

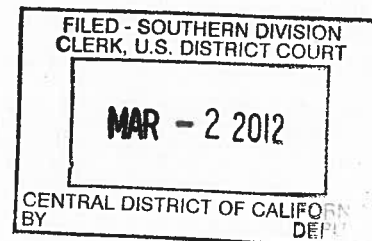
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Attorneys for Plaintiff MEDTRONIC, INC.



**UNITED STATES DISTRICT COURT  
FOR THE CENTRAL DISTRICT OF CALIFORNIA**

MEDTRONIC, INC.,

Plaintiff,

v.

EDWARDS LIFESCIENCES  
CORPORATION, EDWARDS  
LIFESCIENCES LLC, AND  
EDWARDS LIFESCIENCES  
(U.S.) INC.,

Defendants.

Case No. **SACV12-00327 CJC (MLGx)**

**COMPLAINT FOR PATENT  
INFRINGEMENT**

Plaintiff Medtronic, Inc. for its Complaint against Defendants Edwards Lifesciences Corporation, Edwards Lifesciences LLC, and Edwards Lifesciences (U.S.) Inc. (collectively "Edwards"), hereby states and alleges as follows:

**I.****INTRODUCTION**

1. This is an action for infringement by Defendants of United States patents owned by Medtronic, Inc.

2. Plaintiff Medtronic, Inc. is a corporation organized and existing under the laws of Minnesota, with its principal place of business in Minneapolis, Minnesota.

3. Upon information and belief, Defendant Edwards Lifesciences Corporation is a corporation organized and existing under the laws of Delaware with its principal place of business in Irvine, California.

4. Upon information and belief, Defendant Edwards Lifesciences LLC is a wholly-owned subsidiary of Edwards Lifesciences (U.S.) Inc. that is organized under the laws of Delaware with its principal place of business in Irvine, California.

5. Upon information and belief, Defendant Edwards Lifesciences (U.S.) Inc. is a wholly-owned subsidiary of Edwards Lifesciences Corporation that is organized under the laws of Delaware with its principal place of business in Irvine, California. Edwards Lifesciences Corporation, Edwards Lifesciences LLC and Edwards Lifesciences (U.S.) Inc. are collectively hereinafter referred to as "Edwards."

**II.****JURISDICTION AND VENUE**

6. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. § 1331 and § 1338(a) in that this action arises under the patent laws of the United States.

7. Venue is proper in this district pursuant to 28 U.S.C. §§ 1391(b), 1391(c) and 1400(b).

8. This Court has personal jurisdiction over the Defendants because, upon information and belief, Defendants conduct business within this judicial

1 district, and have their principal places of business within this judicial district.  
 2 Upon information and belief, Defendants are committing and will continue to  
 3 commit acts of patent infringement within this judicial district.

### 4 III.

#### 5 FACTUAL BACKGROUND

6 9. Plaintiff Medtronic, Inc. is the lawful owner of United States Patent  
 7 No. 8,036,741 ("the '741 Patent"), which was duly and legally issued by the United  
 8 States Patent and Trademark Office on October 11, 2011. The '741 Patent is  
 9 entitled "Method and System for Nerve Stimulation and Cardiac Sensing Prior to  
 10 and During a Medical Procedure." A copy of the '741 Patent is attached hereto as  
 11 Exhibit 1.

12 10. Plaintiff Medtronic, Inc. is the lawful owner of United States Patent  
 13 No. 7,184,829 ("the '829 Patent"), which was duly and legally issued by the United  
 14 States Patent and Trademark Office on February 27, 2007. The '829 Patent is  
 15 entitled "Method and System for Nerve Stimulation Prior to and During a Medical  
 16 Procedure." A copy of the '829 Patent is attached hereto as Exhibit 2.

17 11. Medtronic, Inc. has the exclusive right under the patent laws of the  
 18 United States to exclude others from making, using, offering for sale, selling, or  
 19 importing their patented inventions, including the right to bring this action for  
 20 injunctive relief, and accounting and damages.

### 21 IV.

#### 22 COUNT I

#### 23 (Claim for Patent Infringement of U.S. Patent No. 8,036,741)

24 12. Medtronic, Inc. hereby restates and re-alleges the allegations set forth  
 25 in Paragraphs 1 through 11 and incorporates them into this count by reference.

26 13. Upon information and belief Defendant Edwards manufactures or sells  
 27 in the Central District of California and elsewhere within the United States devices,  
 28 the use of which directly infringes, either literally or under the Doctrine of

1 Equivalents, one or more claims of the '741 Patent. Such devices include, but are  
2 not limited to, the SAPIEN Transcatheter Heart Valve, which Edwards co-markets  
3 with the Transfemoral RetroFlex 3 Delivery System.

4 14. Upon information and belief, Edwards has knowledge of the '741  
5 Patent, at least by the time of the filing and service of the Complaint in this action.

6 15. In conjunction with the sale of infringing devices and delivery  
7 systems, Defendant Edwards is acting with specific intent to actively induce  
8 purchasers and users of its devices to infringe, either literally or under the Doctrine  
9 of Equivalents, at least one claim of the '741 Patent.

10 16. Upon information and belief, and not by way of limitation, Edwards'  
11 SAPIEN Transcatheter Heart Valve and the Transfemoral RetroFlex 3 Delivery  
12 System are being used by surgeons or other physicians to directly infringe at least  
13 one claim of the '741 Patent. Edwards is intentionally and actively inducing  
14 purchasers and users of at least the SAPIEN Transcatheter Heart Valve and the  
15 Transfemoral RetroFlex 3 Delivery System to directly infringe by providing  
16 manuals, written instructions and other printed materials in the United States, as  
17 well as providing training and instruction in the United States in the use of the  
18 SAPIEN Transcatheter Heart Valve and the Transfemoral RetroFlex 3 Delivery  
19 System in a manner that infringes at least one claim of the '741 Patent.

20 17. The unlawful infringing activities by Defendant Edwards are  
21 continuing and will continue unless enjoined by this Court.

22 18. As a result of the infringing acts herein described, Medtronic, Inc. is  
23 sustaining damages and will continue to sustain damages in the future, including  
24 irreparable harm, unless Defendant Edwards is enjoined from infringing the '741  
25 Patent.

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**COUNT II****(Claim for Patent Infringement of U.S. Patent No. 7,184,829)**

19. Medtronic, Inc. hereby restates and re-alleges the allegations set forth in Paragraphs 1 through 11 and incorporates them into this count by reference.

20. Upon information and belief Defendant Edwards manufactures or sells in the Central District of California and elsewhere within the United States devices, the use of which directly infringes, either literally or under the Doctrine of Equivalents, one or more claims of the '829 Patent. Such devices include, but are not limited to, the SAPIEN Transcatheter Heart Valve, which Edwards co-markets with the Transfemoral RetroFlex 3 Delivery System.

21. Upon information and belief, Edwards has knowledge of the '829 Patent, at least by the time of the filing and service of the Complaint in this action.

22. In conjunction with the sale of infringing devices and delivery systems, Defendant Edwards is acting with specific intent to actively induce purchasers and users of its devices to infringe, either literally or under the Doctrine of Equivalents, at least one claim of the '829 Patent.

23. Upon information and belief, and not by way of limitation, Edwards' SAPIEN Transcatheter Heart Valve and the Transfemoral RetroFlex 3 Delivery System are being used by surgeons or other physicians to directly infringe at least one claim of the '829 Patent. Edwards is intentionally and actively inducing purchasers and users of at least the SAPIEN Transcatheter Heart Valve and the Transfemoral RetroFlex 3 Delivery System to directly infringe by providing manuals, written instructions and other printed materials in the United States, as well as providing training and instruction in the United States in the use of the SAPIEN Transcatheter Heart Valve and the Transfemoral RetroFlex 3 Delivery System in a manner that infringes at least one claim of the '829 Patent.

24. The unlawful infringing activities by Defendant Edwards are continuing and will continue unless enjoined by this Court.



ROBINS, KAPLAN, MILLER & CIRESI L.L.P.  
ATTORNEYS AT LAW  
LOS ANGELES

**DEMAND FOR JURY TRIAL**

Pursuant to Rule 38 of the Federal Rules of Civil Procedure, Plaintiff demands a jury trial as to all matters so triable.

Dated: March 2, 2012

**ROBINS, KAPLAN, MILLER & CIRESI L.L.P.**

By: 

David Martinez  
Lauren E. Wood  
Martin Lueck  
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# EXHIBIT “1”





US008036741B2

(12) **United States Patent**  
**Jahns et al.**

(10) **Patent No.:** **US 8,036,741 B2**  
(45) **Date of Patent:** **Oct. 11, 2011**

(54) **METHOD AND SYSTEM FOR NERVE STIMULATION AND CARDIAC SENSING PRIOR TO AND DURING A MEDICAL PROCEDURE**

(75) **Inventors:** **Scott E. Jahns**, Hudson, WI (US);  
**Michael R. S. Hill**, Minneapolis, MN (US); **James R. Keogh**, Maplewood, MN (US)

(73) **Assignee:** **Medtronic, Inc.**, Minneapolis, MN (US)

(\*) **Notice:** Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 74 days.

(21) **Appl. No.:** **12/557,950**

(22) **Filed:** **Sep. 11, 2009**

(65) **Prior Publication Data**  
US 2010/0004708 A1 Jan. 7, 2010

#### Related U.S. Application Data

(60) Continuation of application No. 11/796,663, filed on Apr. 27, 2007, now abandoned, which is a continuation of application No. 10/724,978, filed on Dec. 1, 2003, now Pat. No. 7,225,019, which is a continuation-in-part of application No. 10/207,725, filed on Jul. 29, 2002, now Pat. No. 6,718,208, which is a continuation-in-part of application No. 09/670,441, filed on Sep. 26, 2000, now Pat. No. 6,449,507, which is a continuation-in-part of application No. 09/433,323, filed on Nov. 3, 1999, now Pat. No. 6,266,564, which is a continuation of application No. 09/070,506, filed on Apr. 30, 1998, now Pat. No. 6,006,134, which is a continuation-in-part of application No. 08/640,013, filed on Apr. 30, 1996, now abandoned, said application No. 10/724,978 is a continuation-in-part of application No. 10/629,491, filed on Jul. 29, 2003, now abandoned, which is a division of application No. 09/669,355, filed on Sep. 26, 2000, now Pat. No. 6,628,987, said application No. 10/724,978 is a continuation-in-part of application No. 10/421,459, filed on Apr. 23, 2003, now Pat. No. 6,904,318, which is a continuation of application No. 09/669,961, filed on Sep. 26, 2000, now abandoned, said application No. 10/724,978 is a

continuation-in-part of application No. 10/657,353, filed on Sep. 8, 2003, now abandoned, which is a continuation of application No. 10/408,647, filed on Apr. 7, 2003, now abandoned, which is a continuation of application No. 09/670,440, filed on Feb. 20, 2001, now abandoned.

(51) **Int. Cl.**  
**A61N 1/362** (2006.01)  
(52) **U.S. Cl.** ..... 607/2; 607/3; 607/9; 607/10; 607/42  
(58) **Field of Classification Search** ..... 607/2-3, 607/9, 10, 14, 42  
See application file for complete search history.

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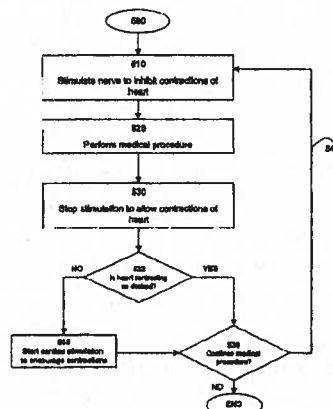
*Primary Examiner* — Scott Getzow

*Assistant Examiner* — Joseph M Dietrich

(57) **ABSTRACT**

A method of performing a medical procedure, such as surgery, is provided. A nerve is stimulated in order to adjust the beating of the heart to a first condition, such as a stopped or slowed condition. The medical procedure is performed on the heart or another organ. The stimulation of the nerve is stopped in order to adjust the beating of the heart to a second condition, such as a beating condition. The heart itself may also be stimulated to a beating condition, such as by pacing. The stimulation of the nerve may be continued in order to allow the medical procedure to be continued. A sensor to sense a characteristic of a fluid or tissue, such as an impending contraction, may be also used during the medical procedure. Systems and devices for performing the medical procedure are also provided.

**28 Claims, 14 Drawing Sheets**



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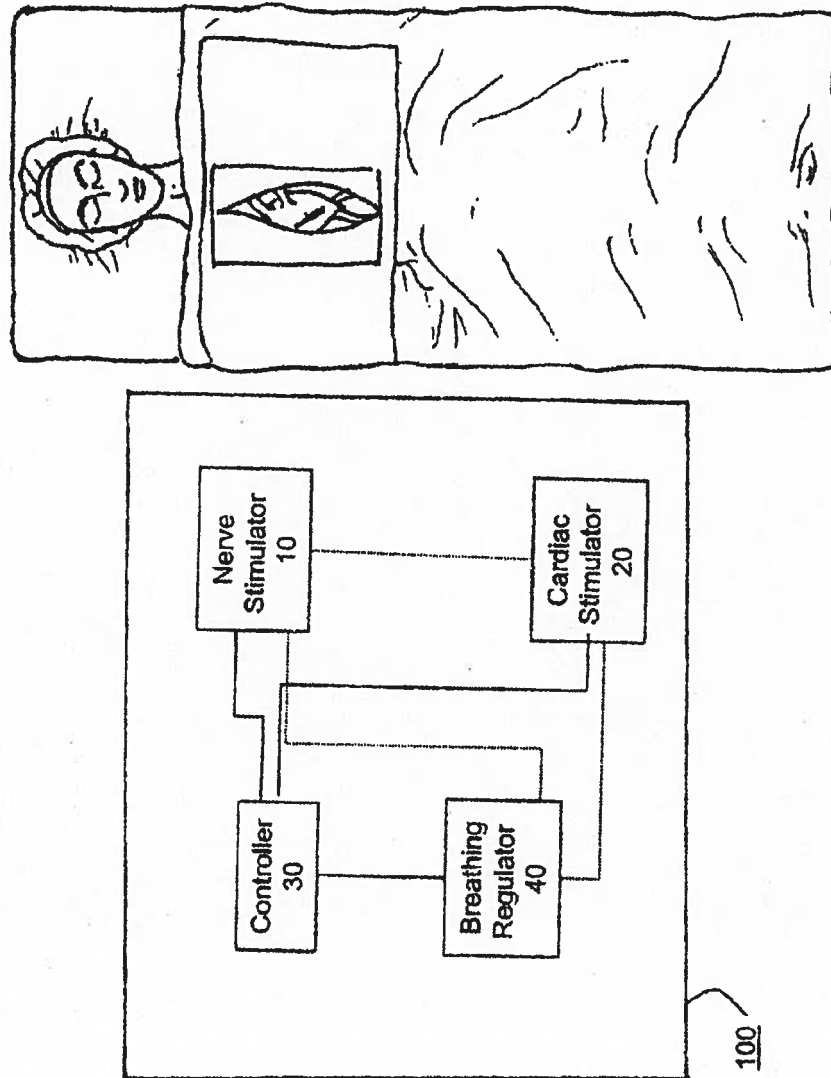
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**FIG. 1**



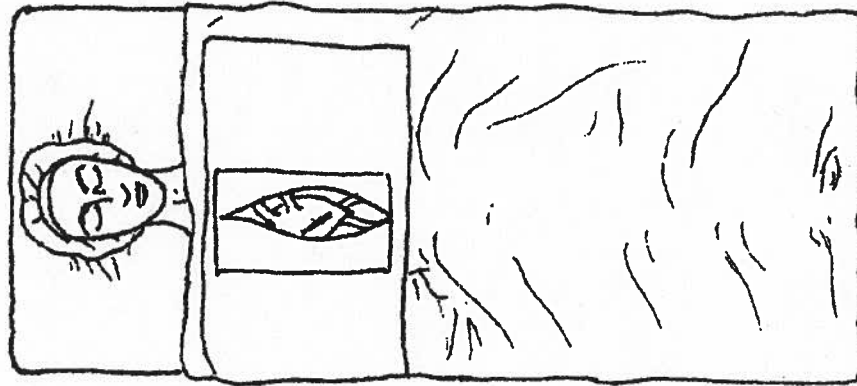
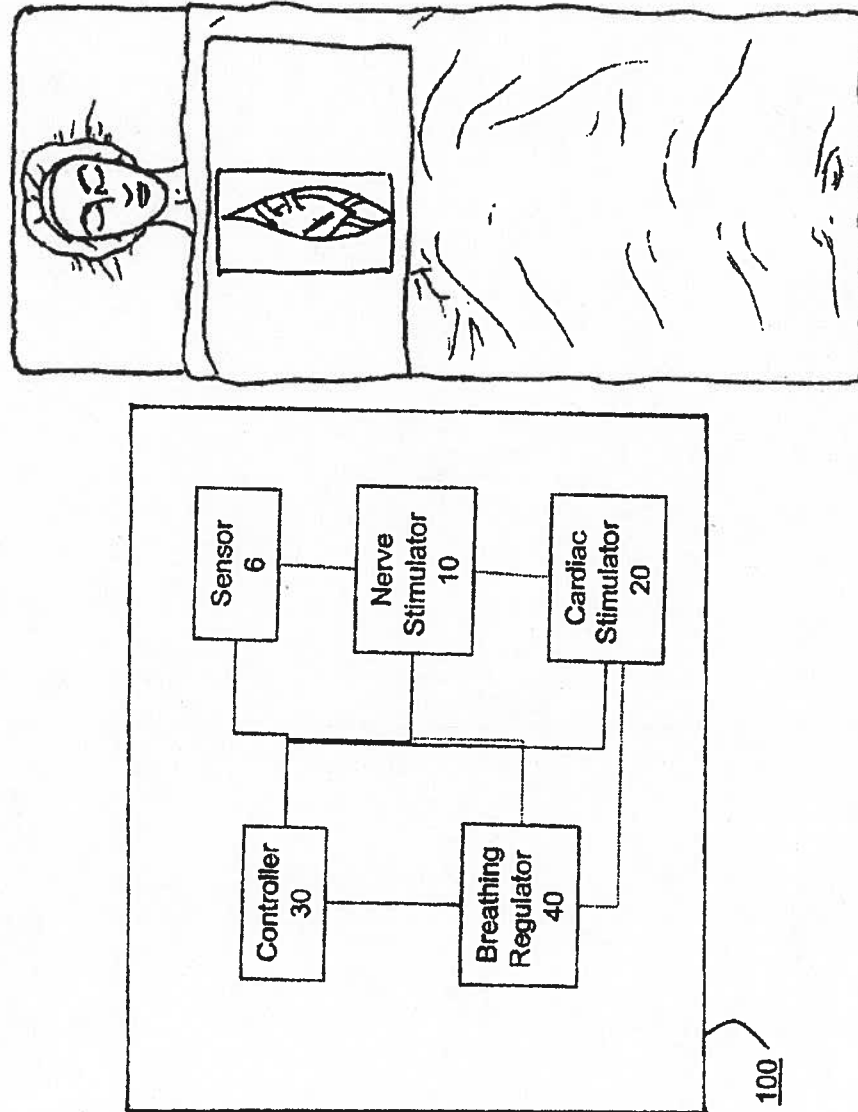
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**FIG. 2**



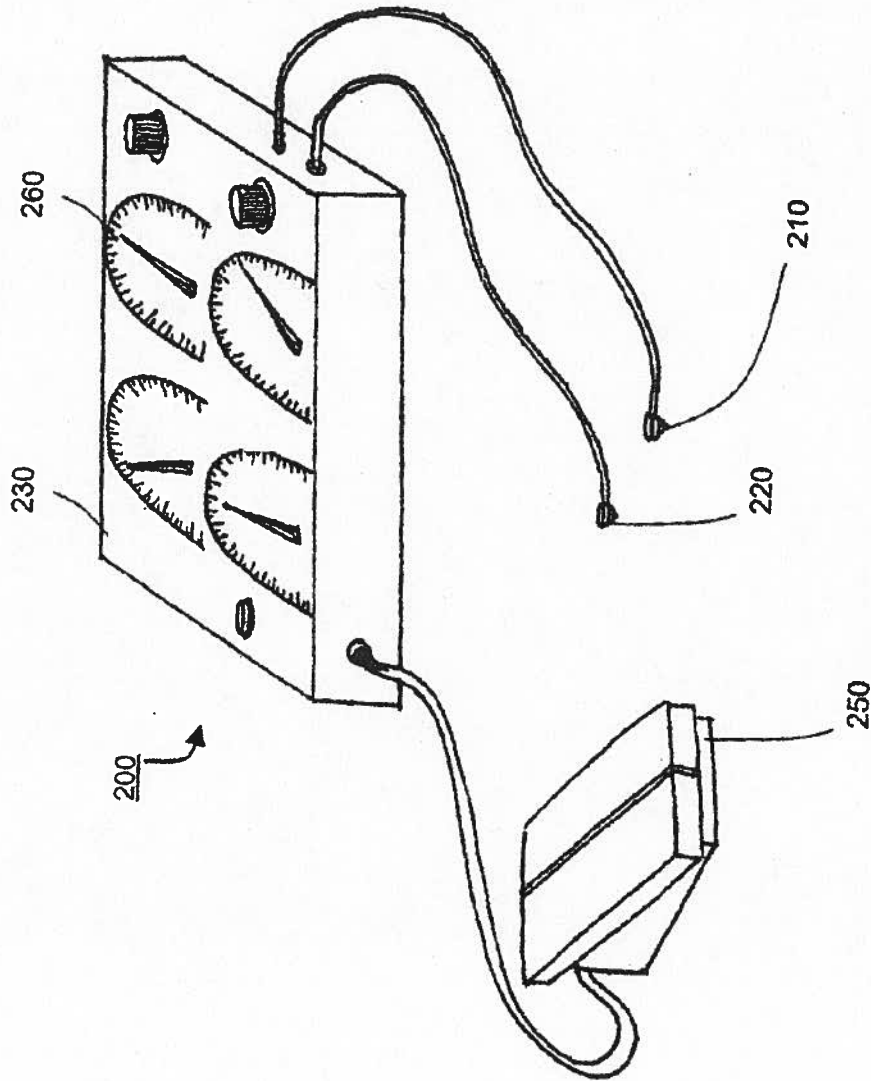
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**FIG. 3**



