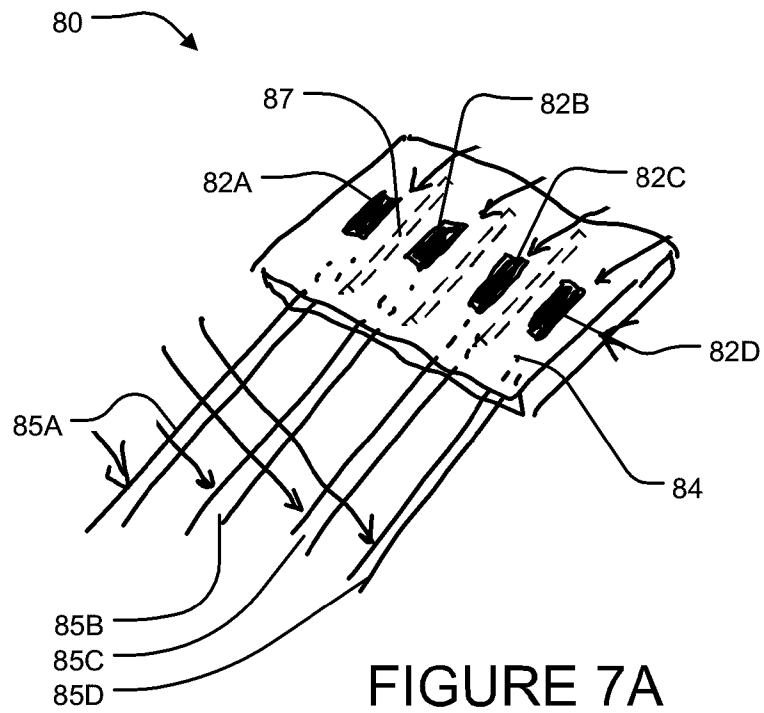


FIGURE 5C





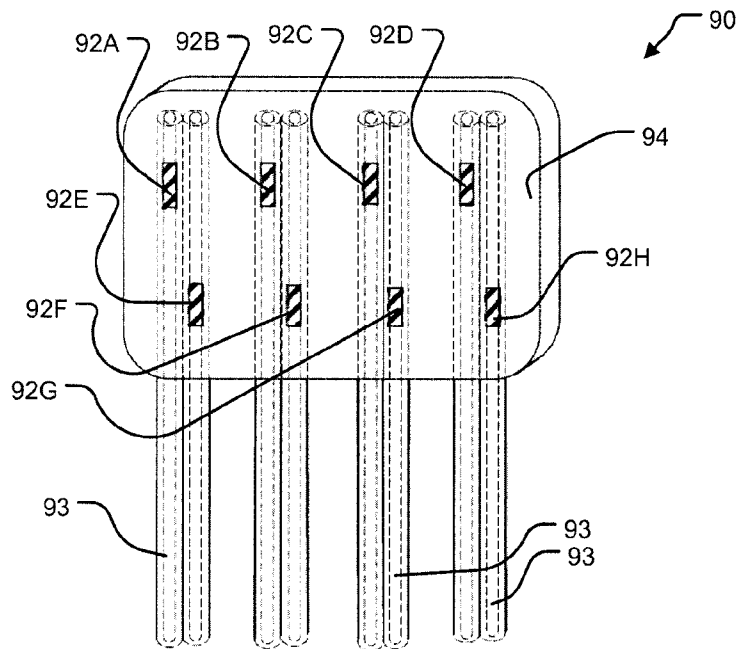


FIGURE 7C

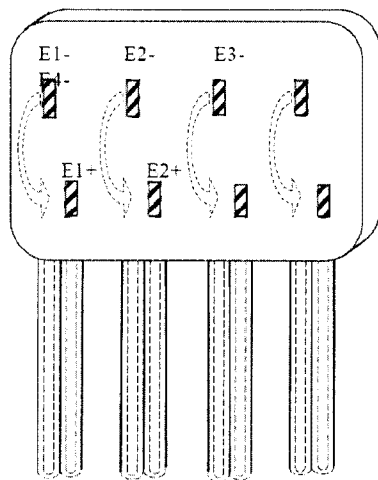


FIGURE 7D

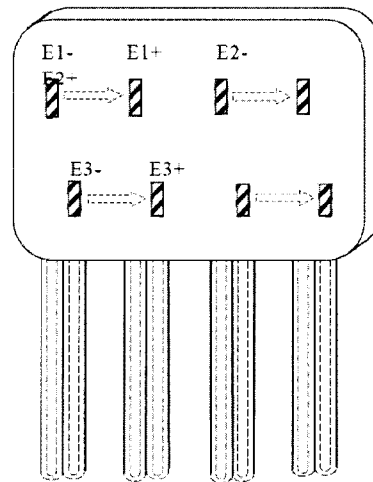


FIGURE 7E

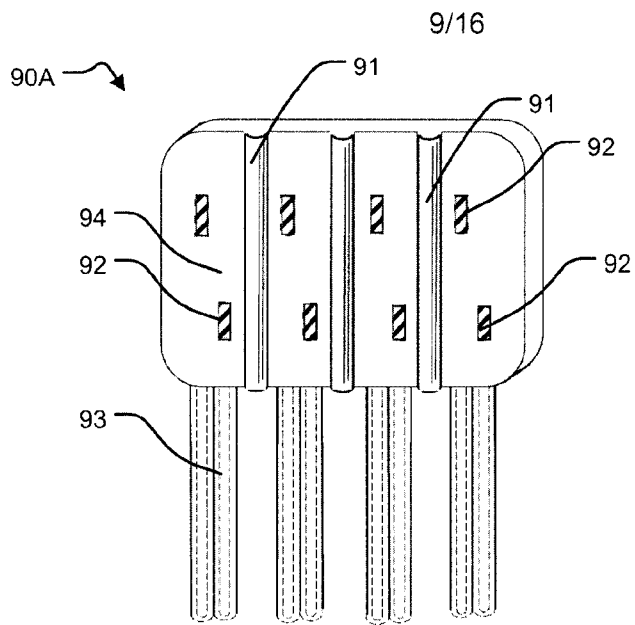


FIGURE 7F

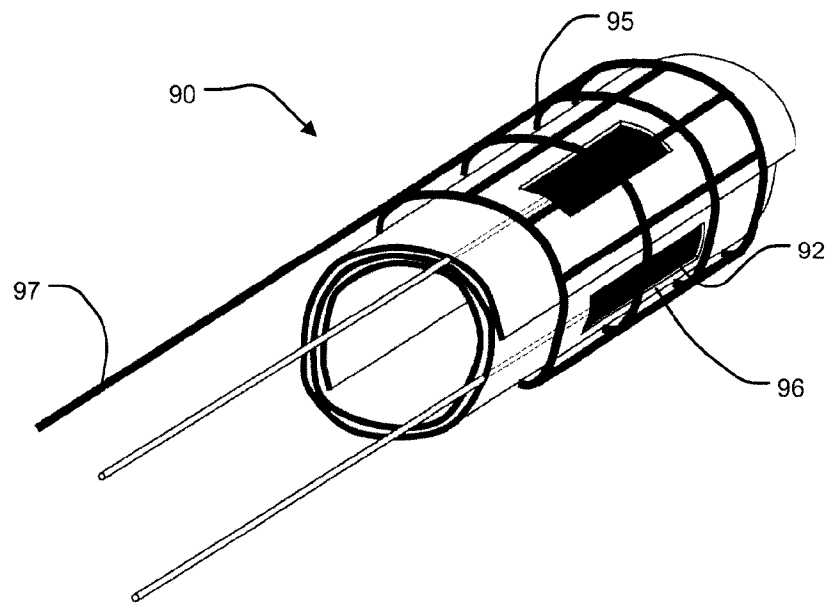