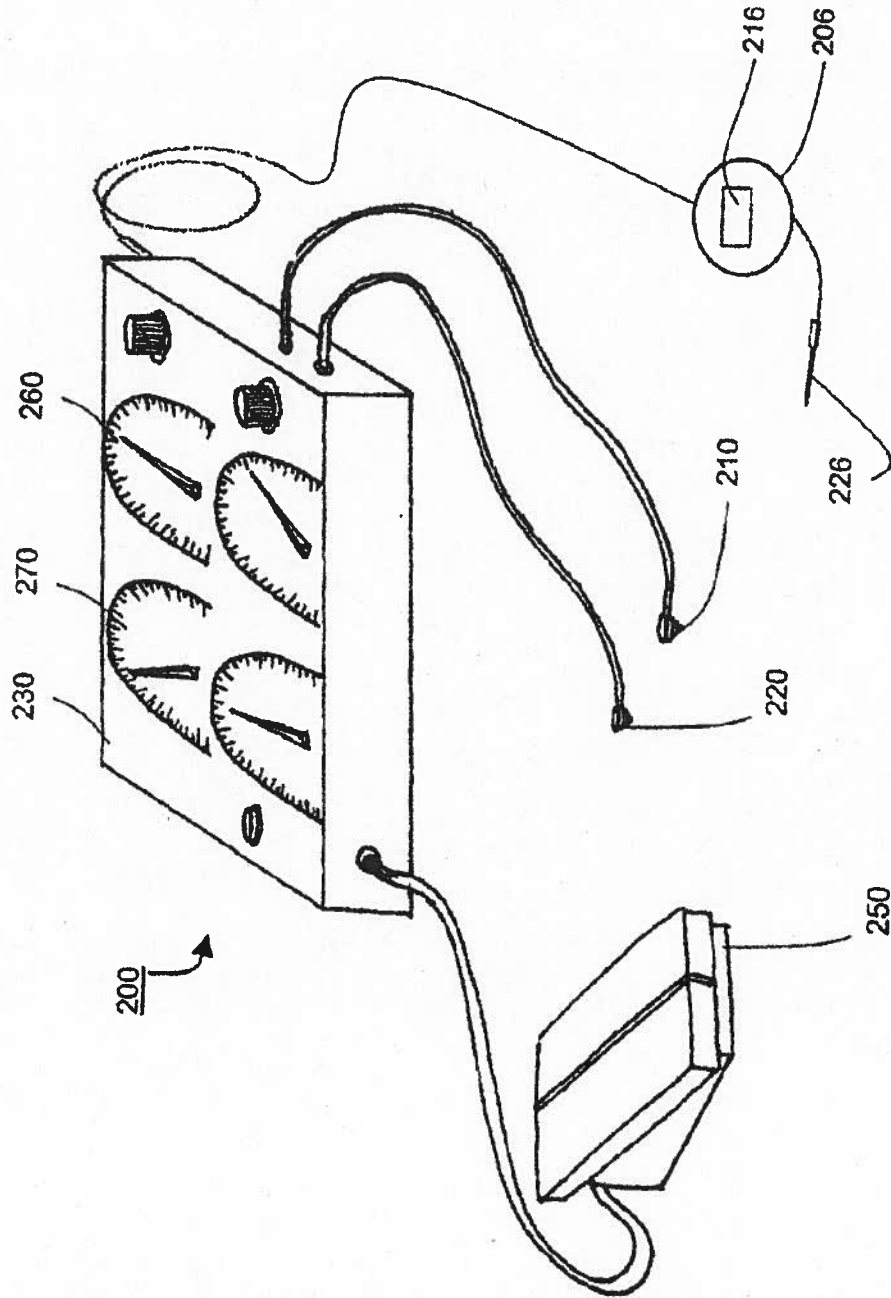
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**FIG. 4**





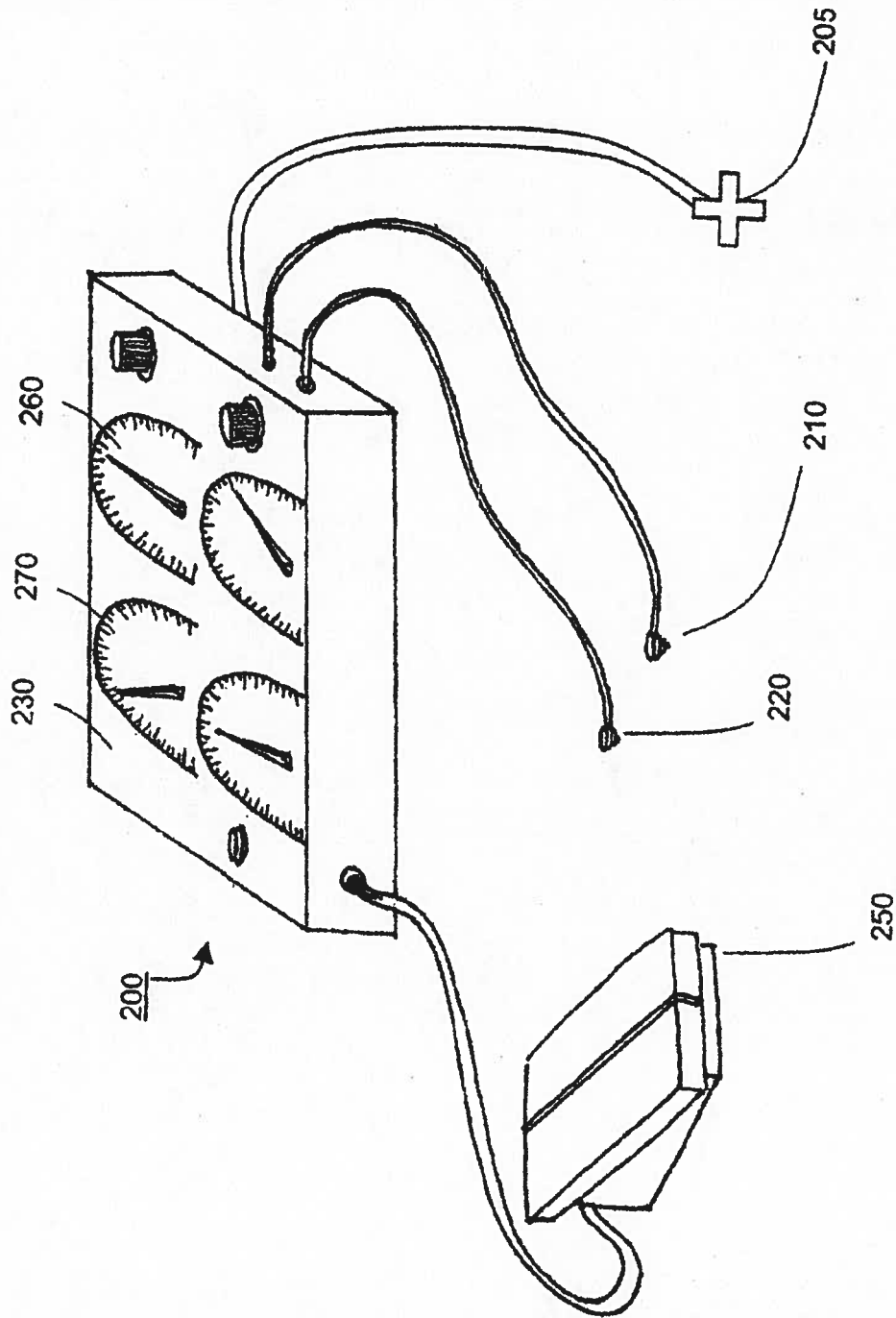
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**FIG. 5**



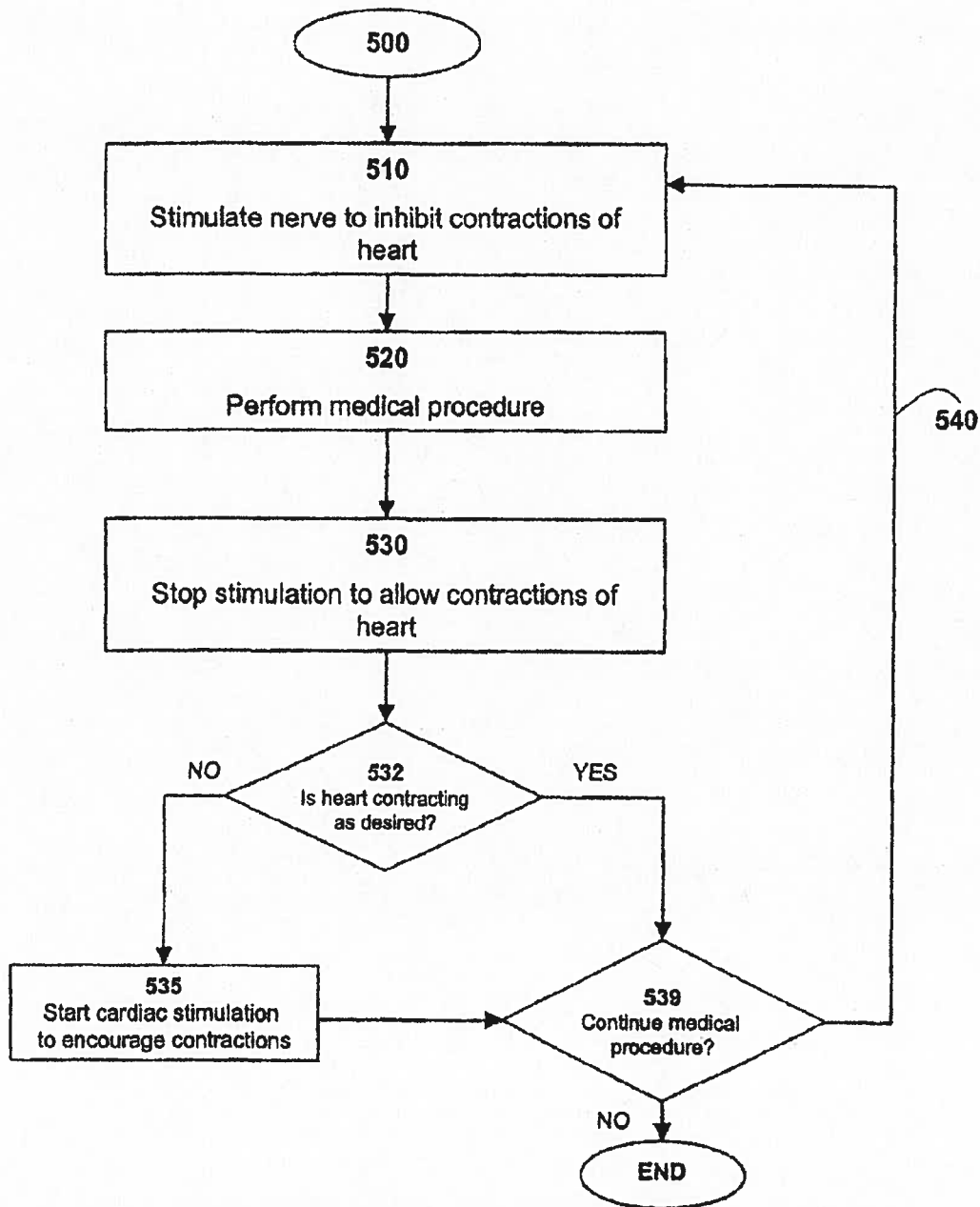
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FIG. 6



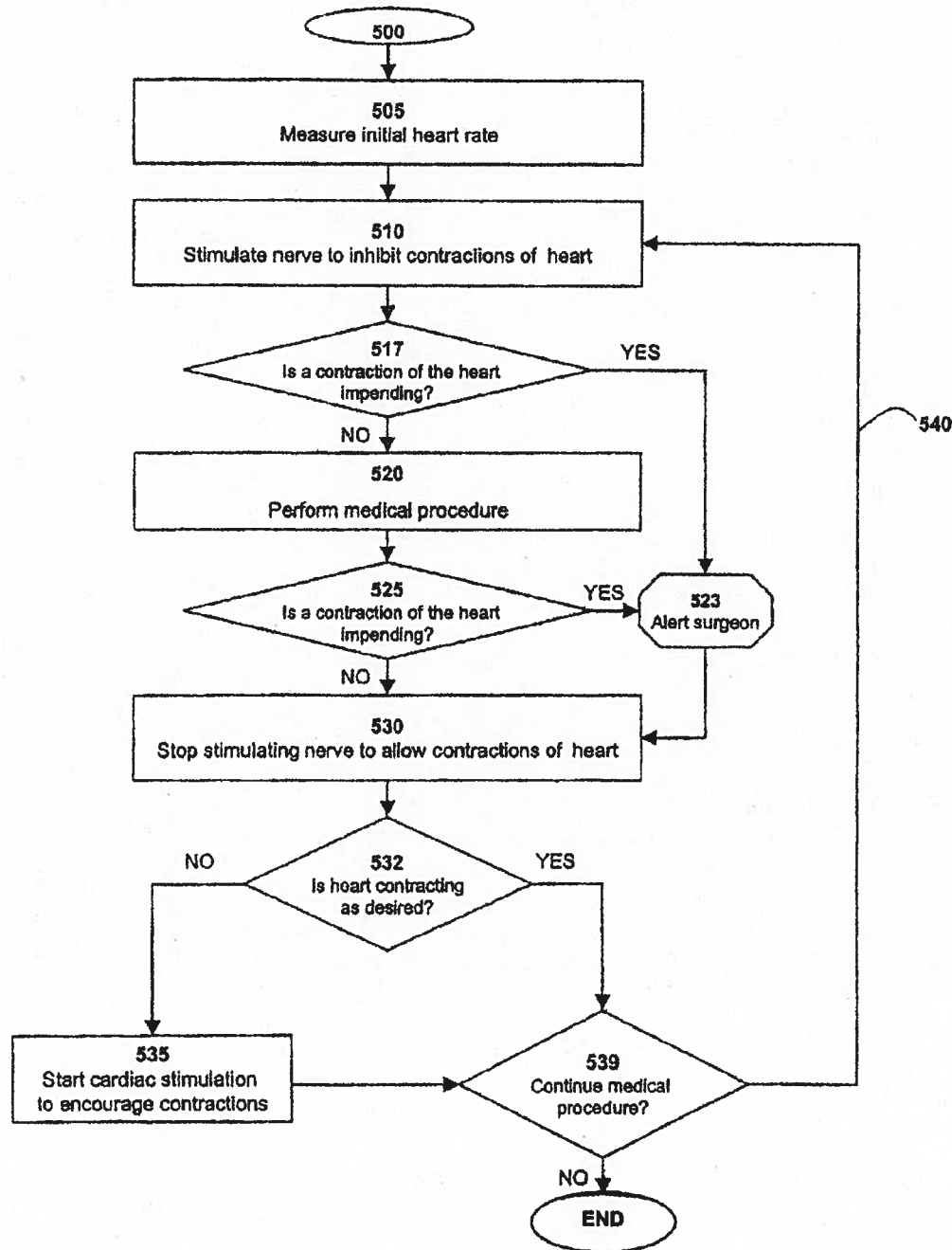
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Fig. 7

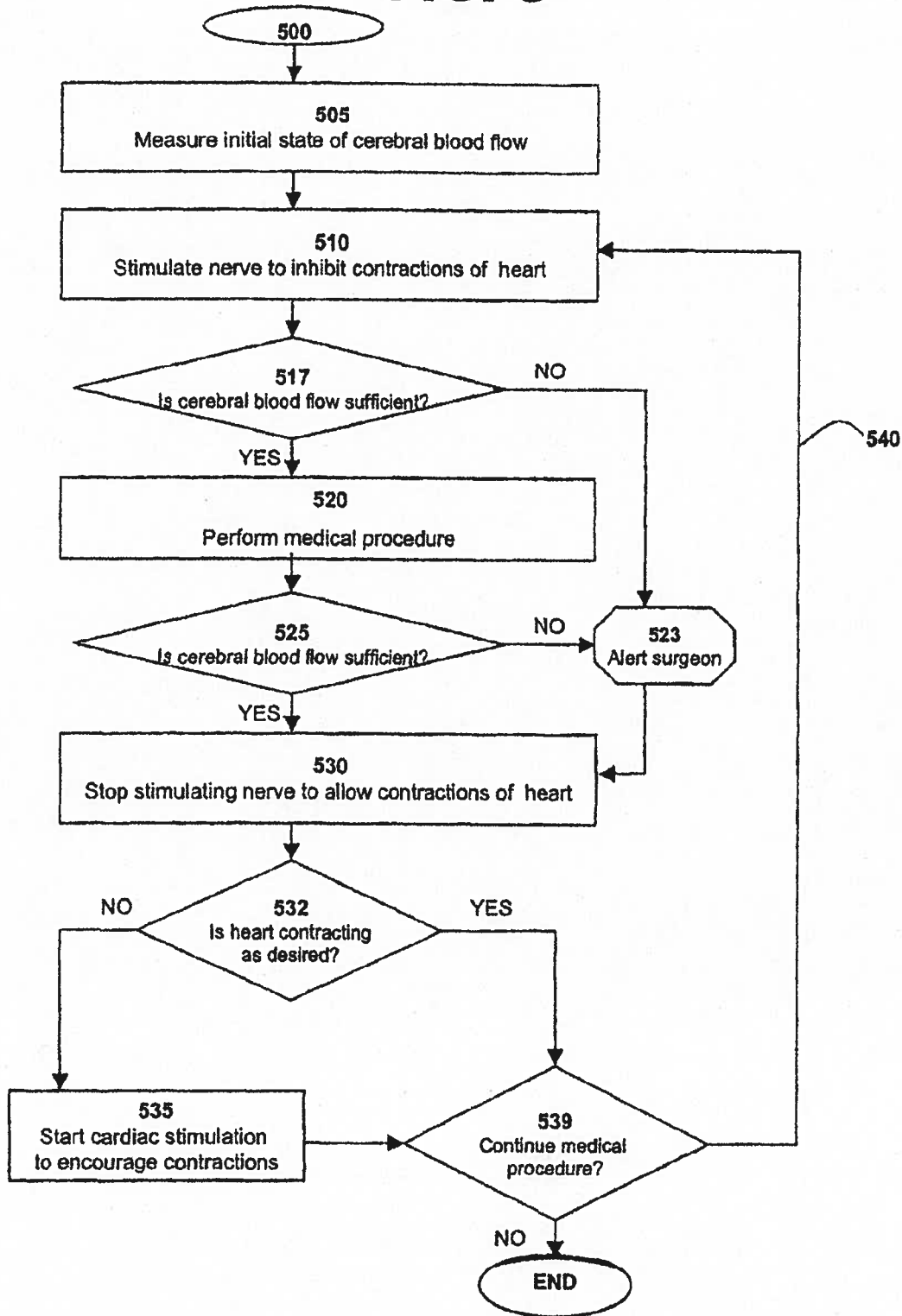


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**FIG. 8**

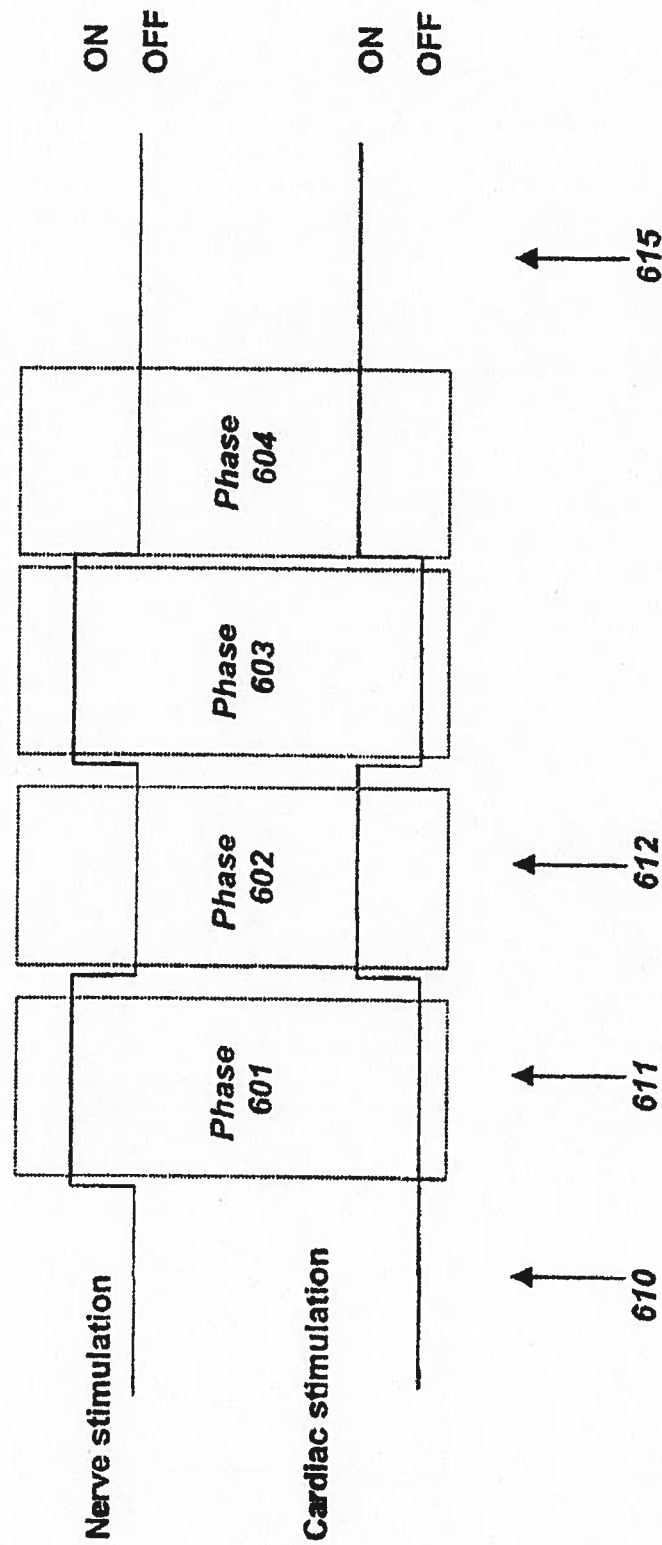
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**FIG. 9**





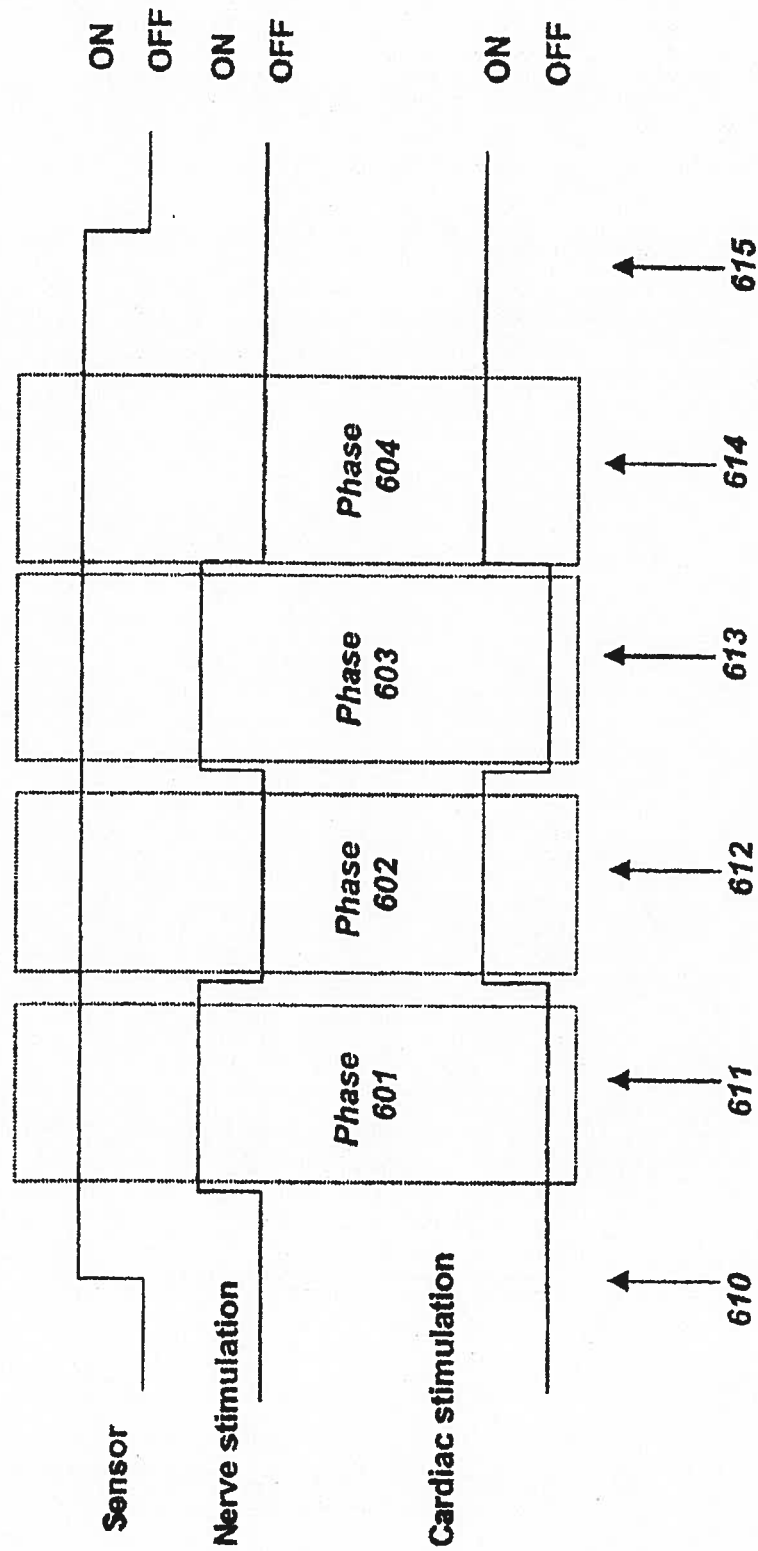
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FIG. 10



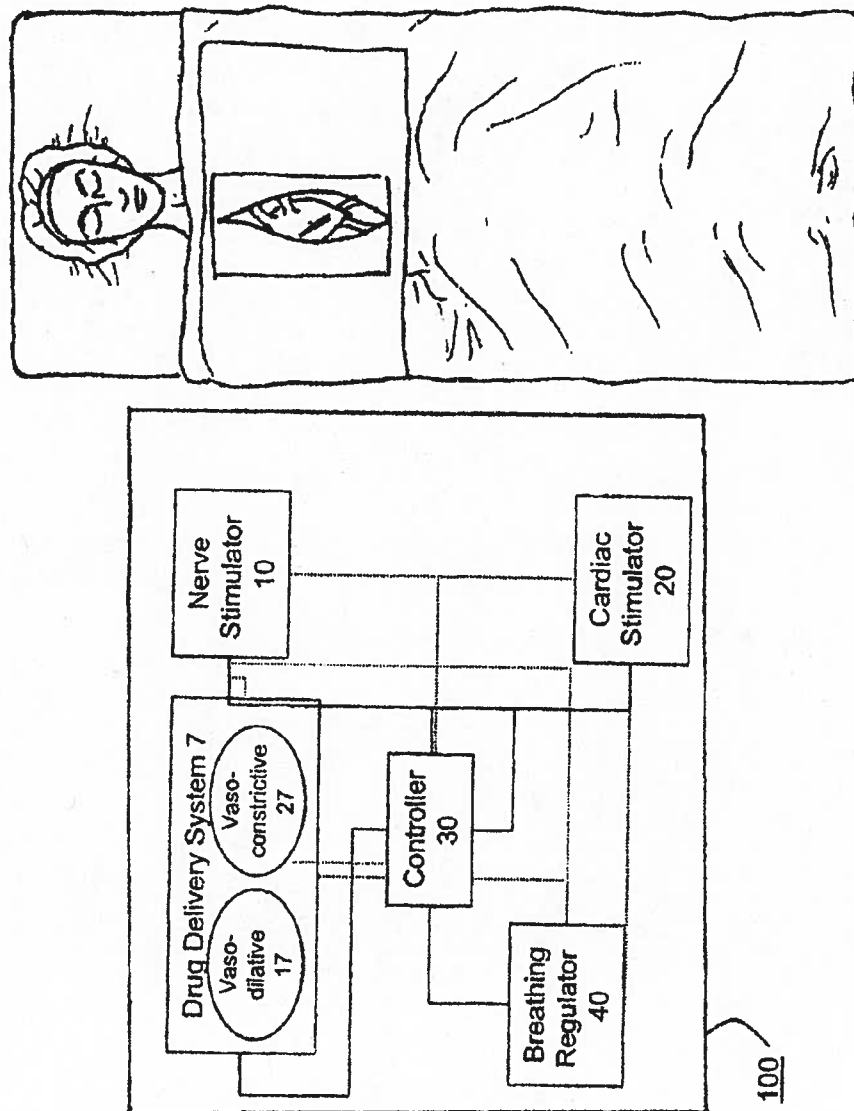
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**FIG. 11**



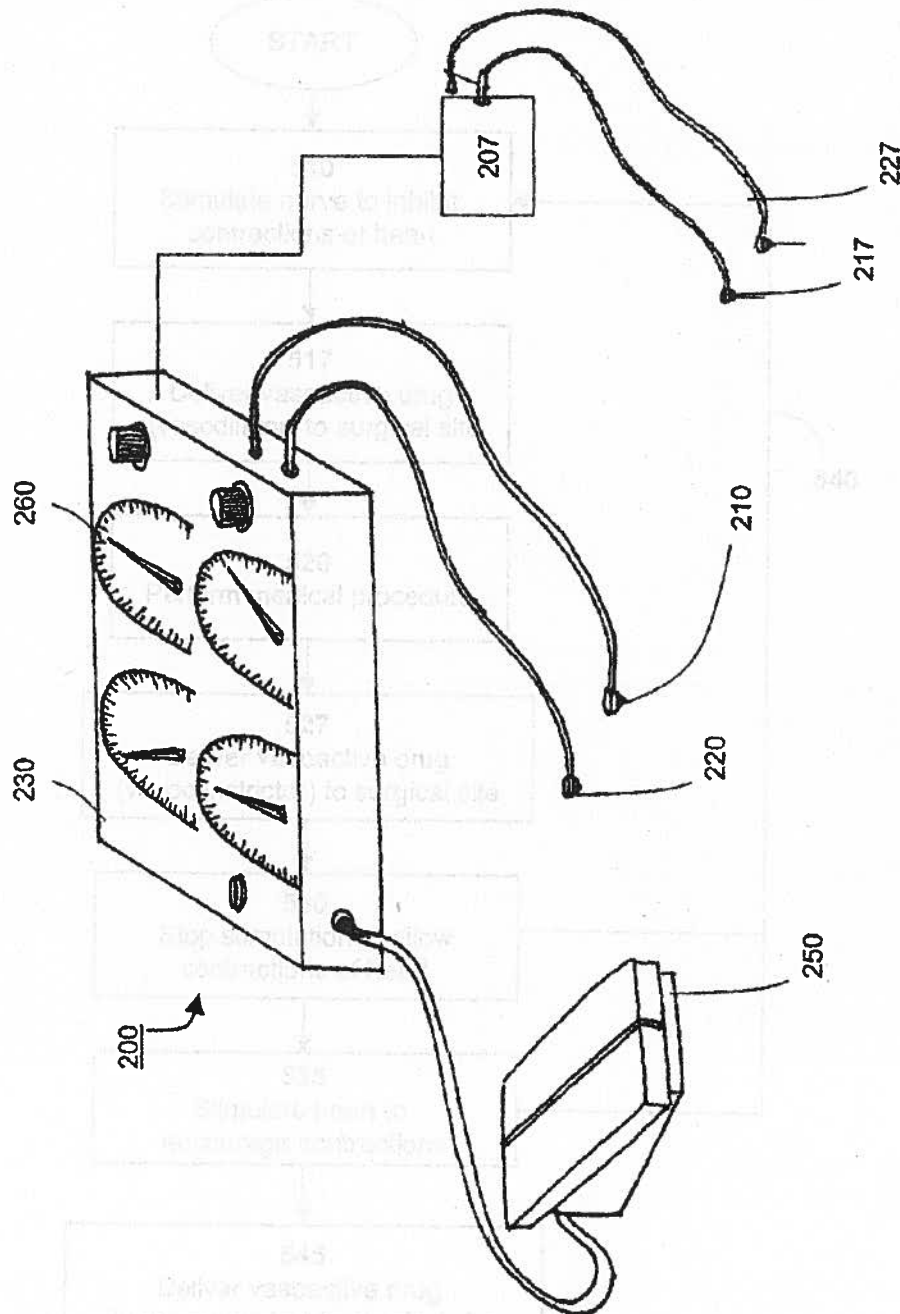
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FIG. 12



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# METHOD AND SYSTEM FOR NERVE STIMULATION AND CARDIAC SENSING PRIOR TO AND DURING A MEDICAL PROCEDURE

## CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. Ser. No. 11/796,663, filed Apr. 27, 2007, now abandoned, which is a continuation of U.S. Ser. No. 10/724,978, filed Dec. 1, 2003, now U.S. Pat. No. 7,225,019, which is a continuation-in-part of U.S. Ser. No. 10/207,725, filed Jul. 29, 2002, now U.S. Pat. No. 6,718,208, which is a continuation-in-part of U.S. Ser. No. 09/670,441, filed Sep. 26, 2000, now U.S. Pat. No. 6,449,507, which is a continuation-in-part of U.S. Ser. No. 09/433,323, filed Nov. 3, 1999, now U.S. Pat. No. 6,266,564, which is a continuation of U.S. Ser. No. 09/070,506, filed Apr. 30, 1998, now U.S. Pat. No. 6,006,134, which is a continuation-in-part of U.S. Ser. No. 08/640,013, filed Apr. 30, 1996, now abandoned. U.S. Ser. No. 10/724,978 is also a continuation-in-part of U.S. Ser. No. 10/629,491, filed Jul. 29, 2003, now abandoned, which is a divisional of U.S. Ser. No. 09/669,355, filed Sep. 26, 2000, now U.S. Pat. No. 6,628,987. U.S. Ser. No. 10/724,978 is also a continuation-in-part of U.S. Ser. No. 10/421,459, filed Apr. 23, 2003, now U.S. Pat. No. 6,904,318, which is a continuation of U.S. Ser. No. 09/669,961, filed Sep. 26, 2000, now abandoned. U.S. Ser. No. 10/724,978 is also a continuation-in-part of U.S. Ser. No. 10/657,353, filed Sep. 8, 2003, now abandoned, which is a continuation of U.S. Ser. No. 10/408,647, filed Apr. 7, 2003, now abandoned, which is a continuation of U.S. Ser. No. 09/670,440, filed Feb. 20, 2001, now abandoned.

## FIELD OF THE INVENTION

This invention relates to methods and systems for performing a medical procedure, especially a procedure during which it is necessary to adjust the beating of the heart in order to allow the medical procedure to be performed on the heart or another organ. More particularly, this invention relates to methods and systems of stimulating a nerve in order to modify the beating of a heart to allow a medical procedure to be performed or for blood flow to be controlled. This invention also relates to methods and systems for sensing imminent cardiac contractions during such a procedure. In addition, this invention relates to methods and systems for monitoring and controlling one or more physiological and/or chemical parameters of a fluid such as blood or oxygen in the systemic and/or pulmonary circulatory systems during a medical procedure.

## BACKGROUND OF THE INVENTION

The current leading cause of death in the United States is coronary artery disease in which the coronary arteries are blocked by atherosclerotic plaques or deposits of fat. The typical treatment to relieve a partially or fully blocked coronary artery is coronary artery bypass graft (CABG) surgery.

CABG surgery, also known as "heart bypass" surgery, generally entails using a graft to bypass the coronary obstruction. The procedure is generally lengthy, traumatic and subject to patient risks. Among the risk factors involved is the use of a cardiopulmonary bypass (CPB) circuit, also known as a "heart-lung machine," to pump blood and oxygenate the blood so that the patient's heart may be stopped during the surgery.

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Conventional CABG procedures are typically conducted on a stopped heart while the patient is on a (CPB) circuit. A stopped heart and a CPB circuit enables a surgeon to work in a bloodless, still operative field. However, there are a number of problems associated with CABG procedures performed while on CPB including the initiation of a systemic inflammatory response due to interactions of blood elements with the artificial material surfaces of the CPB circuit and global myocardial ischemia due to cardioplegic cardiac arrest. For these reasons, avoiding the use of CPB or cardioplegic cardiac arrest may help minimize post-operative complications.

One method, as disclosed in U.S. Pat. No. 5,651,378 to inventors Matheny and Taylor and in U.S. Pat. No. 5,913,876 to inventors Taylor et al., for facilitating coronary bypass surgery on a beating heart and thereby avoid the use of CPB and cardioplegic cardiac arrest includes stimulating the vagal nerve electrically in order to temporarily stop or substantially reduce the beating of the heart. This may be followed by pacing the heart to start its beating.

Another method, as disclosed in two published PCT applications, WO 99/09971 and WO 99/09973, both to inventor Puskas, involves stopping the beating of the heart during coronary bypass surgery using electrical stimulation of the vagal nerve in combination with administration of drugs.

Another method, as disclosed in U.S. Pat. No. 6,060,454 to inventor Duhaylongsod, involves stopping the beating of the heart during coronary bypass surgery via the local delivery of drugs to the heart.

Although it is desirable to stop the heart for a period of time in order to allow the surgeon to accomplish a required task without interference from heart movement, i.e. a motionless operative field, it is undesirable to have the heart stopped for too long a period of time since the body needs, among other things, a constant supply of oxygen. In fact, it is particularly important to maintain sufficient blood flow, and therefore oxygen flow, to the brain. A system for sensing biological parameters, such as the amount of blood flow or oxygen flow to the brain, could help determine whether these parameters are sufficient during a medical procedure. Stopping the heart for prolonged periods of time may cause damage to the patient.

Moreover, once stopped or still, the heart may still contract occasionally. This is sometimes referred to as an "escape beat." Such an "escape beat" may occur without any warning to the surgeon and the movement associated with the escape beat may interfere with the medical procedure being carried out.

In addition, the field in which the invention is to be performed may be limited in size. For example, when surgery is performed on a particular blood vessel, the vessel's size is usually quite small and a great deal of precision is required to perform the surgery or even to locate the vessel. Such precision requires more time during which the heart is stopped.

## SUMMARY OF THE INVENTION

One aspect of the present invention provides a method of performing a medical procedure wherein the method includes stimulating a nerve to adjust the beating of the heart to a first condition. A medical procedure is then performed on an organ. Stimulation of the nerve is then reduced to adjust the beating of a heart to a second condition. The nerve is then stimulated a subsequent time in order to re-adjust the beating of the heart to the first condition and then the medical procedure is continued. Nerve stimulation may be stopped to achieve the second condition. The first condition may be a stopped or a slowed condition. The second condition may be



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a beating condition. The heart may also be stimulated to adjust the beating of the heart to the second condition. The heart may be stimulated by pacing.

Another aspect of the present invention provides a system for performing a medical procedure wherein the system includes a nerve stimulator to inhibit beating of the heart and a cardiac stimulator in communication with the nerve stimulator to stimulate beating of the heart. The system may also include drug delivery means for delivering at least one drug during the medical procedure.

Another aspect of the present invention provides a device for performing a medical procedure wherein the device includes a processor connected to a nerve stimulation electrode and a cardiac stimulation electrode. The processor processes output from the nerve stimulation electrode and adjusts output from the cardiac stimulation electrode based on output from the nerve stimulation electrode. Stimulation from the nerve stimulation electrode may occur in an inverse relationship to stimulation from the cardiac stimulation electrode.

Another aspect of the present invention provides a system for performing a medical procedure wherein the system includes a sensor to sense a biological characteristic, a nerve stimulator to inhibit beating of a heart when the sensor senses the biological characteristic at a first value and a cardiac stimulator to stimulate beating of the heart when the sensor senses the biological characteristic at a second value.

The biological characteristic may be a chemical characteristic of a tissue, a chemical characteristic of a fluid, a physical characteristic of a tissue, a physical characteristic of a fluid, a physiological characteristic of a tissue, and a physiological characteristic of a fluid. The biological characteristic may be a characteristic of a body component such as the blood, cardiac tissue, or a nerve. The biological characteristic may be fluid flow, fluid pressure, mechanical pressure, temperature, electrical current, temperature, chemical concentration, presence of a peptide, concentration of a peptide, presence of a protein, concentration of a protein, a metabolic process, presence of a gas, concentration of a gas, presence of oxygen, concentration of an oxygen, presence of carbon dioxide, concentration of carbon dioxide.

The system may also include drug delivery means such as a spray, a cream, an ointment, a medicament, a pill, a patch, a catheter, a cannula, a needle and syringe, a pump, and an iontophoretic drug delivery device to deliver at least one drug during the procedure. The drug may be a beta-blocker, a cholinergic agent, a cholinesterase inhibitor, a calcium channel blocker, a sodium channel blocker, a potassium channel agent, adenosine, an adenosine receptor agonist, an adenosine deaminase inhibitor, dipyridamole, a monoamine oxidase inhibitor, digoxin, digitalis, lignocaine, a bradykinin agent, a serotonergic agonist, an antiarrhythmic agent, a cardiac glycoside, a local anesthetic, atropine, a calcium solution, an agent that promotes heart rate, an agent that promotes heart contractions, dopamine, a catecholamine, an inotrope glucagon, a hormone, forskolin, epinephrine, norepinephrine, thyroid hormone, a phosphodiesterase inhibitor, prostacyclin, prostaglandin and a methylxanthine, may be delivered during the procedure. The drug may be naturally occurring or chemically synthesized.

The nerve stimulator may stimulate a nerve such as a vagal nerve, a carotid sinus nerve, a fat pad. The nerve stimulator may be stopped automatically when the sensor senses the biological characteristic at the second value. Cardiac stimulation may begin automatically when the sensor senses the biological characteristic at the second value. The nerve stimulator may be, for example, one or more electrodes such as

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nerve stimulation electrodes, endotracheal electrodes, endoesophageal electrodes, intravascular electrodes, transcutaneous electrodes, intracutaneous electrodes, balloon-type electrodes, basket-type electrodes, umbrella-type electrodes, tape-type electrodes, suction-type electrodes, screw-type electrodes, barb-type electrodes, bipolar electrodes, monopolar electrodes, metal electrodes, wire electrodes, patch electrodes, cuff electrodes, clip electrodes, needle electrodes and probe electrodes.

The sensor may be an imaging system, an electrical sensor; a chemical sensor, an electromagnetic interference sensor, an electrochemical sensor; a pressure sensor, a sound wave sensor; a magnetic sensor; an ultraviolet sensor; a visible light sensor; an infrared sensor; a radiation sensor; a flow sensor; a temperature sensor, a gas sensor, an optical sensor, a pH sensor, a potentiometric sensor, a fluorescence sensor and a biosensor.

The cardiac stimulator may be, for example, one or more electrodes such as cardiac stimulation electrodes, clip electrodes, needle electrodes, probe electrodes, pacing electrodes, epicardial electrodes, patch electrodes, intravascular electrodes, balloon-type electrodes, basket-type electrodes, tape-type electrodes, umbrella-type electrodes, suction-type electrodes, endotracheal electrodes, endoesophageal electrodes, transcutaneous electrodes, intracutaneous electrodes, screw-type electrodes, barb-type electrodes, bipolar electrodes, monopolar electrodes, metal electrodes, wire electrodes and cuff electrodes.

The system may also include a breathing regulator, which may control a respirator. The breathing regulator may stimulate a phrenic nerve. The breathing regulator may be, for example, one or more electrodes such as nerve stimulation electrodes, endotracheal electrodes, endoesophageal electrodes, intravascular electrodes, transcutaneous electrodes, intracutaneous electrodes, balloon-type electrodes, basket-type electrodes, umbrella-type electrodes, tape-type electrodes, suction-type electrodes, screw-type electrodes, barb-type electrodes, bipolar electrodes, monopolar electrodes, metal electrodes, wire electrodes, patch electrodes, cuff electrodes, clip electrodes, needle electrodes and probe electrodes.