FIGURE 7G

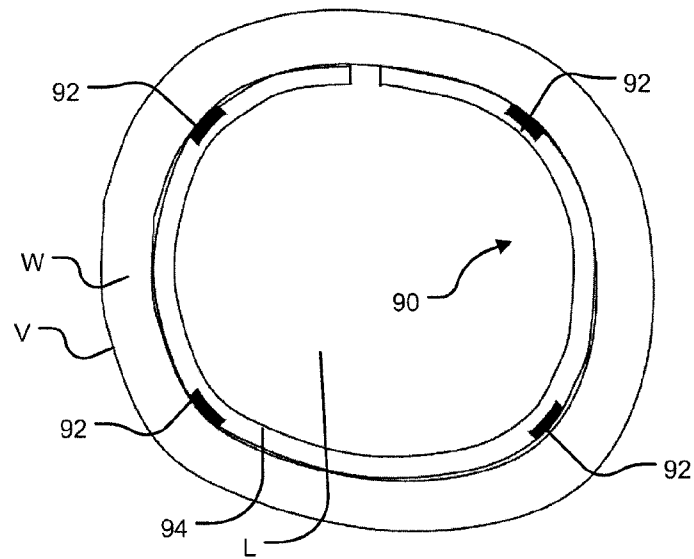


FIGURE 7H

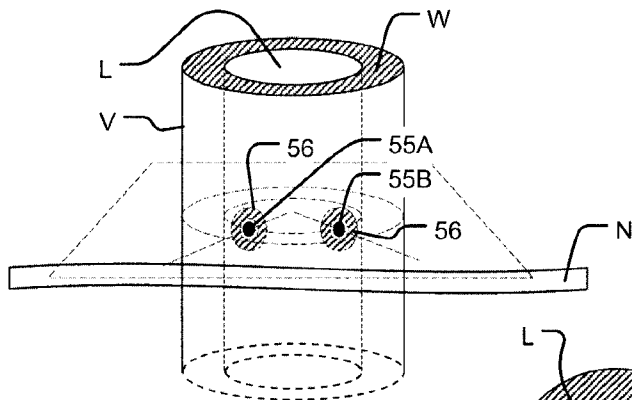


FIGURE 8A

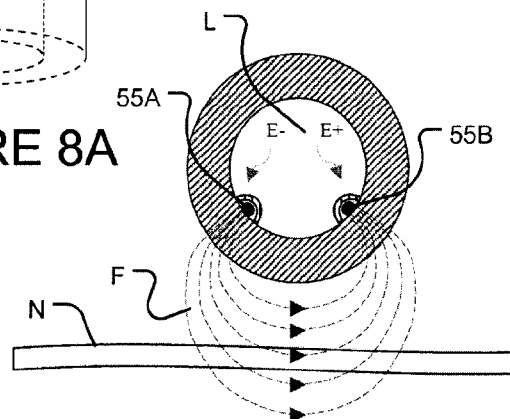