The medical procedure may be a surgical procedure, a non-surgical procedure, a fluoroscopic procedure, a cardiac procedure, a vascular procedure, a neurosurgical procedure, an electrophysiological procedure, a diagnostic procedure, a therapeutic procedure, an ablation procedure, an endovascular procedure, a liver procedure, a spleen procedure, a pulmonary procedure, an aneurysm repair, an imaging procedure, a CAT scan procedure, a MRI procedure, a pharmacological therapy, a drug delivery procedure, biological delivery procedure, a genetic therapy, a cellular therapy, a cancer therapy, a radiation therapy, a transplantation procedure, a coronary angioplasty procedure, a stent delivery procedure, an atherectomy procedure, a procedure that requires precise control of cardiac motion, a procedure that requires precise control of bleeding, a non-invasive procedure, a minimally invasive procedure, an invasive procedure, a port-access, an endoscopic procedure, a sternotomy procedure, a thoracotomy procedure and a robotic procedure.

Another aspect of the present invention provides a method for performing a medical procedure wherein a biological characteristic is sensed at a first value and a first signal related to the sensed biological characteristic is sent. Beating of a heart is inhibited in response to the first signal. The medical procedure is then performed. The biological characteristic is then sensed at a second value and a second signal related to



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the sensed biological characteristic at the second value is sent. Beating of the heart is stimulated in response to the second signal.

Beating of the heart may be inhibited automatically in response to the first signal. Beating of the heart may be stimulated automatically in response to the second signal. At least one drug may be delivered during the medical procedure. A nerve may be stimulated to inhibit beating of the heart. Breathing may be stopped while beating of the heart is inhibited. Breathing may be stopped automatically.

The biological characteristic may be a characteristic of blood, a characteristic of cardiac tissue, a characteristic of a nerve, a fluid flow characteristic, a pressure characteristic, a temperature characteristic, an electrical characteristic, a chemical concentration, a presence of a peptide, a concentration of a peptide, a presence of a protein, a concentration of a protein, a component of a metabolic process, a presence of a gas, a concentration of a gas, a presence of oxygen, a concentration of an oxygen, a presence of carbon dioxide, a concentration of carbon dioxide, a chemical characteristic, a physiological characteristic, and a physiological characteristic.

Another aspect of the present invention provides a device for performing a medical procedure wherein the device includes a processor, a sensor to sense a biological characteristic and at least one nerve stimulation electrode. The processor receives a signal from the sensor and adjusts output from the nerve stimulation electrode in response to the signal.

The sensor may be an imaging system, an electrical sensor; a chemical sensor, an electromagnetic interference sensor, an electrochemical sensor; a pressure sensor, a sound wave sensor; a magnetic sensor; an ultraviolet sensor; a visible light sensor; an infrared sensor; a radiation sensor; a flow sensor; a temperature sensor, a gas sensor, an optical sensor, a pH sensor, a potentiometric sensor, a fluorescence sensor and a biosensor.

The nerve stimulation electrode may be one or more electrodes such as endotracheal electrodes, endoesophageal electrodes, intravascular electrodes, transcutaneous electrodes, intracutaneous electrodes, balloon-type electrodes, basket-type electrodes, umbrella-type electrodes, tape-type electrodes, suction-type electrodes, screw-type electrodes, barb-type electrodes, bipolar electrodes, monopolar electrodes, metal electrodes, wire electrodes, patch electrodes, cuff electrodes, clip electrodes, needle electrodes and probe electrodes.

The device may include a cardiac stimulation electrode to stimulate beating of the heart. The processor receives a signal from the sensor and adjusts output from the cardiac stimulation electrode in response to the signal. The cardiac electrode may be, for example, one or more electrodes such as clip electrodes, needle electrodes, probe electrodes, pacing electrodes, epicardial electrodes, patch electrodes, intravascular electrodes, balloon-type electrodes, basket-type electrodes, tape-type electrodes, umbrella-type electrodes, suction-type electrodes, endotracheal electrodes, endoesophageal electrodes, transcutaneous electrodes, intracutaneous electrodes, screw-type electrodes, barb-type electrodes, bipolar electrodes, monopolar electrodes, metal electrodes, wire electrodes and cuff electrodes.

The device may also include a breathing regulation electrode for controlling breathing. The processor adjusts the output from the breathing regulation electrode in response to the signal. The breathing regulation electrode may be, one or more electrodes such as nerve stimulation electrodes, endotracheal electrodes, endoesophageal electrodes, intravascular electrodes, transcutaneous electrodes, intracutaneous electrodes, balloon-type electrodes, basket-type electrodes,

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umbrella-type electrodes, tape-type electrodes, suction-type electrodes, screw-type electrodes, barb-type electrodes, bipolar electrodes, monopolar electrodes, metal electrodes, wire electrodes, patch electrodes, cuff electrodes, clip electrodes, needle electrodes and probe electrodes.

The device may also include a drug pump for delivering at least one drug. The processor adjusts the output of the drug. The drug may be, for example, a beta-blocker, a cholinergic agent, a cholinesterase inhibitor, a calcium channel blocker, a sodium channel blocker, a potassium channel agent, adenosine, an adenosine receptor agonist, an adenosine deaminase inhibitor, dipyridamole, a monoamine oxidase inhibitor, digoxin, digitalis, lignocaine, a bradykinin agent, a serotonergic agonist, an antiarrhythmic agent, a cardiac glycoside, a local anesthetic, atropine, a calcium solution, an agent that promotes heart rate, an agent that promotes heart contractions, dopamine, a catecholamine, an inotrope glucagon, a hormone, forskolin, epinephrine, norepinephrine, thyroid hormone, a phosphodiesterase inhibitor, prostacyclin, prostaglandin and a methylxanthine.

Another aspect of the present invention provides a system for performing a medical procedure wherein the system includes a sensor to sense a state of a cardiac tissue and an indicator to indicate the state of the cardiac tissue. The system may also include a nerve stimulator in communication with the sensor to inhibit beating of a heart when the state indicated by the indicator is a non-contracting state. The system may also include a cardiac stimulator in communication with the sensor to stimulate beating of a heart when the state indicated by the indicator is a contracting state. The system may also include a drug delivery means and/or a breathing regulator. The breathing regulator may control a respirator and/or a the breathing regulator may stimulate a phrenic nerve.

Another aspect of the present invention provides a method for performing a medical procedure wherein the beating of a heart is inhibited. The medical procedure is performed and a state of cardiac tissue is sensed while beating of the heart is inhibited. The beating of the heart may be inhibited automatically when the state of cardiac tissue is a non-contracting state. A nerve may also be stimulated to inhibit beating of the heart when the state of cardiac tissue is a non-contracting state. Stimulation of the nerve may be stopped when the state of cardiac contraction is a contracting state. Beating of the heart may be allowed to occur when the state of cardiac tissue is a contracting state. Beating of the heart may also be stimulated automatically when the state of cardiac tissue is a contracting state. At least one drug may be delivered during the medical procedure. Breathing may be stopped when the state of cardiac tissue is a non-contracting state.

Another aspect of the present invention provides a device for performing a medical procedure wherein the device includes a processor, a sensor to sense a state of cardiac tissue at least one nerve stimulation electrode. The processor receives a signal from the sensor and adjusts output from the nerve stimulation electrode in response to the signal. The device may also include at least one cardiac stimulation electrode to stimulate beating of the heart. The processor receives a signal from the sensor and adjusts output from the cardiac stimulation electrode in response to the signal. The device may also include a drug pump for delivering at least one drug and/or a breathing regulation electrode for controlling breathing. The processor adjusts the output of the drug and/or output from the breathing regulation electrode in response to a signal.

Another aspect of the present invention provides a method of performing a medical procedure wherein a first vasoactive substance is delivered to a site of the medical procedure. The

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medical procedure is the performed. A second vasoactive substance is then delivered to the site. The first vasoactive substance may be a vasodilator such as an organic nitrate, isosorbide mononitrate, a mononitrate, isosorbide dinitrate, a dinitrate, nitroglycerin, a trinitrate, minoxidil, sodium nitroprusside, hydralazine hydrochloride, nitric oxide, nicardipine hydrochloride, fenoldopam mesylate, diazoxide, enalaprilat, epoprostenol sodium, a prostaglandin, milrinone lactate, a bipyridine, a dopamine D1-like receptor agonist, a dopamine D1-like receptor stimulant and a dopamine D1-like receptor activator. The second vasoactive substance may be a vasoconstrictor such as a sympathomimetic, methoxamine hydrochloride, epinephrine, midodrine hydrochloride, desglymidodrine, an alpha-receptor agonist, an alpha-receptor stimulant, and an alpha-receptor activator.

At least one systemic drug such as a beta-blocker, a cholinergic agent, a cholinesterase inhibitor, a calcium channel blocker, a sodium channel blocker, a potassium channel agent, adenosine, an adenosine receptor agonist, an adenosine deaminase inhibitor, dipyridamole, a monoamine oxidase inhibitor, digoxin, digitalis, lignocaine, a bradykinin agent, a serotonergic agonist, an antiarrhythmic agent, a cardiac glycoside, a local anesthetic, atropine, a calcium solution, an agent that promotes heart rate, an agent that promotes heart contractions, dopamine, a catecholamine, an inotrope glucagon, a hormone, forskolin, epinephrine, norepinephrine, thyroid hormone, a phosphodiesterase inhibitor, prostacyclin, prostaglandin and a methylxanthine may also be delivered during the procedure. The systemic drug may be naturally occurring or chemically synthesized.

A nerve may also be stimulated to adjust the beating of a heart to a first condition. Stimulation of the nerve may be reduced to adjust the beating of a heart to a second condition.

Another aspect of the present invention provides a method of performing a medical procedure on a vessel of a heart. A nerve is stimulated to adjust the beating of a heart to a first condition. A first vasoactive substance is delivered to the vessel. The medical procedure is performed on the vessel. A second vasoactive substance is delivered to the vessel. The heart is stimulated to adjust the beating of a heart to a second condition. The nerve may be stimulated a subsequent time to re-adjust beating of the heart to the first condition the procedure may be continued. The nerve may be a vagal nerve, a carotid sinus nerve, a fat pad. The first vasoactive substance may be a vasodilator such as an organic nitrate, isosorbide mononitrate, a mononitrate, isosorbide dinitrate, a dinitrate, nitroglycerin, a trinitrate, minoxidil, sodium nitroprusside, hydralazine hydrochloride, nitric oxide, nicardipine hydrochloride, fenoldopam mesylate, diazoxide, enalaprilat, epoprostenol sodium, a prostaglandin, milrinone lactate, a bipyridine, a dopamine D1-like receptor agonist, a dopamine D1-like receptor stimulant and a dopamine D1-like receptor activator. The second vasoactive substance may be a vasoconstrictor such as a sympathomimetic, methoxamine hydrochloride, epinephrine, midodrine hydrochloride, desglymidodrine, an alpha-receptor

Another aspect of the present invention provides a method of harvesting a vessel. A nerve is stimulated to adjust beating of a heart to a first condition. A vasodilative substance is delivered to the heart and the vessel is harvested. A vasoconstrictive substance is then delivered to the heart and the heart is stimulated to adjust its beating to a second condition.

Another aspect of the present invention provides a system for performing a medical procedure wherein the system includes drug delivery means to deliver vasoactive substances to a site of the medical procedure, a nerve stimulator in communication with the drug delivery means to inhibit beat-

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ing of a heart and a cardiac stimulator in communication with the drug delivery means to stimulate beating of the heart. The drug delivery means may be, for example, a spray, a cream, an ointment, a medicament, a pill, a patch, a catheter, a cannula, a needle and syringe, a pump, and an iontophoretic drug delivery device. The drug may be an organic nitrate, isosorbide mononitrate, a mononitrate, isosorbide dinitrate, a dinitrate, nitroglycerin, a trinitrate, minoxidil, sodium nitroprusside, hydralazine hydrochloride, nitric oxide, nicardipine hydrochloride, fenoldopam mesylate, diazoxide, enalaprilat, epoprostenol sodium, a prostaglandin, milrinone lactate, a bipyridine, a dopamine D1-like receptor agonist, a dopamine D1-like receptor stimulant and a dopamine D1-like receptor activator, sympathomimetic, methoxamine hydrochloride, epinephrine, midodrine hydrochloride, desglymidodrine, an alpha-receptor agonist, an alpha-receptor stimulant and an alpha-receptor activator. The drug may be naturally occurring or chemically synthesized.

Another aspect of the present invention provides a system for performing a medical procedure wherein the system includes a drug delivery means to deliver vasoactive substances to a site of the medical procedure, a nerve stimulator in communication with the drug delivery means to inhibit beating of a heart and a cardiac stimulator in communication with the drug delivery means to stimulate beating of the heart.

The drug delivery means may be, for example, a spray, a cream, an ointment, a medicament, a pill, a patch, a catheter, a cannula, a needle and syringe, a pump, and an iontophoretic drug delivery device. The drug may be an organic nitrate, isosorbide mononitrate, a mononitrate, isosorbide dinitrate, a dinitrate, nitroglycerin, a trinitrate, minoxidil, sodium nitroprusside, hydralazine hydrochloride, nitric oxide, nicardipine hydrochloride, fenoldopam mesylate, diazoxide, enalaprilat, epoprostenol sodium, a prostaglandin, milrinone lactate, a bipyridine, a dopamine D1-like receptor agonist, a dopamine D1-like receptor stimulant and a dopamine D1-like receptor activator, sympathomimetic, methoxamine hydrochloride, epinephrine, midodrine hydrochloride, desglymidodrine, an alpha-receptor agonist, an alpha-receptor stimulant and an alpha-receptor activator. The drug may be naturally occurring or chemically synthesized.

Another aspect of the present invention provides a device for delivering vasoactive substances during a medical procedure. The device includes a processor, a vasoactive delivery component operatively connected to the processor; and a nerve stimulation electrode operatively connected to the processor. The processor processes output from the nerve stimulation electrode and automatically delivers vasoactive substances based on output from the nerve stimulation electrode. The device may also include a cardiac stimulation electrode. The processor processes output from the cardiac stimulation electrode and automatically delivers vasoactive substances based on output from the cardiac stimulation electrode. The device may also include a breathing regulation electrode for controlling breathing. The processor adjusts the output from the breathing regulation electrode. The device may also include a drug pump for delivering at least one systemic drug. The processor adjusts the output of the drug.

The foregoing, and other, features and advantages of the invention will become further apparent from the following detailed description of the presently preferred embodiments, read in conjunction with the accompanying drawings. The detailed description and drawings are merely illustrative of the invention rather than limiting, the scope of the invention being defined by the appended claims in equivalence thereof.



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## BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a schematic view of one embodiment of a system for performing a medical procedure in accordance with the present invention;

FIG. 2 is a schematic view of one embodiment of a system for sensing imminent cardiac contractions during a medical procedure in accordance with the present invention;

FIG. 3 is a schematic view of one embodiment of a medical device in accordance with the present invention;

FIG. 4 is a schematic view of one embodiment of a medical device in accordance with the present invention;

FIG. 5 is a schematic view of one embodiment of a medical device in accordance with the present invention;

FIG. 6 is a flow diagram of one embodiment of a method of performing a medical procedure in accordance with the present invention;

FIG. 7 is a flow diagram of one embodiment of a method of performing a medical procedure in accordance with the present invention;

FIG. 8 is a flow diagram of one embodiment of a method of performing a medical procedure in accordance with the present invention;

FIG. 9 is a timeline view of one embodiment of a system for controllably stopping or slowing the heart intermittently in a patient monitoring blood flow in the brain during a medical procedure in accordance with the present invention;

FIG. 10 is a timeline view of one embodiment of a system for sensing imminent cardiac contractions during a medical procedure in accordance with the present invention.

FIG. 11 is a schematic view of one embodiment of a system for delivering vasoactive drugs during a medical procedure in accordance with the present invention;

FIG. 12 is a schematic view of one embodiment of a medical device in accordance with the present invention;

FIG. 13 is a flow diagram of one embodiment of a method of performing a medical procedure in accordance with the present invention; and

FIG. 14 is a timeline view of one embodiment of a system for delivering vasoactive drugs during a medical procedure in accordance with the present invention.

## DETAILED DESCRIPTION OF THE PRESENTLY PREFERRED EMBODIMENTS

FIG. 1 shows a schematic view of one embodiment of a system for performing a medical procedure in accordance with the present invention at 100. System 100 comprises a nerve stimulator 10, and a cardiac stimulator 20. System 100 may also feature a controller 30 and a breathing regulator 40.

FIG. 2 shows a schematic view of an alternative embodiment of a system for performing a medical procedure in accordance with the present invention at 100. System 100 comprises a sensor 6, a nerve stimulator 10, and a cardiac stimulator 20. System 100 may also feature a controller 30 and a breathing regulator 40. Sensor 6 may be any suitable sensor, e.g., an electrical sensor, a chemical sensor or a biosensor, for detecting one or more signals indicative of a cardiac contraction or heartbeat. Alternatively, sensor 6 may be any suitable blood gas sensor for measuring the concentration or saturation of a gas in the blood stream. For example, sensor 6 may be a sensor for measuring the concentration or saturation of oxygen or carbon dioxide in the blood. Alternatively, sensor 6 may be any suitable sensor for measuring blood pressure or flow, for example a Doppler ultrasound sensor system, or a sensor for measuring hematocrit (HCT) levels.

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Alternatively, sensor 6 may be a biosensor, for example, comprising an immobilized biocatalyst, enzyme, immunoglobulin, bacterial, mammalian or plant tissue, cell and/or subcellular fraction of a cell. For example, the tip of a biosensor may comprise a mitochondrial fraction of a cell, thereby providing the sensor with a specific biocatalytic activity.

Sensor 6 may be based on potentiometric technology or fiber optic technology. For example, the sensor may comprise a potentiometric or fiber optic transducer. An optical sensor may be based on either an absorbance or fluorescence measurement and may include an UV, a visible or an IR light source.

Sensor 6 may be used to detect naturally detectable properties representative of one or more characteristics, e.g., chemical, physical or physiological, of a patient's bodily tissues or fluids. For example, naturally detectable properties of patient's bodily tissues or fluids may include pH, fluid flow, electrical current, temperature, pressure, components of metabolic processes, chemical concentrations, for example, the absence or presence of specific peptides, proteins, enzymes, gases, ions, etc.

Sensor 6 may include one or more imaging systems, camera systems operating in UV, visible, or IR range; electrical sensors; voltage sensors; current sensors; piezoelectric sensors; electromagnetic interference (EMI) sensors; photographic plates, polymer-metal sensors; charge-coupled devices (CCDs); photo diode arrays; chemical sensors, electrochemical sensors; pressure sensors, sound wave sensors; magnetic sensors; UV light sensors; visible light sensors; IR light sensors; radiation sensors; flow sensors; temperature sensors; or any other appropriate or suitable sensor. Sensor 5 may be a continuous, in-line monitoring system or it may be attached to an extracorporeal device.

In one embodiment of the invention, sensor 6 may be a cerebral blood flow sensor, in which case, the sensor may be placed in any suitable manner for sensing cerebral blood flow. For example, sensor 6 may be inserted between the skull and the dura of the brain. Alternatively, sensor 6 may be placed in the patient's neck. For example, at least a portion of sensor 6 may be placed in an artery, such as the carotid artery. Such a placement would allow measurement of blood as it flows to the brain. Alternatively, sensor 6 may be placed in a vein, such as the jugular vein. This placement would allow measurement of blood as it flows from the brain.

In the case of blood oxygen saturation sensing, a certain level of oxygen generally remains in the blood as it flows from the brain. This level may be established by measuring the patient's oxygen prior to surgery. If blood measured by sensor 6 in the vein has oxygen below the established level, the brain is consuming all or most of the oxygen flowing to it and probably requires additional oxygen. Other suitable placements of sensor 6 may be possible. Sensor 6 may be used to alert a surgeon to changes in the patient's circulatory system.

In one embodiment of the present invention, nerve stimulator 10 may be used to electrically manipulate cardiac rhythm by stimulating the vagus nerve. This vagal stimulation may produce asystole (slowing or stopping of the heart's beating.) Once this induced asystole is stopped, i.e. once the vagal stimulation is stopped, the heart may be allowed to return to its usual cardiac rhythm. Alternatively, the heart may be paced with an electrical pacing system, thereby maintaining a normal cardiac output. Vagal stimulation, alone or in combination with electrical pacing, may be used selectively and intermittently to allow a surgeon to perform a medical procedure during intermittent periods of asystole.

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It is known that stimulation of the vagus nerve can reduce the sinus rate, as well as prolong AV conduction time or, if stimulation energies are high enough, induce AV node block. Use of vagal nerve stimulation to treat supraventricular arrhythmias and angina pectoris is disclosed in the article "Vagal Tuning" by Bilgutay et al., *Journal of Thoracic and Cardiovascular Surgery*, Vol. 56, No. 1, July, 1968, pp. 71-82. It is also known that stimulation of the carotid sinus nerve produces a similar result, as disclosed in the article "Carotid Sinus Nerve Stimulation in the Treatment of Angina Pectoris and Supraventricular Tachycardia" by Braunwald et al., published in *California Medicine*, Vol. 112, pp. 41-50, March, 1970.

As set forth in "Functional Anatomy of the Cardiac Efferent Innervation" by Randall et al., in *Neurocardiology*, edited by Kulbertus et al, Futura Publishing Co., 1988, direct surgical excision of the fat pad associated with the SA node affects the functioning of the SA node without significantly affecting the AV node. Similarly, excision of the fat pad associated with the AV node affects functioning of the AV node without significantly affecting the SA node.

As set forth in the article "Parasympathetic Postganglionic Pathways to the Sinoatrial Node", Bluemel et al., *Am. J. Physiol.* 259, (Heart Circ. Physiol. 28) H1504-H1510, 1990, stimulation of the fat pad associated with the SA node results in slowing of the sinus rate without the accompanying prolongation of AV conduction time which normally results from vagal nerve stimulation. The article also indicates that stimulation of the fat pad associated with the AV node is believed to produce corresponding effects limited to the AV node, i.e., extension of the AV conduction time without concurrent slowing of the sinus rate.

As set forth in the article "Neural Effects on Sinus Rate and Atrial Ventricular Conduction Produced by Electrical Stimulation From a Transvenous Electrode Catheter in the Canine Right Pulmonary Artery" by Cooper et al., published in *Circulation Research*, Vol. 46, No. 1, January, 1980, pp. 48-57, the fat pads associated with both the AV node and the SA node may be stimulated by means of electrodes located in the right pulmonary artery. The results obtained include both a depression of the sinus rate and a prolongation of the AV conduction time in response to continuous stimulation at 2-80 Hz at up to 50 ma.

Generally in healthy individuals, the SA node functions as the pacemaker. Normal heart rhythm associated with the SA node is typically referred to as sinus rhythm. When the SA node fails, the AV node generally takes over creating a heart rate of approximately 35 to 60 beats per minute. Heart rhythm associated with the AV node is typically referred to as nodal rhythm. When the AV node itself is blocked or injured, a new even slower pacemaker site may form at the junction of the AV node and the His bundle. Heart rhythm associated with this junction is typically referred to as junctional escape rhythm. When this junction site is inhibited, the Purkinje fibers in the His bundle or below may act as a pacemaker creating a heart rate of approximately 30 beats per minute. Heart rhythm associated with the Purkinje fibers is typically referred to as idioventricular rhythm.

In one embodiment of the present invention, nerve stimulator 10 may be used to electrically manipulate cardiac rhythm by stimulating the carotid sinus nerve, the fat pad associated with the SA node, the fat pad associated with the AV node, the junction of the AV node and the His bundle and/or the Purkinje fibers.

In one embodiment of the present invention, nerve stimulator 10 is used alone or in combination with other heart rate inhibiting agents to temporarily stop or slow the beating

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heart, thereby eliminating or reducing heart motion and/or blood flow during a medical procedure. For example, the present invention may be used to eliminate or reduce motion in the anastomosis field during CABG procedures such that a facilitated anastomosis procedure may be performed safely and effectively. The number of occasions that the vagal nerve may be stimulated depends on the type of medical procedure to be performed. Likewise, the type of medical procedure to be performed will dictate the duration of the individual electrical stimulations.

Nerve stimulator 10 may be powered by AC current, DC current or it may be battery powered by a disposable or re-chargeable battery. Nerve stimulator 10 may be configured to synchronize activation and deactivation of breathing regulator 40 with vagal stimulation, thereby minimizing or eliminating unwanted heart and chest motion associated with the patient's breathing. Nerve stimulator 10 may comprise a surgeon controlled switch box. A switch may be incorporated in or on one of the surgeon's instruments, such as surgical site retractor, or any other location easily and quickly accessed by the surgeon for regulation of the nerve stimulator 10 by the surgeon. The switch may be, for example, a hand switch, a foot switch, or a voice-activated switch comprising voice-recognition technologies.

A visual and/or audible signal used to alert a surgeon to the completion or resumption of vagal nerve stimulation may be incorporated into nerve stimulator 10. For example, a beeping tone or flashing light that increases in frequency as the nerve stimulation period should end or begin may be used.

Nerve stimulator 10 may be slaved to cardiac stimulator 20 or cardiac stimulator 20 may be slaved to nerve stimulator 10. For example, the output of cardiac stimulator 20 may be off whenever the output of nerve stimulator 10 is on. Software controlling cardiac stimulator 20 may be designed to automatically commence cardiac pacing if the heart does not resume beating within a pre-determined interval after cessation of vagal nerve stimulation. In addition, the software controlling nerve stimulator 10 may be designed to automatically stop vagal nerve stimulation if the heart has been stopped for too long. For example, a predetermined time interval may be set to automatically stop vagal stimulation. In one embodiment of the invention, if sensor 6 of the present invention indicates that not enough blood is flowing to the brain, vagal stimulation may be stopped, thereby allowing the heart to beat again.

In one embodiment of the present invention, cardiac stimulator 20 may be used to stimulate the heart as desired. For example in one embodiment of the present invention, sensor 6 may indicate that not enough blood is flowing to the brain causing nerve stimulator 10 to be automatically turned off and cardiac stimulator 20 to be automatically turned on. Alternatively, the surgeon may turn on cardiac stimulator 20 to begin stimulation. As with nerve stimulator 10, cardiac stimulator 20 may be intermittently stopped and started to allow the surgeon to perform individual steps of a medical procedure.

Cardiac stimulator 20 may be a conventional ventricular demand pacer or dual chamber (atrial-ventricular) pacer. Cardiac stimulator 20 may be powered by AC current, DC current or it may be battery powered either by a disposable or re-chargeable battery. Cardiac stimulator 20 may be configured to synchronize activation and deactivation of breathing regulator 40 with pacing, thereby minimizing or eliminating unwanted heart and chest motion associated with the patient's breathing. Cardiac stimulator 20 may be any conventional pacing device suitable for ventricular demand pacing and having leads electrically coupled to a switch box. Cardiac stimulator 20 may be combined in a single unit with a switch



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box. Cardiac stimulator 20 may comprise a surgeon controlled switch box. A switch may be incorporated in or on one of the surgeon's instruments, such as surgical site retractor, or any other location easily and quickly accessed by the surgeon for regulation of the cardiac stimulator by the surgeon. The switch may be, for example, a hand switch, a foot switch, or a voice-activated switch comprising voice-recognition technologies. A single switch may be used to regulate both cardiac stimulator 20 and nerve stimulator 10.

A visual and/or audible signal used to prepare a surgeon for the resumption of pacing may be incorporated into cardiac stimulator 20. For example, a beeping tone or flashing light that increases in frequency as the pacing period ends may be used. A single signaling method or device may be used for both cardiac stimulator 20 and nerve stimulator 10.

Nerve stimulator 10 and/or cardiac stimulator 20 may be slaved to a robotic system or a robotic system may be slaved to nerve stimulator 10 and/or cardiac stimulator 20. Breathing regulator 40 and/or sensor 6 and other components may also be slaved to such a system or the system may be slaved to breathing regulator 40 and/or sensor 6 and/or other components. Computer- and voice-controlled robotic systems that position and maneuver endoscopes and/or other surgical instruments for performing microsurgical procedures such as anastomoses through small incisions may be used by a surgeon to perform precise and delicate maneuvers. These robotic systems may allow a surgeon to perform a variety of microsurgical procedures including endoscopic CABG. Endoscopic CABG may allow multiple occluded coronary arteries to be bypassed without a thoracotomy or mini-thoracotomy. Heart valve repair and replacement may also be other surgical applications for these robotic systems. In general, robotic systems may include head-mounted displays which integrate 3-D visualization of surgical anatomy and related diagnostic and monitoring data, miniature high resolution 2-D and 3-D digital cameras, a computer, a high power light source and a standard video monitor.

In one embodiment of the present invention, breathing regulator 40 may be used to stimulate the phrenic nerve in order to provide a diaphragmatic pacemaker. Breathing regulator 40 may comprise one or more electrodes for supplying electrical current to the phrenic nerve to control breathing during vagal and/or cardiac stimulation and/or destimulation. Electrodes used to stimulate the phrenic nerve may be, for example, non-invasive, e.g., clips, or invasive, e.g., needles or probes. The application of an electrical stimulus to the phrenic nerve may include, but is not limited to bipolar and/or monopolar techniques. Different electrode positions are accessible through various access openings, for example, in the cervical or thorax regions. Nerve stimulation electrodes may be positioned through a thoracotomy, sternotomy, endoscopically through a percutaneous port, through a stab wound or puncture, through a small incision, placed on the skin or in combinations thereof. The present invention may include various electrodes, catheters and electrode catheters suitable for phrenic nerve stimulation to control breathing.

Phrenic nerve stimulation electrodes may be intravascular, patch-type, balloon-type, basket-type, umbrella-type, tape-type, cuff-type, suction-type, screw-type, barb-type, bipolar, monopolar, metal, wire, endotracheal, endoesophageal, intravascular, transcutaneous or intracutaneous electrodes. Guided or steerable catheter devices comprising electrodes may be used alone or in combination with the nerve stimulation electrodes. For example, a catheter comprising one or more wire, metal strips or metal foil electrodes or electrode arrays may be used. The catheter may comprise, for example,

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a balloon which may be inflated with air or liquid to press the electrodes firmly against a vessel wall that lays adjacent the phrenic nerve.

Phrenic nerve stimulation electrodes may be oriented in any fashion along the catheter device, including longitudinally or transversely. Various techniques such as ultrasound, fluoroscopy and echocardiography may be used to facilitate positioning of the electrodes. If desired or necessary, avoidance of obstruction of blood flow may be achieved with notched catheter designs or with catheters which incorporate one or more tunnels or passageways.

In another embodiment of the present invention, breathing regulator 40 may comprise a connector which interfaces with a patient's respirator, and sends a logic signal to activate or deactivate the respirator to control breathing during vagal and/or cardiac stimulation and/or destimulation.

FIG. 3 shows one embodiment of the present invention at 200. In this embodiment, the elements named above may be combined or connected to a control unit along with other components. The unit 200 may be used to coordinate the various elements. Unit 200 may incorporate a controller or any suitable processor 230.

Unit 200 may incorporate a nerve stimulator. For example, FIG. 3 shows an electrode for nerve stimulation at 210. Electrodes used to stimulate a nerve such as the vagal nerve may be, for example, non-invasive, e.g., clips, or invasive, e.g., needles or probes. The application of an electrical stimulus to the right or left vagal nerve may include, but is not limited to bipolar and/or monopolar techniques. Different electrode positions are accessible through various access openings, for example, in the cervical or thorax regions. Nerve stimulation electrodes 210 may be positioned through a thoracotomy, sternotomy, endoscopically through a percutaneous port, through a stab wound or puncture, through a small incision in the neck or chest, through the internal jugular vein, the esophagus, the trachea, placed on the skin or in combinations thereof. Electrical stimulation may be carried out on the right vagal nerve, the left vagal nerve or to both nerves simultaneously or sequentially. The present invention may include various electrodes, catheters and electrode catheters suitable for vagal nerve stimulation to temporarily stop or slow the beating heart alone or in combination with other heart rate inhibiting agents.

Nerve stimulation electrodes 210 may be endotracheal, endoesophageal, intravascular, transcutaneous, intracutaneous, patch-type, balloon-type, cuff-type, basket-type, umbrella-type, tape-type, screw-type, barb-type, metal, wire or suction-type electrodes. Guided or steerable catheter devices comprising electrodes may be used alone or in combination with the nerve stimulation electrodes 210. For example, a catheter comprising one or more wire, metal strips or metal foil electrodes or electrode arrays may be inserted into the internal jugular vein to make electrical contact with the wall of the internal jugular vein, and thus stimulate the vagal nerve adjacent to the internal jugular vein. Access to the internal jugular vein may be via, for example, the right atrium, the right atrial appendage, the inferior vena cava or the superior vena cava. The catheter may comprise, for example, a balloon which may be inflated with air or liquid to press the electrodes firmly against the vessel wall. Similar techniques may be performed by insertion of a catheter-type device into the trachea or esophagus. Additionally, tracheal tubes and esophageal tubes comprising electrodes may be used.

Nerve stimulation electrodes 210 may be oriented in any fashion along the catheter device, including longitudinally or transversely. Various techniques such as ultrasound, fluoroscopy and echocardiography may be used to facilitate posi-



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tioning of the electrodes. If desired or necessary, avoidance of obstruction of blood flow may be achieved with notched catheter designs or with catheters which incorporate one or more tunnels or passageways.

In one embodiment of the present invention, the location of the electrodes 210 is chosen to elicit maximum bradycardia effectiveness while minimizing current spread to adjacent tissues and vessels and to prevent the induction of post stimulation tachycardia. Furthermore, a non-conductive material such as plastic may be employed to sufficiently enclose the electrodes of all the configurations to shield them from the surrounding tissues and vessels, while exposing their confronting edges and surfaces for positive contact with the vagal nerve or selected tissues.

Unit 200 may also incorporate a cardiac stimulator. For example, FIG. 2 shows an electrode for stimulation of the heart at 220. Cardiac electrodes 220 used to stimulate the heart may be, for example, non-invasive, e.g., clips, or invasive, e.g., needles or probes. Electrodes 220 may be positioned through a thoracotomy, sternotomy, endoscopically through a percutaneous port, through a stab wound or puncture, through a small incision in the chest, placed on the chest or in combinations thereof. The present invention may also use various electrodes, catheters and electrode catheters suitable for pacing the heart, e.g., epicardial, patch-type, intravascular, balloon-type, basket-type, umbrella-type, tape-type electrodes, suction-type, pacing electrodes, endotracheal electrodes, endoesophageal electrodes, transcutaneous electrodes, intracutaneous electrodes, screw-type electrodes, barb-type electrodes, bipolar electrodes, monopolar electrodes, metal electrodes, wire electrodes and cuff electrodes. Guided or steerable catheter devices comprising electrodes may be used alone or in combination with the electrodes.

Controller 230 may be used to gather information from nerve stimulation electrodes 210 and cardiac stimulation electrodes 220. Controller 230 may also be used to control the stimulation levels and stimulation duration of nerve stimulation electrodes 210 and cardiac stimulation electrodes 220. Controller 230 may also gather and process information from the various components of the system, e.g., sensor 6. This information may be used to adjust stimulation levels and stimulation times of nerve stimulation electrodes 210 and cardiac stimulation electrodes 220.

Unit 200 may incorporate one or more switches to facilitate regulation of the various components by the surgeon. One example of such a switch is shown as foot pedal 250. The switch may also be, for example, a hand switch, or a voice-activated switch comprising voice-recognition technologies. The switch may be incorporated in or on one of the surgeon's instruments, such as surgical site retractor, or any other location easily and quickly accessed by the surgeon.

Unit 200 may also include a display 260. Unit 200 may also include other means of indicating the status of various components to the surgeon such as a numerical display, gauges, a monitor display or audio feedback. Unit 200 may also include one or more visual and/or audible signals used to prepare a surgeon for the start or stop of nerve stimulation and/or cardiac stimulation.

FIG. 4 shows one embodiment of the present invention wherein sensor 6 may comprise a cardiac contraction sensor 206 incorporated with control unit 200. In this embodiment, the elements named above may be combined or connected to control unit 200 along with other components. Control unit 200 may be used to coordinate the various elements.

As shown in FIG. 4, sensor 206 may be a monitor for mounting on or near the heart during surgery. Such a monitor may monitor the electrical activity of the heart by picking up

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and amplifying electrical signals from the heart and displaying an output. For example, the output may be displayed on display 216. The surgeon may check this output periodically to see if the output reaches a level that indicates an escape beat is probable. Alternatively, the monitor may be programmed to indicate by a signal, such as an audio or visual signal, that the electrical activity has reached a predetermined level that is indicative of an imminent escape beat.

Unit 200 may include display 270 in addition to display 216 or instead of display 216. Unit 200 may include other means of indicating to the surgeon such as a numerical display, gauges, a monitor display or audio feedback that the electrical activity has reached a predetermined level that is indicative of an imminent escape beat. Unit 200 may also include one or more visual and/or audible signals used to prepare a surgeon of an imminent escape beat.

Cardiac contraction sensor 206 may be a sensor that detects cardiac depolarizations. The electrical signal generated by the sinus node of the heart causes the atria to contract to force blood into the ventricles. After a brief delay, the ventricles contract to force blood out through the body. The contraction of the ventricles is reflected by the passage of a depolarization wavefront through the heart muscle. If a depolarization is sensed, an escape beat is likely to occur. One such depolarization sensor is disclosed in U.S. Pat. No. 5,156,149 entitled "Sensor for Detecting Cardiac Depolarizations Particularly Adapted for use in a Cardiac Pacemaker", Oct. 2, 1992, to inventor Hudrlik. This patent is assigned to Medtronic, Inc. and is incorporated herein by reference.

Cardiac contraction sensor 206 may be coupled to cardiac stimulator 20. Such a sensor may detect the response of tissue near the stimulator 20. If the tissue is stimulated during the procedure by stimulator 20, the cardiac stimulation may cause an escape beat even after stimulation has been reduced or stopped, particularly if cardiac stimulation is only reduced during the procedure rather than fully stopped. One such detector is disclosed in U.S. Pat. No. 5,265,603 entitled "Electronic Capture Detection for a Pacer," Nov. 30, 1993, to inventor Hudrlik. This patent is assigned to Medtronic, Inc. and is incorporated herein by reference.

Cardiac contraction sensor 206 may be an apparatus that senses power levels of depolarizations in heart tissue. Such a sensor may be used to distinguish between normally conducted and ectopic heart beats while the heart is beating or may be used to sense an imminent heart beat while the heart is slowed or substantially stilled during a medical procedure. One apparatus that may serve as such a sensor is disclosed in U.S. Pat. No. 5,411,529 entitled "Waveform Discriminator for Cardiac Stimulation Devices", May 2, 1995, to inventor Hudrlik. This patent is assigned to Medtronic, Inc. and is incorporated herein by reference.

Other suitable sensors may also serve as cardiac contraction sensor 206. Sensor 206 may be or may incorporate one or more sensing electrodes 226. Sensing electrodes 226 incorporated with sensor 206 may be, for example, non-invasive, e.g., clips, or invasive, e.g., needles or probes. Electrodes 226 may be positioned through a thoracotomy, sternotomy, endoscopically through a percutaneous port, through a stab wound or puncture, through a small incision in the chest, placed on the chest or in combinations thereof. The present invention may also use various electrodes, catheters and electrode catheters, e.g., epicardial, patch-type, intravascular, balloon-type, basket-type, umbrella-type, tape-type electrodes, suction-type, pacing electrodes, endotracheal electrodes, endoesophageal electrodes, transcutaneous electrodes, intracutaneous electrodes, screw-type electrodes, barb-type electrodes, bipolar electrodes, monopolar electrodes, metal electrodes, wire

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electrodes and cuff electrodes. Guided or steerable catheter devices comprising electrodes may be used alone or in combination with the electrodes. Although FIG. 4 shows a separate sensor 206 and cardiac stimulator 220, one sensing/stimulating electrode may serve both functions in one embodiment of the invention.

All or a portion of cardiac contraction sensor 206 may be placed in any suitable manner for sensing an imminent cardiac contraction. For example, sensor 206 may incorporate a lead as shown at 226, which may be used to attach the sensor to the heart. The lead may also be used to monitor electrical signals of the heart as described above. Sensor 206 may be placed in any suitable area of the heart. For example, sensor 206 may be placed near the location of the cardiac stimulator 220 as described above. Sensor 206 may be placed near the right ventricle, the left ventricle, the right atrium, or the left atrium. Other suitable placements of the sensor 206 may be possible. The sensor's optimal location will depend primarily on the sensor's mode of operation.

FIG. 5 shows one embodiment of the present invention wherein sensor 6 may comprise a blood sensor 205 incorporated with control unit 200. In this embodiment, the elements named above may be combined or connected to a control unit along with other components. Unit 200 may be used to coordinate the various elements. Unit 200 may incorporate a controller as described above or any suitable processor 230. For example, the processor may process sensed blood information from sensor 205. The controller may store and/or process such information before, during and/or after a medical procedure. For example, the patient's oxygen concentration or blood pressure may be sensed, stored and processed prior to and during surgery. Unit 200 may include display 270 for displaying sensed blood information from sensor 205. Unit 200 may also include other means of indicating the status of various components to the surgeon such as a numerical display, gauges, a monitor display or audio feedback. Unit 200 may also include one or more visual and/or audible signals used to prepare a surgeon for the start or stop of nerve stimulation and/or cardiac stimulation.

FIG. 6 shows a flow diagram of one embodiment of the present invention. The patient is prepared for a medical procedure at 500.

At block 510, a nerve that controls the beating of the heart is stimulated. Such a nerve may be for example a vagal nerve. During this time, one or more of a variety of pharmacological agents or drugs may be delivered. These drugs may produce reversible asystole of a heart while maintaining the ability of the heart to be electrically paced. Other drugs may be administered for a variety of functions and purposes as described below. Drugs delivered may be administered at the beginning of the procedure, intermittently during the procedure, continuously during the procedure, or following the procedure. At Block 520, a medical procedure may be performed or begun. Such a procedure may be for example surgery on the heart. Alternatively, the procedure may be surgery performed on another organ of the body.

After a time, the medical procedure or one phase of the procedure is completed at 520. After some phase of the medical procedure is performed, cardiac contractions are allowed to occur (Block 530). Cardiac contractions may need to occur intermittently during the procedure to ensure adequate blood flow. In one embodiment, the stimulation from the nerve stimulator 10 is stopped or slowed enough to allow the heart to contract. For example, the vagal nerve stimulation is removed, thereby allowing cardiac contractions to occur.

In one embodiment of the present invention, the heart may be stimulated to ensure that cardiac contractions occur (Block

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535). For example, cardiac stimulator 20 may be used to apply pacing pulses to the heart to encourage the heart to contract normally. In particular, the pacing pulses may be applied to the ventricle as is well known in the field.

The present invention permits the heart to be stilled for selected and controllable periods of time in order to permit cardiac or other medical procedure to be performed. While such a period of stillness is desired, it must not last too long, otherwise insufficient blood and oxygen is delivered to organs. Thus, it is necessary to have the periods when the heart is beating (Blocks 530, 535).

If additional medical procedures or additional stages of medical procedures need to be performed, the heart may again be stilled using the methods of stilling the heart described above. Therefore from Block 530 or Block 535, the method may be repeated at 540. For example, the heart may again be prevented from contracting by stimulation of the vagal nerve (Block 510). Additional drugs may be delivered or the drugs previously administered may continue to be administered.

Additional surgery, additional steps in the medical procedure or additional medical procedures may again be performed (Block 520) while the heart is still. Then, this stage of stillness may be followed by another stage when the stimulation is removed (Block 530) and the heart is allowed to contract. Again, the heart may be stimulated to encourage contractions (Block 535).

This cycle may be repeated until the procedure, such as the surgery, is completed. After the procedure is completed, step 535 may be performed until the heart is beating normally. At the procedure's end, one or more of a variety of pharmacological agents or drugs may be delivered or may continue to be delivered for example to alleviate pain or aid in recuperation. Other drugs may be administered for a variety of functions and purposes as described above.

For example, a surgical procedure at 520 may require several stitches to be made by the surgeon. The surgeon may stimulate the vagal nerve at 510 to stop the heart. Then the surgeon may make the first stitch at 520. The surgeon may then reduce or halt stimulation at 530 and allow the heart to contract. The surgeon may also pace the heart at 535. Then at 540, the surgeon may return to 510 to inhibit contractions of the heart. At 520, the surgeon will then make the second stitch. This process may be repeated (the loop designated by 540 may be repeated) until all the required stitches have been made.

FIG. 7 shows a flow diagram of one embodiment of the present invention. The patient is prepared for a medical procedure at 500. In one embodiment of the invention, the patient's initial heart rate may be measured (Block 505). This initial reading is then used as a gauge to compare with the electrical signals detected by sensor 6 during the procedure. In one embodiment, the sensor alerts the surgeon if the sensed electrical (or depolarization) signals reach a predetermined level.