FIGURE 8B

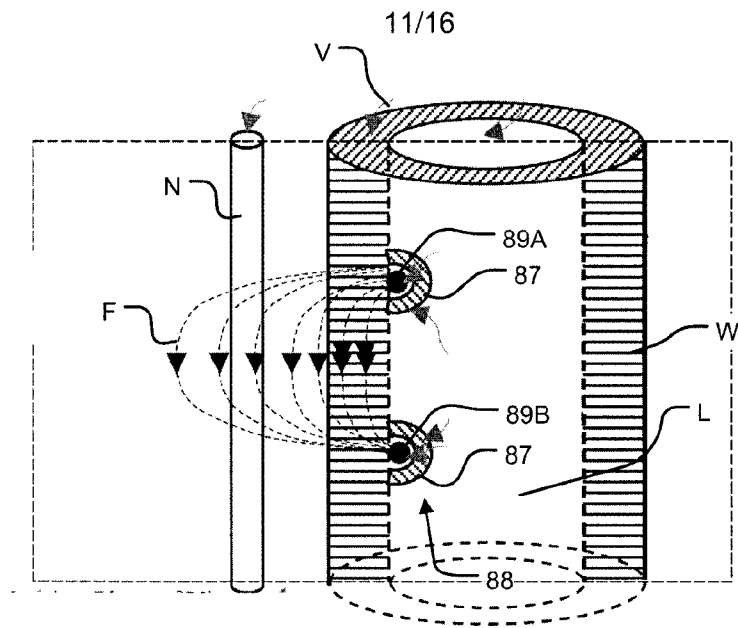


FIGURE 8C

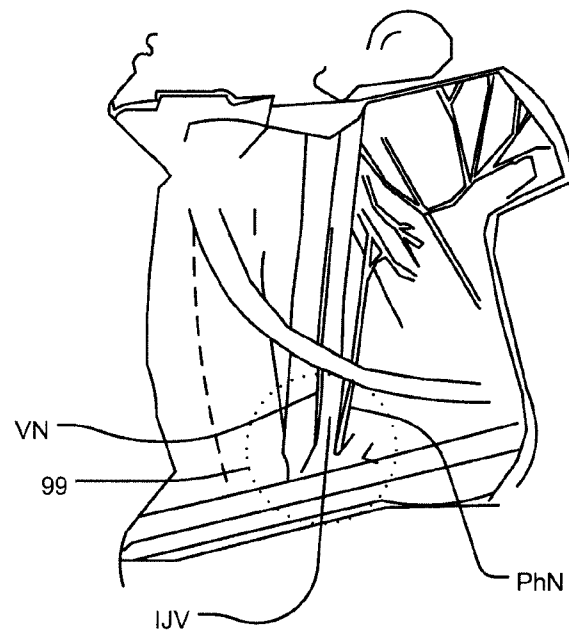


FIGURE 9
PRIOR ART