At Block 510, a nerve that controls the beating of the heart is stimulated. Such a nerve may be for example a vagal nerve. At Block 510, one or more of a variety of pharmacological agents or drugs may be delivered. These drugs may produce reversible asystole of a heart while maintaining the ability of the heart to be electrically paced. Other drugs may be administered for a variety of functions and purposes as described below. Drugs delivered during the medical procedure may be administered at the beginning of the procedure, intermittently during the procedure, continuously during the procedure or following the procedure.



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Drugs, drug formulations or compositions suitable for administration to a patient during a medical procedure may include a pharmaceutically acceptable carrier or solution in an appropriate dosage. There are a number of pharmaceutically acceptable carriers that may be used for delivery of various drugs, for example, via direct injection, oral delivery, suppository delivery, transdermal delivery, epicardial delivery and/or inhalation delivery. Pharmaceutically acceptable carriers include a number of solutions, preferably sterile, for example, water, saline, Ringer's solution and/or sugar solutions such as dextrose in water or saline. Other possible carriers that may be used include sodium citrate, citric acid, amino acids, lactate, mannitol, maltose, glycero, sucrose, ammonium chloride, sodium chloride, potassium chloride, calcium chloride, sodium lactate, and/or sodium bicarbonate. Carrier solutions may or may not be buffered.

Drug formulations or compositions may include antioxidants or preservatives such as ascorbic acid. They may also be in a pharmaceutically acceptable form for parenteral administration, for example to the cardiovascular system, or directly to the heart, such as intracoronary infusion or injection. Drug formulations or compositions may comprise agents that provide a synergistic effect when administered together. A synergistic effect between two or more drugs or agents may reduce the amount that normally is required for therapeutic delivery of an individual drug or agent. Two or more drugs may be administered, for example, sequentially or simultaneously. Drugs may be administered via one or more bolus injections and/or infusions or combinations thereof. The injections and/or infusions may be continuous or intermittent. Drugs may be administered, for example, systemically or locally, for example, to the heart, to a coronary artery and/or vein, to a pulmonary artery and/or vein, to the right atrium and/or ventricle, to the left atrium and/or ventricle, to the aorta, to the AV node, to the SA node, to a nerve and/or to the coronary sinus. Drugs may be administered or delivered via intravenous, intracoronary and/or intraventricular administration in a suitable carrier. Examples of arteries that may be used to deliver drugs to the AV node include the AV node artery, the right coronary artery, the right descending coronary artery, the left coronary artery, the left anterior descending coronary artery and Kugel's artery. Drugs may be delivered systemically, for example, via oral, transdermal, intranasal, suppository or inhalation methods. Drugs also may be delivered via a pill, a spray, a cream, an ointment or a medicament formulation.

Drugs may be delivered via a drug delivery device that may comprise a catheter, such as a drug delivery catheter or a guide catheter, a patch, such as a transepical patch that slowly releases drugs directly into the myocardium, a cannula, a pump and/or a hypodermic needle and syringe assembly. A drug delivery catheter may include an expandable member, e.g., a low-pressure balloon, and a shaft having a distal portion, wherein the expandable member is disposed along the distal portion. A catheter for drug delivery may comprise one or more lumens and may be delivered endovascularly via insertion into a blood vessel, e.g., an artery such as a femoral, radial, subclavian or coronary artery. The catheter can be guided into a desired position using various guidance techniques, e.g., fluoroscopic guidance and/or a guiding catheter or guide wire techniques.

Drugs may be delivered via an iontophoretic drug delivery device placed on the heart. In general, the delivery of ionized drugs may be enhanced via a small current applied across two electrodes. Positive ions may be introduced into the tissues from the positive pole, or negative ions from the negative pole. The use of iontophoresis may markedly facilitate the

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transport of certain ionized drug molecules. For example, lidocaine hydrochloride may be applied to the heart via a drug patch comprising the drug. A positive electrode could be placed over the patch and current passed. The negative electrode would contact the heart or other body part at some desired distance point to complete the circuit. One or more of the electrodes may also be used as nerve stimulation electrodes 210, as cardiac stimulation electrodes 220 or as sensing electrodes 226.

The two divisions of the autonomic nervous system that regulate the heart have opposite functions. First, the adrenergic or sympathetic nervous system increases heart rate by releasing epinephrine and norepinephrine. Second, the parasympathetic system also known as the cholinergic nervous system or the vagal nervous system decreases heart rate by releasing acetylcholine. Catecholamines such as norepinephrine (also called noradrenaline) and epinephrine (also called adrenaline) are agonists for beta-adrenergic receptors. An agonist is a stimulant biomolecule or agent that binds to a receptor.

Beta-adrenergic receptor blocking agents compete with beta-adrenergic receptor stimulating agents for available beta-receptor sites. When access to beta-receptor sites are blocked by receptor blocking agents, also known as beta-adrenergic blockade, the chronotropic or heart rate, inotropic or contractility, and vasodilator responses to receptor stimulating agents are decreased proportionately. Therefore, beta-adrenergic receptor blocking agents are agents that are capable of blocking beta-adrenergic receptor sites.

Since beta-adrenergic receptors are concerned with contractility and heart rate, stimulation of beta-adrenergic receptors, in general, increases heart rate, the contractility of the heart and the rate of conduction of electrical impulses through the AV node and the conduction system.

Drugs, drug formulations and/or drug compositions that may be used according to this invention may include any naturally occurring or chemically synthesized (synthetic analogues) beta-adrenergic receptor blocking agents. Beta-adrenergic receptor blocking agents or  $\beta$ -adrenergic blocking agents are also known as beta-blockers or  $\beta$ -blockers and as class II antiarrhythmics.

The term "beta-blocker" appearing herein may refer to one or more agents that antagonize the effects of beta-stimulating catecholamines by blocking the catecholamines from binding to the beta-receptors. Examples of beta-blockers include, but are not limited to, acebutolol, alprenolol, atenolol, betantolol, betaxolol, bevantolol, bisoprolol, carterolol, celiprolol, chlorthalidone, csmolol, labetalol, metoprolol, nadolol, penbutolol, pindolol, propranolol, oxprenolol, sotalol, teratolol, timolol and combinations, mixtures and/or salts thereof.

The effects of administered beta-blockers may be reversed by administration of beta-receptor agonists, e.g., dobutamine or isoproterenol.

The parasympathetic or cholinergic system participates in control of heart rate via the sinoatrial (SA) node, where it reduces heart rate. Other cholinergic effects include inhibition of the AV node and an inhibitory effect on contractile force. The cholinergic system acts through the vagal nerve to release acetylcholine, which, in turn, stimulates cholinergic receptors. Cholinergic receptors are also known as muscarinic receptors. Stimulation of the cholinergic receptors decreases the formation of cAMP. Stimulation of cholinergic receptors generally has an opposite effect on heart rate compared to stimulation of beta-adrenergic receptors. For example, beta-adrenergic stimulation increases heart rate, whereas cholinergic stimulation decreases it. When vagal tone is high and adrenergic tone is low, there is a marked

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slowing of the heart (sinus bradycardia). Acetylcholine effectively reduces the amplitude, rate of increase and duration of the SA node action potential. During vagal nerve stimulation, the SA node does not arrest. Rather, pacemaker function may shift to cells that fire at a slower rate. In addition, acetylcholine may help open certain potassium channels thereby creating an outward flow of potassium ions and hyperpolarization. Acetylcholine also slows conduction through the AV node.

Drugs, drug formulations and/or drug compositions that may be used according to this invention may include any naturally occurring or chemically synthesized (synthetic analogues) cholinergic agent. The term "cholinergic agent" appearing herein may refer to one or more cholinergic receptor modulators or agonists. Examples of cholinergic agents include, but are not limited to, acetylcholine, carbachol (carbamyl choline chloride), bethanechol, methacholine, arecoline, norarecoline and combinations, mixtures and/or salts thereof.

Drugs, drug formulations and/or drug compositions that may be used according to this invention may include any naturally occurring or chemically synthesized cholinesterase inhibitor. The term "cholinesterase inhibitor" appearing herein may refer to one or more agents that prolong the action of acetylcholine by inhibiting its destruction or hydrolysis by cholinesterase. Cholinesterase inhibitors are also known as acetylcholinesterase inhibitors. Examples of cholinesterase inhibitors include, but are not limited to, edrophonium, neostigmine, neostigmine methylsulfate, pyridostigmine, tacrine and combinations, mixtures and/or salts thereof.

There are ion-selective channels within certain cell membranes. These ion selective channels include calcium channels, sodium channels and/or potassium channels. Therefore, other drugs, drug formulations and/or drug compositions that may be used according to this invention may include any naturally occurring or chemically synthesized calcium channel blocker. Calcium channel blockers inhibit the inward flux of calcium ions across cell membranes of arterial smooth muscle cells and myocardial cells. Therefore, the term "calcium channel blocker" appearing herein may refer to one or more agents that inhibit or block the flow of calcium ions across a cell membrane. The calcium channel is generally concerned with the triggering of the contractile cycle. Calcium channel blockers are also known as calcium ion influx inhibitors, slow channel blockers, calcium ion antagonists, calcium channel antagonist drugs and as class IV antiarrhythmics. A commonly used calcium channel blocker is verapamil.

Administration of a calcium channel blocker, e.g., verapamil, generally prolongs the effective refractory period within the AV node and slows AV conduction in a rate-related manner, since the electrical activity through the AV node depends significantly upon the influx of calcium ions through the slow channel. A calcium channel blocker has the ability to slow a patient's heart rate, as well as produce AV block. Examples of calcium channel blockers include, but are not limited to, amiloride, amlodipine, bepridil, diltiazem, flolodipine, isradipine, mibefradil, nicardipine, nifedipine (dihydropyridines), nickel, nimodipine, nisoldipine, nitric oxide (NO), norverapamil and verapamil and combinations, mixtures and/or salts thereof. Verapamil and diltiazem are very effective at inhibiting the AV node, whereas drugs of the nifedipine family have a lesser inhibitory effect on the AV node. Nitric oxide (NO) indirectly promotes calcium channel closure. NO may be used to inhibit contraction. NO may also be used to inhibit sympathetic outflow, lessen the release of norepinephrine, cause vasodilation, decrease heart rate and

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decrease contractility. In the SA node, cholinergic stimulation leads to formation of NO.

Other drugs, drug formulations and/or drug compositions that may be used according to this invention may include any naturally occurring or chemically synthesized sodium channel blocker. Sodium channel blockers are also known as sodium channel inhibitors, sodium channel blocking agents, rapid channel blockers or rapid channel inhibitors. Antiarrhythmic agents that inhibit or block the sodium channel are known as class I antiarrhythmics, examples include, but are not limited to, quinidine and quinidine-like agents, lidocaine and lidocaine-like agents, tetrodotoxin, encainide, flecainide and combinations, mixtures and/or salts thereof. Therefore, the term "sodium channel blocker" appearing herein may refer to one or more agents that inhibit or block the flow of sodium ions across a cell membrane or remove the potential difference across a cell membrane. For example, the sodium channel may also be totally inhibited by increasing the extracellular potassium levels to depolarizing hyperkalemic values, which remove the potential difference across the cell membrane. The result is inhibition of cardiac contraction with cardiac arrest (cardioplegia). The opening of the sodium channel (influx of sodium) is for swift conduction of the electrical impulse throughout the heart.

Other drugs, drug formulations and/or drug compositions that may be used according to this invention may include any naturally occurring or chemically synthesized potassium channel agent. The term "potassium channel agent" appearing herein may refer to one or more agents that impact the flow of potassium ions across the cell membrane. There are two major types of potassium channels. The first type of channel is voltage-gated and the second type is ligand-gated. Acetylcholine-activated potassium channels, which are ligand-gated channels, open in response to vagal stimulation and the release of acetylcholine. Opening of the potassium channel causes hyperpolarization which decreases the rate at which the activation threshold is reached. Adenosine is one example of a potassium channel opener. Adenosine slows conduction through the AV node. Adenosine, a breakdown product of adenosine triphosphate, inhibits the AV node and atria. In atrial tissue, adenosine causes the shortening of the action potential duration and causes hyperpolarization. In the AV node, adenosine has similar effects and also decreases the action potential amplitude and the rate of increase of the action potential. Adenosine is also a direct vasodilator by its actions on the adenosine receptor on vascular smooth muscle cells. In addition, adenosine acts as a negative neuromodulator, thereby inhibiting release of norepinephrine. Class III antiarrhythmic agents also known as potassium channel inhibitors lengthen the action potential duration and refractoriness by blocking the outward potassium channel to prolong the action potential. Amiodarone and d-sotalol are both examples of class III antiarrhythmic agents.

Potassium is the most common component in cardioplegic solutions. High extracellular potassium levels reduce the membrane resting potential. Opening of the sodium channel, which normally allows rapid sodium influx during the upstroke of the action potential, is therefore inactivated because of a reduction in the membrane resting potential. The present invention may be combined with conventional CPB, the induced asystole as described by this invention may serve as a substitute for conventional cardioplegic arrest. For example, the combination of drugs and vagal stimulation may be used as a cardioplegic agent in a variety of medical procedures.

Drugs, drug formulations and/or drug compositions that may be used during according to this invention may comprise



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one or more of any naturally occurring or chemically synthesized beta-blocker, cholinergic agent, cholinesterase inhibitor, calcium channel blocker, sodium channel blocker, potassium channel agent, adenosine, adenosine receptor agonist, adenosine deaminase inhibitor, dipyridamole, monoamine oxidase inhibitor, digoxin, digitalis, lignocaine, bradykinin agents, serotonergic agonist, antiarrhythmic agents, cardiac glycosides, local anesthetics and combinations or mixtures thereof. Digitalis and digoxin both inhibit the sodium pump. Digitalis is a natural inotrope derived from plant material, while digoxin is a synthesized inotrope. Dipyridamole inhibits adenosine deaminase which breaks down adenosine. Drugs, drug formulations and/or drug compositions capable of reversibly suppressing autonomous electrical conduction at the SA and/or AV node, while still allowing the heart to be electrically paced to maintain cardiac output may be used according to this invention.

In one embodiment, the cardiac asystole produced in accordance with the present invention is reversible, e.g., chemically such as by the administration of atropine or by natural forces. Beta-adrenergic stimulation or administration of calcium solutions may be used to reverse the effects of a calcium channel blocker such as verapamil. Agents that promote heart rate and/or contraction may be used in a preferred embodiment of the present invention. For example, dopamine, a natural catecholamine, is known to increase contractility. Positive inotropes are agents that specifically increase the force of contraction of the heart. Glucagon, a naturally occurring hormone, is known to increase heart rate and contractility. Glucagon may be used to reverse the effects of a beta-blocker since its effects bypass the beta receptor. Forskolin is known to increase heart rate and contractility. As mentioned earlier, epinephrine and norepinephrine naturally increase heart rate and contractility. Thyroid hormone, phosphodiesterase inhibitors and prostacyclin, a prostaglandin, are also known to increase heart rate and contractility. In addition, methylxanthines are known to prevent adenosine from interacting with its cell receptors.

Typically, vagal nerve stimulation prevents the heart from contracting. This non-contraction must then be followed by periods without vagal nerve stimulation during which the heart is allowed to contract, and blood flow is restored throughout the body.

At 517, sensor 6 may be checked to determine if an escape beat is imminent. The sensor may be checked periodically during the procedure, for example, as shown at 517. Alternatively, the sensor may interrupt the procedure at any point by indicating that an escape beat is imminent. For example, a visual and/or audible signal, such as a flashing light or beeping tone, may be used to alert a surgeon that an escape beat is imminent. If no contraction is imminent, then all or a portion of the medical procedure may be carried out (Block 520). However, if a contraction is imminent, then a signal may indicate an escape beat is about to occur (as seen at 523). If the sensor indicates an escape beat is imminent, the surgeon may stop the medical procedure to allow the beat to occur. In one embodiment, the surgeon may then proceed to Block 530, where the nerve stimulation is ceased and the heart is allowed to contract. Alternatively, unit 200 may automatically proceed to Block 530 to cease nerve stimulation when sensor 6 indicates that a beat is imminent.

The output of sensor 6 may be communicated to the surgeon by a number of suitable means. For example, the output may be indicated on a display or monitor. A visual or audio signal may indicate when the electrical signals from the heart reach a certain level, e.g. a level indicating an imminent escape beat. Alternatively, the system of the present invention

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may "lock" the controls of the vagal stimulator in an "off" state when an escape beat is sensed. Alternatively, the system of the present invention may "lock" the controls of the surgical instruments being used to perform the surgery to indicate to the surgeon that an escape beat is imminent. The system may then release the controls when the signals indicate that the heart is again appropriately stilled.

Additionally, the amount of vagal nerve stimulation used and/or the amount of drugs administered may be adjusted based on the output of the sensor 6. For example, the level of stimulation may be increased if sensor 6 indicates that too many escape beats are occurring or are likely to occur. This adjustment may be automatic or may be controlled by the surgeon.

At Block 520, a medical procedure may be performed or begun. Such a procedure may be for example surgery on the heart. Alternatively, the procedure may be surgery performed on another organ of the body. At Block 520, one or more of a variety of pharmacological agents or drugs may be delivered or may continue to be delivered. These drugs may produce reversible asystole of a heart while maintaining the ability of the heart to be electrically paced. Other drugs may be administered for a variety of functions and purposes as described above.

The term "medical procedure" may mean any one or more medical or surgical procedures such as, for example cardiac surgery, performed with or without cardiopulmonary bypass (CPB) circuits, heart valve repair, heart valve replacement, MAZE procedures, revascularization procedures, transmyocardial revascularization (TMR) procedures, percutaneous myocardial revascularization (PMR) procedures, CABG procedures, anastomosis procedures, heart positioning procedures, non-surgical procedures, fluoroscopic procedures, beating heart surgery, vascular surgery, neurosurgery, brain surgery, electrophysiology procedures, placement of one or more leads, diagnostic and therapeutic procedures, ablation procedures, ablation of arrhythmias, endovascular procedures, treatment of the liver, spleen, heart, lungs, and major blood vessels, aneurysm repair, imaging procedures of the heart and great vessels, CAT scans or MRI procedures, pharmacological therapies, drug delivery procedures, gene therapies, cellular therapies, cancer therapies, radiation therapies, genetic, cellular, tissue and/or organ manipulation or transplantation procedures, coronary angioplasty procedures, placement or delivery of coated or noncoated stents, atherectomy procedures, atherosclerotic plaque manipulation and/or removal procedures, procedures where bleeding needs to be precisely controlled, procedures that require precise control of cardiac motion and/or bleeding.

When the medical procedure comprises one or more medical devices, e.g., coated stents, these devices may be coated with one or more radioactive materials and/or biological agents such as, for example, an anticoagulant agent, an anti-thrombotic agent, a clotting agent, a platelet agent, an anti-inflammatory agent, an antibody, an antigen, an immunoglobulin, a defense agent, an enzyme, a hormone, a growth factor, a neurotransmitter, a cytokine, a blood agent, a regulatory agent, a transport agent, a fibrous agent, a protein, a peptide, a proteoglycan, a toxin, an antibiotic agent, an antibacterial agent, an antimicrobial agent, a bacterial agent or component, hyaluronic acid, a polysaccharide, a carbohydrate, a fatty acid, a catalyst, a drug, a vitamin, a DNA segment, a RNA segment, a nucleic acid, a lectin, an antiviral agent, a viral agent or component, a genetic agent, a ligand and a dye (which acts as a biological ligand). Biological agents may be found in nature (naturally occurring) or may be chemically synthesized.



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The medical procedure may be non-invasive, minimally invasive and/or invasive. The medical procedure may entail a port-access approach, a partially or totally endoscopic approach, a sternotomy approach or a thoracotomy approach. The medical procedure may include the use of various mechanical stabilization devices or techniques as well as various robotic or imaging systems.

In one method, the heart may be temporarily slowed or intermittently stopped for short periods of time to permit the surgeon to accomplish the required surgical task and yet still allow the heart itself to supply blood circulation to the body. For example, stimulation of the vagus nerve in order to temporarily and intermittently slow or stop the heart is described in U.S. Pat. No. 6,006,134 entitled "Method and Device for Electronically Controlling the Beating of a Heart Using Venous Electrical Stimulation of Nerve Fibers," Dec. 21, 1999, to inventors Illi and Junkman. This patent is assigned to Medtronic, Inc. and is incorporated herein by reference.

During the medical procedure, cardiac contractions or cardiac signals may be monitored constantly or intermittently as described above. An assessment of the likelihood of a contraction may again be taken at Block 525. If no contraction is imminent, the physician may continue with the medical procedure that is in progress. However, if a contraction is likely to occur, the surgeon may increase nerve stimulation and/or the administration of drugs. Alternatively, the surgeon may choose to proceed to Block 530 and allow the heart to beat normally for a period of time. The heart will therefore be allowed to contract and thus blood will again be allowed to flow to the brain and vital organs.

After a time, the medical procedure or one phase of the procedure is completed at 520. After some phase of the medical procedure is performed, cardiac contractions are allowed to occur (Block 530). Cardiac contractions may need to occur intermittently during the procedure to ensure adequate blood flow. In one embodiment, the stimulation from the nerve stimulator 10 is stopped or slowed enough to allow the heart to contract. For example, the vagal nerve stimulation is removed, thereby allowing cardiac contractions to occur.

In one embodiment of the present invention, it may be determined if the heart is contracting as desired (532). If appropriate, the heart may be stimulated to ensure that cardiac contractions occur (Block 535). For example, cardiac stimulator 20 may be used to apply pacing pulses to the heart to encourage the heart to contract normally. In particular, the pacing pulses may be applied to the ventricle as is well known in the field. Additionally, the amount of cardiac stimulation used may be adjusted based on the output of the sensor 6. For example, the level of stimulation may be decreased or the duration of stimulation may be decreased if the sensor 6 indicates that too many escape beats are occurring or are likely to occur at such a level of stimulation.

The present invention permits the heart to be stilled or quiescent for selected and controllable periods of time in order to permit a medical procedure to be performed. While such a period of quiescence is desired, it must not last too long, otherwise insufficient blood and oxygen is delivered to organs. Thus, it is necessary to have the periods when the heart is beating (Blocks 530, 535). At Blocks 530, 535, one or more of a variety of pharmacological agents or drugs may be delivered or may continue to be delivered. These drugs may produce reversible asystole of a heart while maintaining the ability of the heart to be electrically paced. Particularly at Blocks 530, 535, drugs may be administered to encourage heart contractions. Other drugs may be administered for a variety of functions and purposes as described above.