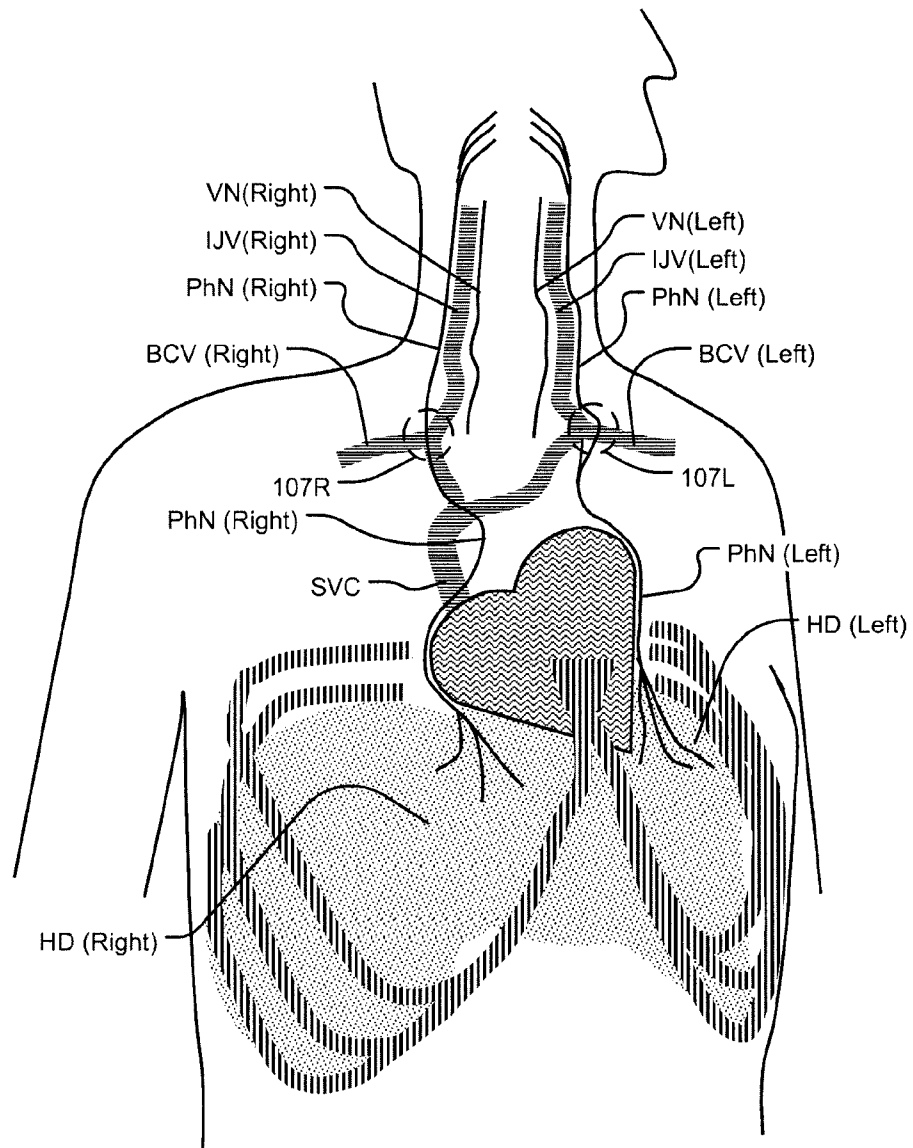


FIGURE 10A
PRIOR ART



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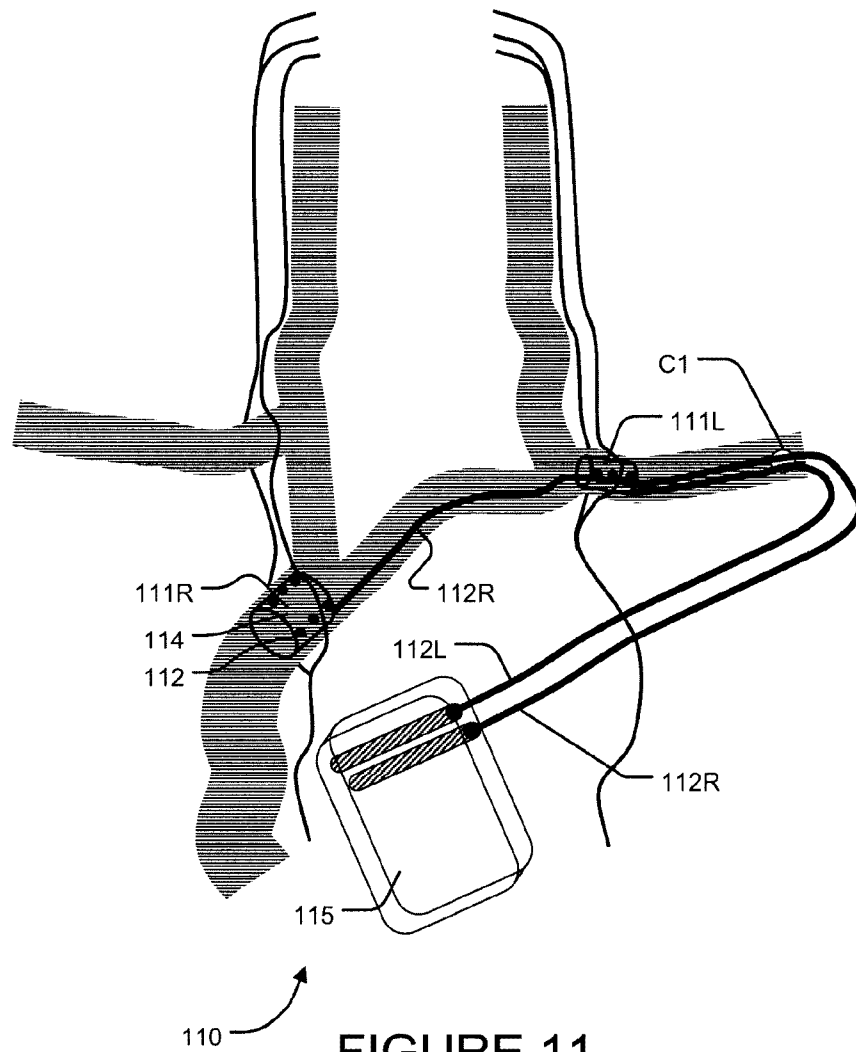


FIGURE 11