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Sensor 6 may also be used to determine whether the heart is beating as desired at Block 532. Such output may be communicated to the surgeon by a number of suitable means. For example, the output may be indicated on a display or monitor. A visual or audio signal may also indicate output. Alternatively, the system of the present invention may "lock" the controls of the cardiac stimulator in an "on" state after an escape beat has occurred in order to return the heart to a normal rate. Alternatively, the system of the present invention may "lock" the controls of the cardiac stimulator in an "off" state to prevent an escape beat. The system may then release the controls when the electrical signals sensed by the sensor are again as desired.

At 539, it may be determined if additional medical procedures or additional stages of medical procedures need to be performed. If so, the heart may again be stilled using the methods of stilling the heart described above. The method may then be repeated (as in the loop designated by 540). For example, the heart may again be prevented from contracting by stimulation of the vagal nerve (510). Additional drugs may be delivered or the drugs previously administered may continue to be administered.

This cycle may be repeated until the procedure, such as surgery, is completed. As the cycle continues, sensor 6 enables monitoring of heart rate and, if necessary, appropriate adjustment of nerve stimulation and cardiac stimulation to ensure the heart is beating appropriately.

For example, a surgical procedure at 520 may require several stitches to be made by the surgeon. The surgeon may stimulate the vagal nerve at 510 to stop the heart. Then the surgeon may make the first stitch at 520. The surgeon may then reduce or halt stimulation at 530 and allow the heart to contract. The surgeon may also pace the heart at 535. Then at 540, the surgeon may return to 510 to inhibit contractions of the heart. At 520, the surgeon will then make the second stitch. This process may be repeated (the loop designated by 540 may be repeated) until all the required stitches have been made. Meanwhile, the heart's electrical signals are monitored continuously or, for example at Blocks 517, 525 by sensor 6. The procedure may proceed uninterrupted if no contractions are imminent.

After the procedure is completed, step 535 may be performed until the heart is beating normally. Once it has been determined at 539 that the medical procedure is complete, the surgeon may continue stimulating the heart until satisfied that the heart is beating normally. Additionally, sensor 6 may be used to monitor heart rate until it has reached an acceptable level. At the procedure's end, one or more of a variety of pharmacological agents or drugs may be delivered or may continue to be delivered for example to alleviate pain or aid in recuperation. Other drugs may be administered for a variety of functions and purposes as described above.

FIG. 8 shows a flow diagram of one embodiment of the present invention. The patient is prepared for a medical procedure at 500. Once the patient is prepared, the initial state of cerebral blood circulation is measured (Block 505). Such measurements may include for example blood flow, oxygen concentration, carbon dioxide concentration, etc. The initial state of cerebral blood circulation is then used as a gauge to compare with the state of cerebral blood circulation during the procedure.

At this point, a nerve that controls the beating of the heart is stimulated to slow down or stop the contractions of the heart (Block 510). Such a nerve may be for example a vagal nerve. During this time, one or more of a variety of pharmacological agents or drugs, as discussed above, may be delivered to the patient (block 515). These drugs may produce reversible

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asystole of a heart while maintaining the ability of the heart to be electrically paced. Other drugs may be administered for a variety of functions and purposes as described below. As seen in FIG. 8, drugs delivered at block 515 may be administered at the beginning of the procedure, intermittently during the procedure, continuously during the procedure or following the procedure.

Typically, vagal nerve stimulation prevents the heart from contracting. This non-contraction must then be followed by periods without vagal nerve stimulation during which the heart is allowed to contract, and blood flow is restored throughout the body. At block 517, the state of cerebral blood circulation may be monitored. This monitoring may occur at specific points during the procedure, for example, as shown at block 517. Alternatively, monitoring may occur continuously. If cerebral blood circulation is sufficient, then all or a portion of the medical procedure may be carried out (Block 520). However, if the state of cerebral blood circulation is not sufficient, then a signal may indicate that the state of blood circulation to the brain is insufficient. If the sensor indicates that the state of blood circulation is insufficient, the surgeon may proceed to block 530, where the nerve stimulation is ceased and the heart is allowed to contract. The cardiac stimulator may be used to cause the heart to contract. Alternatively, unit 200 may automatically proceed to block 530 to cease nerve stimulation. In addition, Unit 200 may automatically begin cardiac stimulation.

The state of cerebral blood circulation sensed by sensor 6 may be communicated to the surgeon by a number of suitable means. For example, the ambient blood flow may be indicated on a display or monitor. A visual or audio signal may indicate when the level of cerebral blood flow reaches a certain level, e.g. when blood flow is insufficient. Alternatively, the system of the present invention may "lock" the controls of the vagal stimulator in an "off" state when cerebral blood flow reaches a predetermined condition, thereby indicating that blood flow is insufficient. The system may then release the controls when the state of cerebral blood circulation sensed by the sensor is again sufficient.

Additionally, the amount of vagal nerve stimulation used may be adjusted based on the output of the sensor 6. For example, the level of stimulation may be lowered or the duration of stimulation may be lowered if the sensor indicates that cerebral blood circulation at 517 is insufficient. This adjustment may be automatic or may be controlled by the surgeon. At block 520, a medical procedure, as described above, may be performed or begun.

During the medical procedure, the state of cerebral blood circulation may be monitored constantly or intermittently as described above. An assessment, for example, of the amount of blood flowing to the brain may again be taken at block 525. If the state of cerebral blood circulation is sufficient, the physician may continue with the medical procedure that is in progress. However, if the state of cerebral blood circulation is not sufficient, then sensor 6 may indicate that blood circulation to the brain is insufficient. If the sensor indicates that blood circulation is insufficient, the surgeon may proceed to block 530, where the nerve stimulation is ceased. The heart will therefore be allowed to contract and thus blood will again be allowed to flow to the brain and vital organs. The cardiac stimulator may be used to cause the heart to contract. Alternatively, unit 200 may automatically proceed to block 530 to cease nerve stimulation. In addition, Unit 200 may automatically begin cardiac stimulation. Additionally, the amount of vagal nerve stimulation used may be adjusted based on the output of the sensor 6. For example, the level of stimulation

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may be lowered or the duration of stimulation may be lowered if the sensor indicates that cerebral blood circulation at 525 is insufficient.

After a time, the medical procedure or one phase of the procedure is completed at 520. After some phase of the medical procedure is performed, cardiac contractions are allowed to occur (block 530). Cardiac contractions may need to occur intermittently during the procedure to ensure adequate blood flow. In one embodiment, the stimulation from the nerve stimulator 10 is stopped or slowed enough to allow the heart to contract. For example, the vagal nerve stimulation is removed, thereby allowing cardiac contractions to occur.

In another embodiment, the heart may be stimulated to ensure that cardiac contractions occur (block 535). For example, cardiac stimulator 20 may be used to apply pacing pulses to the heart to encourage the heart to contract normally. In particular, the pacing pulses may be applied to the ventricle as is well known in the field. Additionally, the amount of cardiac stimulation used may be adjusted based on the output of the sensor 6. For example, the level of stimulation may be increased or the duration of stimulation may be increased if the sensor indicates that cerebral blood circulation at 525 is insufficient.

The present invention permits the heart to be stilled or quiescent for selected and controllable periods of time in order to permit a medical procedure to be performed. While such a period of stillness or quiescence is desired, it must not last too long, otherwise insufficient blood and oxygen is delivered to organs. Thus, it is necessary to have the periods when the heart is beating (blocks 530, 535).

The state of cerebral blood circulation, for example, sensed by sensor 6 while the heart is beating may be communicated to the surgeon by a number of suitable means. For example, ambient blood flow may be indicated on a display or monitor. A visual or audio signal may indicate when the level of cerebral blood flow reaches a certain level, e.g. when blood flow is insufficient. Alternatively, the system of the present invention may "lock" the controls of the cardiac stimulator in an "on" state when the state of cerebral blood circulation reaches a predetermined condition, thereby indicating that blood circulation is insufficient. The system may then release the controls when the state of blood circulation sensed by the sensor is again sufficient.

If additional medical procedures or additional stages of medical procedures need to be performed, the heart may again be stilled using the methods of stilling the heart described above. Therefore from block 530 or block 535, the method may be repeated (as in the loop designated by 540). For example, the heart may again be prevented from contracting by stimulation of the vagal nerve (510). Additional drugs may be delivered or the drugs previously administered may continue to be administered.

This cycle may be repeated until the procedure, such as the surgery, is completed. As the cycle continues, sensor 6 enables monitoring of the state of blood circulation and, if necessary, appropriate adjustment of nerve stimulation and cardiac stimulation to ensure sufficient blood circulation.

For example, the surgical procedure at 520 may require several stitches to be made by the surgeon. The surgeon may stimulate the vagal nerve at 510 to stop the heart. Then the surgeon may make the first stitch at 520. The surgeon may then reduce or halt stimulation at 530 and allow the heart to contract. The surgeon may also pace the heart at 535. Then at 540, the surgeon may return to 510 to inhibit contractions of the heart. At 520, the surgeon will then make the second stitch. This process may be repeated (the loop designated by 540 may be repeated) until all the required stitches have been



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made. Meanwhile, the state of blood circulation is monitored continuously or, for example at blocks 517 and 525 by sensor 6. The procedure may proceed uninterrupted if the state of blood circulation remains sufficient.

If required, after the procedure is completed, step 535 may be performed until the heart is beating normally. Step 545 may be continued until the physician is satisfied that the heart is beating normally and the state of blood circulation has reached an acceptable level.

FIG. 9 is a timeline showing the relation of the vagal nerve stimulation to the cardiac stimulation in one embodiment of the present invention.

Point 610 indicates a point before the medical procedure has begun. At this point 610, both nerve stimulation and cardiac stimulation are off. At point 610, the heart is beating regularly. Then nerve stimulation is turned on to inhibit beating of the heart. During phase 601, the vagal nerve stimulation is on and the cardiac stimulation is off. This is the condition of the two types of stimulation at step 520 described above. Point 611 is a representative point during phase 601. At point 611, the contractions of the heart are stilled or substantially slowed. Then during phase 602 the vagal stimulation is turned off (as described at step 530) and the cardiac stimulation may be turned on (as described at 535). Point 612 is a representative point during phase 602. At point 612, the contractions are allowed and/or may be induced. During phase 603, the vagal nerve stimulation is again turned on and the cardiac stimulation is turned off. Then during phase 604 the vagal stimulation is again turned off and the cardiac stimulation may again be turned on. The method of the present invention may be repeated as necessary until a point is reached, represented by point 615, when the necessary medical procedures are completed. At this point 615, nerve stimulation is off although cardiac stimulation may be left on in order to pace the heart to its normal rhythm.

FIG. 10 is a timeline illustrating a relationship between a sensor, a nerve stimulator and a cardiac stimulator in one embodiment of the present invention. Point 610 indicates a point before the medical procedure has begun. At this point 610, both nerve stimulation and cardiac stimulation are off. At point 610, the heart is beating regularly. The patient's heart rate may be measured by sensor 6 at point 610. Thus, sensor 6 may be turned on at point 610.

Then nerve stimulation is turned on to inhibit beating of the heart. During phase 601, the vagal nerve stimulation is on and the cardiac stimulation is off. This is the condition of the two types of stimulation at step 520 described above. In one embodiment, as shown in FIG. 10, sensor 6 is on throughout the entire procedure. Alternatively, sensor 6 may be turned on during phase 601 to check, for example, whether a contraction is imminent or the state of cerebral blood circulation is adequate (Block 517).

Point 611 is a representative point during phase 601. At point 611, the contractions of the heart are stilled or substantially slowed. In addition, at point 611, sensor 6 may be used, for example, to determine that no contractions are imminent or if cerebral blood circulation is adequate (as described at Blocks 517 and 525). If no contractions are impending or if cerebral blood circulation is adequate at point 611, then the medical procedure can proceed (as described at Block 520). However, if a contraction is impending or cerebral blood circulation is not adequate at point 611, sensor 6 may provide a signal indicating the impending contraction or inadequate cerebral blood circulation. The surgeon may then stop the medical procedure and allow the heart to beat. After one or more cardiac contractions have occurred, the surgeon may then continue in phase 601 and finish the step of the procedure.

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Alternatively, the surgeon may proceed immediately to phase 602 after one or more contractions have occurred. Alternatively, control unit 200 may automatically proceed to phase 602 after providing the signal.

During phase 602 the vagal stimulation is turned off (as described at step 530) and the cardiac stimulation may be turned on (as described at 535). Point 612 is a representative point during phase 602. At point 612, the contractions are allowed and/or may be induced. In one embodiment, sensor 6 is still on during phase 602 and may be used to determine if the contractions are occurring appropriately or if blood circulation is occurring appropriately. Alternatively, the sensor 6 may be turned on during phase 602 to determine if the contractions are occurring appropriately.

During phase 603, the vagal nerve stimulation is again turned on and the cardiac stimulation is turned off. In one embodiment, sensor 6 has been operating throughout each phase and continues to operate through phase 603. The amount or duration of vagal stimulation during phase 603 may be different than the amount or duration of vagal stimulation during phase 601, based on the data gathered from sensor 6 during phase 601. For example, the vagal stimulation may be increased if sensor 6 detected an undesirable number of escape beats. Alternatively, sensor 6 may be turned on during phase 603 to again determine if an escape beat is imminent (as described at Block 525) or if cerebral blood circulation is adequate. Point 613 is a representative point during phase 603. If no escape beat is imminent at 613 or if cerebral blood circulation is adequate, then the medical procedure can proceed (as described in step 520). However, if an escape beat is impending or if cerebral blood circulation is inadequate, sensor 6 may provide a signal indicating this. The surgeon may then stop the medical procedure and allow the heart to beat. After the heart has beaten, the surgeon may then continue in phase 603 and finish the step of the procedure. Alternatively, the surgeon may proceed immediately to phase 604 after one or more contractions have occurred. Alternatively, control unit 200 may automatically proceed to phase 604 after providing the signal.

During phase 604 the vagal stimulation is again turned off and the cardiac stimulation may again be turned on. The amount or duration of cardiac stimulation during phase 604 may be different than the amount or duration of cardiac stimulation during phase 602, based on the data gathered from sensor 6 during the previous phases. For example, the amount or duration of cardiac stimulation may be decreased if too many escape beats occurred during the previous phases. Point 614 is a representative point during phase 604. At point 614, the contractions are allowed and/or may be induced. In one embodiment, sensor 6 is still on during phase 604 and may be used to determine if the contractions are occurring appropriately or if cerebral blood circulation is occurring adequately. Alternatively, sensor 6 may be turned on during phase 604 to determine if the contractions are occurring appropriately.

The method of the present invention may be repeated as necessary until a point is reached, represented by point 615, when the necessary medical procedures are completed. At this point 615, nerve stimulation is off although cardiac stimulation may be left on in order to pace the heart to its normal rhythm. At point 615, sensor 6 may be used to check the heart rate or cerebral blood circulation for a final time (as described at 532).

FIG. 11 shows a schematic view of one embodiment of a system of the present invention for performing a medical procedure in accordance with the present invention at 100. System 100 comprises a vasoactive drug delivery system 7, a

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nerve stimulator 10, and a cardiac stimulator 20. System 100 may include controller 30 and breathing regulator 40.

Drug delivery system 7 preferably includes a vasodilative delivery component 17 and a vasoconstrictive delivery component 27. Both delivery components 17, 27 may be any suitable means for delivering drugs to a site of a medical procedure. For example drug delivery system 7 may be a system for delivering a vasodilative spray 17 and a vasoconstrictive spray 27. Drug delivery system 7 may be a system for delivering a vasodilative cream and a vasoconstrictive cream. Drug delivery system 7 may also be a system for delivering any vasodilative formulation 17 such as an ointment or medicament etc. and any vasoconstrictive formulation 27 such as an ointment or medicament etc. or any combination thereof.

Drug delivery system 7 may comprise a catheter, such as a drug delivery catheter or a guide catheter, for delivering a vasodilative substance 17 followed by a vasoconstrictive substance 27. A drug delivery catheter may include an expandable member, e.g., a low-pressure balloon, and a shaft having a distal portion, wherein the expandable member is disposed along the distal portion. A catheter for drug delivery may comprise one or more lumens and may be delivered endovascularly via insertion into a blood vessel, e.g., an artery such as a femoral, radial, subclavian or coronary artery. The catheter can be guided into a desired position using various guidance techniques, e.g., fluoroscopic guidance and/or a guiding catheter or guide wire techniques. In one embodiment, one catheter is used to deliver both the vasodilative component and the vasoconstrictive component. Drug delivery system 7 may also be a patch, such as a transepical patch that slowly releases drugs directly into the myocardium, a cannula, a pump and/or a hypodermic needle and syringe assembly.

Drug delivery system 7 may also be an iontophoretic drug delivery device placed on the heart. In general, the delivery of ionized drugs may be enhanced via a small current applied across two electrodes. Positive ions may be introduced into the tissues from the positive pole, or negative ions from the negative pole. The use of iontophoresis may markedly facilitate the transport of certain ionized drug molecules. For example, lidocaine hydrochloride may be applied to the heart via a drug patch comprising the drug. A positive electrode could be placed over the patch and current passed. The negative electrode would contact the heart or other body part at some desired distance point to complete the circuit.

Drug delivery system 7 may be any suitable system for delivering a vasodilative component followed by a vasoconstrictive component or for delivering any appropriate vasoactive formulation.

A vasodilative component 17 may comprise one or more vasodilative drugs in any suitable formulation or combination. Examples of vasodilative drugs include, but are not limited to, a vasodilator, an organic nitrate, isosorbide mononitrate, a mononitrate, isosorbide dinitrate, a dinitrate, nitroglycerin, a trinitrate, minoxidil, sodium nitroprusside, hydralazine hydrochloride, nitric oxide, nicardipine hydrochloride, fenoldopam mesylate, diazoxide, enalaprilat, epoprostenol sodium, a prostaglandin, milrinone lactate, a bipyridine and a dopamine D1-like receptor agonist, stimulant or activator. The vasodilative component 17 may include a pharmaceutically acceptable carrier or solution in an appropriate dosage. Pharmaceutically acceptable carriers include a number of solutions, preferably sterile, for example, water, saline, Ringer's solution and/or sugar solutions such as dextrose in water or saline. Other possible carriers that may be used include sodium citrate, citric acid, amino acids, lactate, mannitol, maltose, glycerol, sucrose, ammonium chloride, sodium chloride, potassium chloride, calcium chloride,

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sodium lactate, and/or sodium bicarbonate. Carrier solutions may or may not be buffered. The vasodilative component 17 may include antioxidants or preservatives such as ascorbic acid. They may also be in a pharmaceutically acceptable form for parenteral administration, for example to the cardiovascular system, or directly to the heart, such as intracoronary infusion or injection. Drug formulations or compositions may comprise agents that provide a synergistic effect when administered together. A synergistic effect between two or more drugs or agents may reduce the amount that normally is required for therapeutic delivery of an individual drug or agent. Two or more drugs may be administered, for example, sequentially or simultaneously. Drugs may be administered via one or more bolus injections and/or infusions or combinations thereof. The injections and/or infusions may be continuous or intermittent.

The vasoconstrictive component 27 may comprise one or more suitable vasoconstrictive drugs in any suitable formulation or combination. Examples of vasoconstrictive drugs include, but are not limited to, a vasoconstrictor, a sympathomimetic, methoxamine hydrochloride, epinephrine, midodrine hydrochloride, desglymidodrine, and an alpha-receptor agonist, stimulant or activator. The vasoconstrictive component 27 may include a pharmaceutically acceptable carrier or solution in an appropriate dosage. Pharmaceutically acceptable carriers include a number of solutions, preferably sterile, for example, water, saline, Ringer's solution and/or sugar solutions such as dextrose in water or saline. Other possible carriers that may be used include sodium citrate, citric acid, amino acids, lactate, mannitol, maltose, glycerol, sucrose, ammonium chloride, sodium chloride, potassium chloride, calcium chloride, sodium lactate, and/or sodium bicarbonate. Carrier solutions may or may not be buffered. The vasoconstrictive component 27 may include antioxidants or preservatives such as ascorbic acid. They may also be in a pharmaceutically acceptable form for parenteral administration, for example to the cardiovascular system, or directly to the heart, such as intracoronary infusion or injection. Drug formulations or compositions may comprise agents that provide a synergistic effect when administered together. A synergistic effect between two or more drugs or agents may reduce the amount that normally is required for therapeutic delivery of an individual drug or agent. Two or more drugs may be administered, for example, sequentially or simultaneously. Drugs may be administered via one or more bolus injections and/or infusions or combinations thereof. The injections and/or infusions may be continuous or intermittent.

All or a portion of drug delivery system 7 may be placed in any suitable manner for application of drugs to the heart. In one embodiment, system 7 is placed to deliver drugs directly to a vessel of the heart. Drug delivery system 7 may be placed invasively or non-invasively. In one embodiment, all or a portion of drug delivery system 7 is implanted adjacent the target area of the heart. Alternatively, all or a portion of drug delivery system 7 is removably applied to the target area of the heart. For example, system 7 may comprise a vasodilative cream manually applied to the target site followed by a vasoconstrictive spray manually applied to the site. Alternatively, system 7 may comprise a guidable or steerable mechanism, such as a catheter, which allows its position to be adjusted during the medical procedure. System 7 may be positioned endoscopically and other suitable placements of system 7, such as on or near a target coronary artery and/or vein, a pulmonary artery and/or vein, the right atrium and/or ventricle, the left atrium and/or ventricle, the aorta, the AV node, and/or the coronary sinus. System 7 may also be positioned to administer or deliver drugs via intravenous, intracoronary



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and/or intraventricular administration in a suitable carrier. Examples of arteries that may be used to deliver drugs to the AV node include the AV node artery, the right coronary artery, the right descending coronary artery, the left coronary artery, the left anterior descending coronary artery and Kugel's artery.

All or a portion of drug delivery system 7 may also be placed in any suitable manner for application of drugs to another area of the body such as the leg or another limb. For example, the system 7 may be placed to apply vasoactive substances to a saphenous vein to be harvested or to any other suitable graft vessel. In one embodiment, system 7 is placed to deliver drugs directly to a suitable graft vessel. Drug delivery system 7 may be placed invasively or non-invasively. In one embodiment, drug delivery system 7 is implanted adjacent the graft vessel. Alternatively, drug delivery system is removably applied to the graft vessel.

Drug delivery system 7 may be powered by AC current, DC current or it may be battery powered by a disposable or re-chargeable battery. Drug delivery system 7 may comprise a surgeon controlled switch box. A switch, or all of drug delivery system 7 may also be incorporated in or on one of the surgeon's instruments, such as surgical site retractor, or any other location easily and quickly accessed by the surgeon for delivery of drugs by the surgeon. The switch may be, for example, a hand switch, a foot switch, or a voice-activated switch comprising voice-recognition technologies.

A visual and/or audible signal used to alert a surgeon to the completion or resumption of vasodilative or vasoconstrictive drugs may be incorporated into system 7. For example, a beeping tone or flashing light may be used to indicate that a vasodilative drug is being delivered followed by a different tone or light to indicate that a vasoconstrictive drug is being delivered.

Drug delivery system 7 may be slaved to nerve stimulator 10 or cardiac stimulator 20. Software controlling drug delivery system may be designed to automatically deliver drugs while nerve stimulator 10 or cardiac stimulator 20 is on.

Drug delivery system 7, nerve stimulator 10 and/or cardiac stimulator 20 may be slaved to a robotic system or a robotic system may be slaved to drug delivery system 7, nerve stimulator 10 and/or cardiac stimulator 20. Breathing regulator 40 and other components, as described above, may also be slaved to such a system.

FIG. 12 shows one embodiment of the present invention at 200. In this embodiment, the elements named above may be combined or connected to a control unit along with other components. The unit 200 may be used to coordinate the various elements. Unit 200 may incorporate a controller or any suitable processor 230.

Drug delivery system 207 may be incorporated into unit 200. For example, FIG. 12 shows drug delivery system 207, including a vasodilative needle assembly 217 for delivery of vasodilative drugs and a vasoconstrictive needle assembly 227 for delivery of vasoconstrictive drugs. Different positions of the vasodilative component 217 and vasoactive component 227 are accessible through various access openings, for example, in the cervical or thorax regions. Drug delivery system 207 or components of drug delivery system may be positioned through a thoracotomy, sternotomy, endoscopically through a percutaneous port, through a stab wound or puncture, through a small incision in the neck or chest, through the internal jugular vein, the esophagus, the trachea, placed on the skin or in combinations thereof.

Drug delivery system 207 may be in communication with a processor 230 as shown in FIG. 12. The processor may thus be used to process the administration of drugs delivered by

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system 207. The processor may store information about the drugs being delivered such as dosage amounts and when particular dosages have been delivered.

Controller 230 may be used to gather information from drug delivery system 207, nerve stimulation electrodes 210 and cardiac stimulation electrodes 220. Controller 230 may also be used to control the stimulation levels and stimulation duration of nerve stimulation electrodes 210 and cardiac stimulation electrodes 220 or the drug delivery levels and duration of system 207. Controller 230 may also gather and process information from the various components of system 100. This information may be used to adjust stimulation levels and stimulation times of nerve stimulation electrodes 210 and cardiac stimulation electrodes 220 or the drug delivery levels and duration of system 207.

As described above, unit 200 may incorporate one or more switches to facilitate regulation of the various components by the surgeon. One example of such a switch is shown as foot pedal 250. The switch may also be, for example, a hand switch, or a voice-activated switch comprising voice-recognition technologies. The switch may be incorporated in or on one of the surgeon's instruments, such as surgical site retractor, or any other location easily and quickly accessed by the surgeon. Unit 200 may also include a display 260. Unit 200 may also include other means of indicating the status of various components to the surgeon such as a numerical display, gauges, a monitor display or audio feedback. Unit 200 may also include one or more visual and/or audible signals used to prepare a surgeon for the start or stop of nerve stimulation and/or cardiac stimulation.

FIG. 13 shows a flow diagram of one embodiment of the present invention. The patient is prepared for a medical procedure at 500.

At block 510, a nerve that controls the beating of the heart is stimulated. Such a nerve may be for example a vagal nerve. During this time, one or more of a variety of pharmacological agents or drugs, as described above, may be delivered locally or systemically in addition to the locally administered vasoactive drugs delivered by system 7 (block 517). These drugs may produce reversible asystole of a heart while maintaining the ability of the heart to be electrically paced. In one embodiment of the invention, a vasodilator is delivered at block 517. Other drugs may be administered for a variety of functions and purposes as described below. Drugs delivered in addition to the vasoactive drugs may be administered at the beginning of the procedure, intermittently during the procedure, continuously during the procedure or following the procedure.

At block 517, a vasoactive drug is delivered to the site of the medical procedure. In one embodiment, a vasodilative drug is delivered locally using vasodilative delivery component 17. The drug may be applied directly to a vessel in order to cause the vessel to dilate. Such a dilated vessel is easier to view and provides an enlarged field upon which to perform the procedure.

At block 520, a medical procedure, as described above, may be performed or begun. Such a procedure may be, for example, surgery on the heart. In one embodiment, the procedure may be surgery on the vessel upon which the vasodilative formulation has been delivered. Alternatively, the procedure may be surgery performed on another organ or another vessel in another organ of the body. For example, a graft vessel, such as the saphenous vein, may be harvested at this point.

As seen in FIG. 13, an additional vasoactive drug or drug formulation may be delivered to the site of the medical procedure at block 527 in one embodiment of the invention. For example, a vasoconstrictive drug may be delivered locally



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using vasoconstrictive delivery component 17. The drug may be applied directly to a vessel in order to cause the vessel to constrict, particularly to constrict to its usual size. Such a constricted vessel may now perform its usual functions.

After a time, the medical procedure or one phase of the procedure is completed. After some phase of the medical procedure is performed, cardiac contractions are allowed to occur (block 530). Cardiac contractions may need to occur intermittently during the procedure to ensure adequate blood flow. In one embodiment, the stimulation from the nerve stimulator 10 is stopped or slowed enough to allow the heart to contract. For example, the vagal nerve stimulation is removed, thereby allowing cardiac contractions to occur.

In another embodiment, the heart may be stimulated to ensure that cardiac contractions occur (block 535). For example, cardiac stimulator 20 may be used to apply pacing pulses to the heart to encourage the heart to contract normally. In particular, the pacing pulses may be applied to the ventricle as is well known in the field.

The present invention permits the heart to be stilled for selected and controllable periods of time in order to permit a medical procedure to be performed. While such a period of stillness is desired, it must not last too long, otherwise insufficient blood and oxygen is delivered to organs. Thus, it is necessary to have the periods when the heart is beating (blocks 530, 535).

If additional medical procedures or additional stages of medical procedures need to be performed, the heart may again be stilled using the methods of stilling the heart described above. Therefore, from block 530 or block 535, the method may be repeated (block 540). For example, the heart may again be prevented from contracting by stimulation of the vagal nerve (510). Additional delivery of a vasodilative formulation (block 517) followed by, for example, surgery (block 520) followed by delivery of a vasoconstrictive formulation (block 527) may occur on the same or a different vessel. Additional drugs may be delivered or the drugs previously administered may continue to be administered.

Additional steps of the medical procedure or additional medical procedures may be performed (Block 520) while the heart is still. Then this stage of stillness may be followed by another stage when the stimulation is removed (block 530) and the heart is allowed to contract. Again, the heart may be stimulated to encourage contractions (block 535).

This cycle may be repeated until the procedure, such as surgery, is completed. After the procedure is completed, step 535 may be performed until the heart is beating normally.

For example, a surgical procedure at 520 may require several stitches to be made by the surgeon. The surgeon may stimulate the vagal nerve at 510 to stop the heart. The surgeon may then apply the vasodilative formulation at 517 to facilitate viewing of and manipulation of the vessel to be stitched. Then the surgeon may make the first stitch at 520. The surgeon may apply a vasoconstrictive formulation if appropriate at 527. The surgeon may then reduce or halt stimulation at 530 and allow the heart to contract. The surgeon may also pace the heart at 535. Then at 540, the surgeon may return to 510 to inhibit contractions of the heart. At 520, the surgeon will then make the second stitch. This process may be repeated (the loop designated by 540 may be repeated) until all the required stitches have been made. Alternatively, the surgeon may apply the vasoconstrictive formulation at block 545 after all the required stitches have been made.

In one embodiment, after the surgery is completed, step 535 is performed until the heart is beating normally. At the procedure's end, one or more of a variety of pharmacological agents or drugs may be delivered or may continue to be

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delivered for example to alleviate pain or aid in recuperation. Other drugs may be administered for a variety of functions and purposes as described above.

FIG. 14 is a timeline illustrating one embodiment of the relationship between vasoactive drug delivery, vagal nerve stimulation and cardiac stimulation.

Point 610 indicates a point before the medical procedure has begun. At this point 610, both nerve stimulation and cardiac stimulation are off. At point 610, the heart is beating regularly. Then nerve stimulation is turned on to inhibit beating of the heart. During phase 601, the vagal nerve stimulation is on and the cardiac stimulation is off. This is the condition of the two types of stimulation at step 520 described above.

Point 611 is a representative point during phase 601. At point 611, the contractions of the heart are stilled or substantially slowed. A vasoactive formulation may be delivered at point 612, once the heart is still or substantially slowed. After all or a portion of the medical procedure is performed during phase 601, a vasoconstrictive substance may be delivered at point 613, which is a point near the end of phase 601. Alternatively, the vasoconstrictive substance may be applied at a later time.

During phase 602 the vagal stimulation is turned off (as described at step 530) and the cardiac stimulation may be turned on (as described at 535). Point 614 is a representative point during phase 602. At point 614, the contractions are allowed and/or may be induced.

During phase 603, the vagal nerve stimulation is again turned on and the cardiac stimulation is turned off. Vasoactive substances may again be delivered during phase 603 in an appropriate manner. The amounts or types of vasoactive substances delivered during phase 603 may be the same or different from those delivered during phase 601. In one embodiment, phase 603 is the final phase of the medical procedure and at point 615, which is a point after the medical procedure has been completed, a vasoconstrictive formulation may be delivered.

Alternatively, the procedure may enter a phase represented by phase 604. During phase 604 the vagal stimulation is again turned off and the cardiac stimulation may again be turned on. Point 616 is a representative point during phase 604. At point 616, the contractions are allowed and/or may be induced.

The method of the present invention may be repeated as necessary until a point is reached, represented by point 617, when the necessary medical procedures are completed. At this point 617, nerve stimulation is off although cardiac stimulation may be left on in order to pace the heart to its normal rhythm. Vasoconstrictive drugs or other drugs may be delivered at point 617.

It will be appreciated by those skilled in the art that while the invention has been described above in connection with particular embodiments and examples, the invention is not necessarily so limited, and that numerous other embodiments, examples, uses, modifications and departures from the embodiments, examples and uses are intended to be encompassed by the claims attached hereto. The entire disclosure of each patent and publication cited herein is incorporated by reference, as if each such patent or publication were individually incorporated by reference herein.

What is claimed is:

1. A method of performing a cardiac medical procedure on a patient, comprising:

- a) electrically stimulating a heart to adjust beating of the heart;
- b) delivering a stent device to the stimulated heart while the heart is beating; and

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c) reducing electrical stimulation of the heart to readjust beating of the heart after delivering the stent device.

2. The method of claim 1, wherein the heart is stimulated by transvascular stimulation.

3. The method of claim 2, wherein the transvascular stimulation comprises delivering a pacemaker lead through a catheter to the ventricle of the heart of the patient.

4. The method of claim 1, wherein the stimulating of the heart comprises pacing the heart.

5. The method of claim 1 further comprising: administering at least one drug during the cardiac medical procedure.

6. The method of claim 5, wherein the drug is selected from the group consisting of: a beta-blocker, a cholinergic agent, a cholinesterase inhibitor, a calcium channel blocker, a sodium channel blocker, a potassium channel agent, adenosine, an adenosine receptor agonist, an adenosine deaminase inhibitor, dipyridamole, a monoamine oxidase inhibitor, digoxin, digitalis, lignocaine, a bradykinin agent, a serotonergic agonist, an antiarrhythmic agent, a cardiac glycoside, a local anesthetic, atropine, a calcium solution, an agent that promotes heart rate, an agent that promotes heart contractions, dopamine, a catecholamine, an inotropic glucagon, a hormone, forskolin, epinephrine, norepinephrine, thyroid hormone, a phosphodiesterase inhibitor, prostacyclin, prostaglandin and a methylxanthine.

7. The method of claim 1, wherein the stimulating of the heart comprises stimulating the Purkinje fibers.

8. The method of claim 1, wherein the cardiac medical procedure is a heart valve replacement procedure.

9. The method of claim 8, wherein the stent device is a replacement heart valve.

10. A method of performing a cardiac medical procedure, comprising:

- a) obtaining a stent device;
- b) electrically stimulating a heart to adjust beating of the heart to a first condition;
- c) delivering the stent device to the stimulated heart when the beating of the stimulated heart has been adjusted to the first condition, when the heart is beating in the first condition; and
- d) reducing electrical stimulation of the heart to adjust beating of the heart to a second condition after delivering the stent device.

11. The method of claim 10 further comprising: stimulating the heart a subsequent time in order to re-adjust beating of the heart to the first condition.

12. The method of claim 10 wherein stimulating the heart comprises transvascular stimulation.

13. The method of claim 10 wherein reducing stimulation of the heart comprises stopping stimulation of the heart to achieve the second condition.

14. The method of claim 10, wherein the first condition is a slowed condition.

15. The method of claim 10, wherein the second condition is a beating condition.

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16. The method of claim 10 further comprising: stimulating the heart in order to adjust beating of the heart to the second condition.

17. The method of claim 10, wherein stimulating comprises pacing the heart to achieve the first condition.

18. The method of claim 10 further comprising: administering at least one drug during the cardiac procedure.

19. The method of claim 18 wherein the drug is selected from the group consisting of: a beta-blocker, a cholinergic agent, a cholinesterase inhibitor, a calcium channel blocker, a sodium channel blocker, a potassium channel agent, adenosine, an adenosine receptor agonist, an adenosine deaminase inhibitor, dipyridamole, a monoamine oxidase inhibitor, digoxin, digitalis, lignocaine, a bradykinin agent, a serotonergic agonist, an antiarrhythmic agent, a cardiac glycoside, a local anesthetic, atropine, a calcium solution, an agent that promotes heart rate, an agent that promotes heart contractions, dopamine, a catecholamine, an inotropic glucagon, a hormone, forskolin, epinephrine, norepinephrine, thyroid hormone, a phosphodiesterase inhibitor, prostacyclin, prostaglandin and a methylxanthine.

20. The method of claim 10, wherein the stimulating of the heart comprises stimulating the Purkinje fibers.

21. The method of claim 10, wherein the stent device is a replacement heart valve.

22. A method of performing a cardiac medical procedure on a human patient, comprising:

- a) obtaining a stent device;
- b) delivering a pacemaker lead through a catheter to the ventricle of the heart of the patient;
- c) electrically stimulating the heart;
- d) delivering the stent device to the heart while the heart is beating; and
- e) decreasing the electrical stimulation of the heart after delivering the stent device.

23. The method of claim 22, wherein the stent device is a stent.

24. The method of claim 22, wherein the stent device is a replacement heart valve.

25. The method of claim 22, wherein stimulating the heart comprises pacing the heart.

26. The method of claim 22, wherein the cardiac medical procedure comprises a heart valve replacement procedure.

27. The method of claim 22, wherein stimulating the heart comprises stimulating the Purkinje fibers.

28. A method of performing a cardiac medical procedure on a patient, comprising:

- a) delivering a pacemaker lead through a catheter to the ventricle of the heart of the patient;
- b) electrically stimulating the heart to adjust beating of the heart to a first rate;
- c) delivering a stent device to the heart when the heart is beating at the first rate;
- d) reducing electrical stimulation of the heart to adjust beating of the heart to a second rate after delivering the stent device;
- e) removing the pacemaker lead from the heart of the patient.

\* \* \* \* \*

# EXHIBIT “2”





US007184829B2

(12) **United States Patent**  
**Hill et al.**

(10) **Patent No.:** **US 7,184,829 B2**  
(45) **Date of Patent:** **\*Feb. 27, 2007**

(54) **METHOD AND SYSTEM FOR NERVE STIMULATION PRIOR TO AND DURING A MEDICAL PROCEDURE**

(58) **Field of Classification Search** ..... 607/2-3, 607/9-10; 128/897-898  
See application file for complete search history.

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(73) **Assignee:** **Medtronic, Inc.**, Minneapolis, MN (US)

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(\*) **Notice:** Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 141 days.

This patent is subject to a terminal disclaimer.

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(21) **Appl. No.:** **10/768,999**

(22) **Filed:** **Jan. 30, 2004**

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(65) **Prior Publication Data**  
US 2004/0186517 A1 Sep. 23, 2004

**Primary Examiner**—Carl Layno  
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**Related U.S. Application Data**

(57) **ABSTRACT**

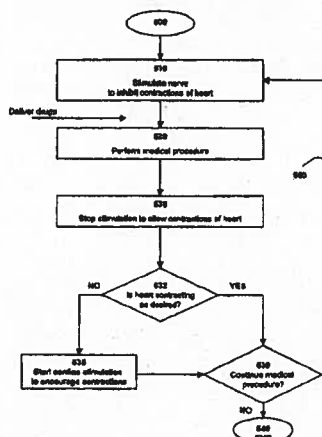
(63) Continuation of application No. 10/207,725, filed on Jul. 29, 2002, now Pat. No. 6,718,208, which is a continuation of application No. 09/670,441, filed on Sep. 26, 2000, now Pat. No. 6,449,507, which is a continuation-in-part of application No. 09/433,323, filed on Nov. 3, 1999, now Pat. No. 6,266,564, which is a continuation of application No. 09/070,506, filed on Apr. 30, 1998, now Pat. No. 6,006,134, which is a continuation-in-part of application No. 08/640,013, filed on Apr. 30, 1996, now abandoned.

A method of performing a medical procedure, such as surgery, is provided. A nerve is stimulated in order to adjust the beating of the heart to a first condition, such as a stopped or slowed condition. The medical procedure is performed on the heart or another organ. The stimulation of the nerve is stopped in order to adjust the beating of the heart to a second condition, such as a beating condition. The heart itself may also be stimulated to a beating condition, such as by pacing. The stimulation of the nerve may be continued in order to allow the medical procedure to be continued. Systems and devices for performing the medical procedure are also provided.

(51) **Int. Cl.**  
**A61N 1/362** (2006.01)

(52) **U.S. Cl.** ..... 607/2; 607/3; 607/9

**46 Claims, 4 Drawing Sheets**



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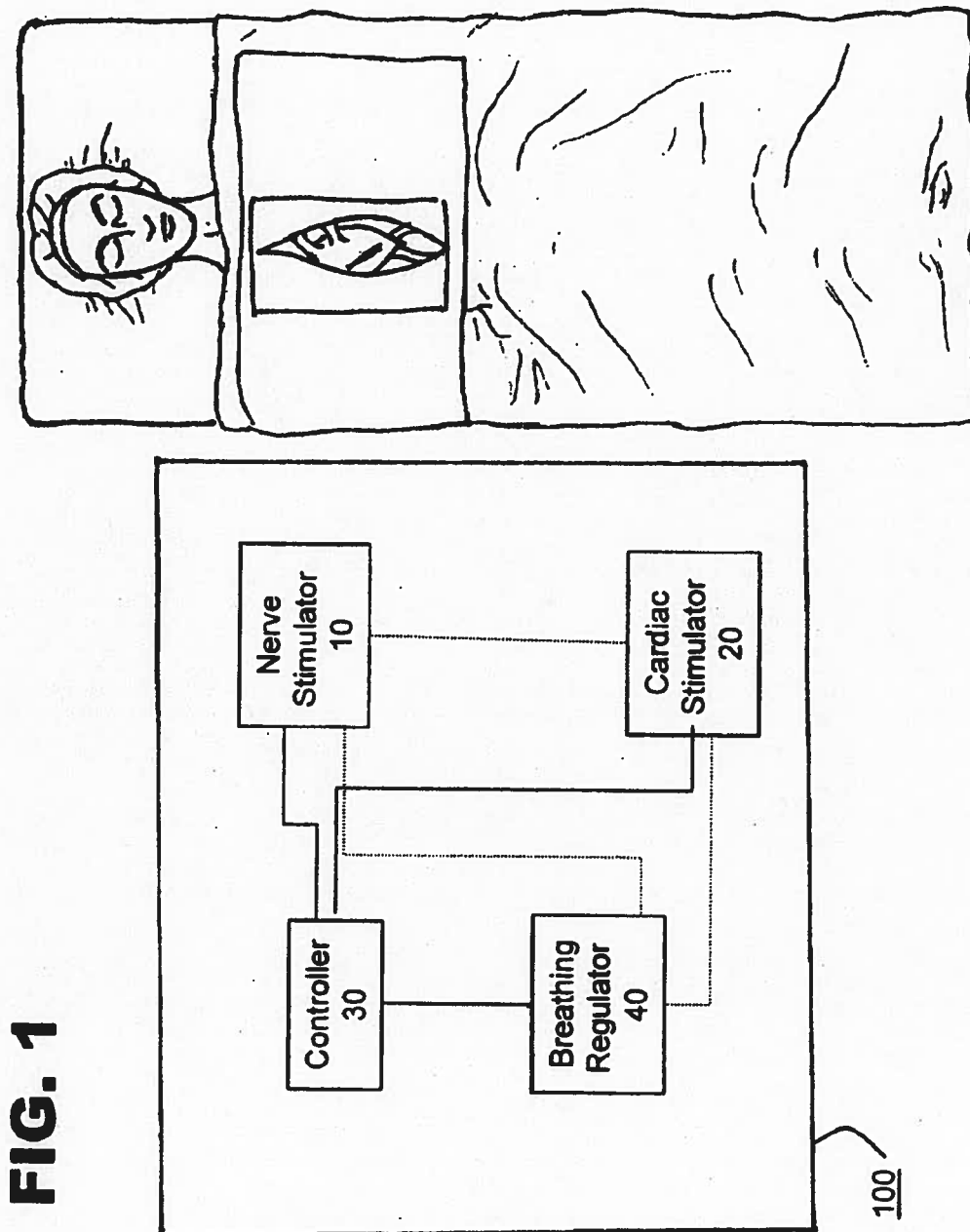


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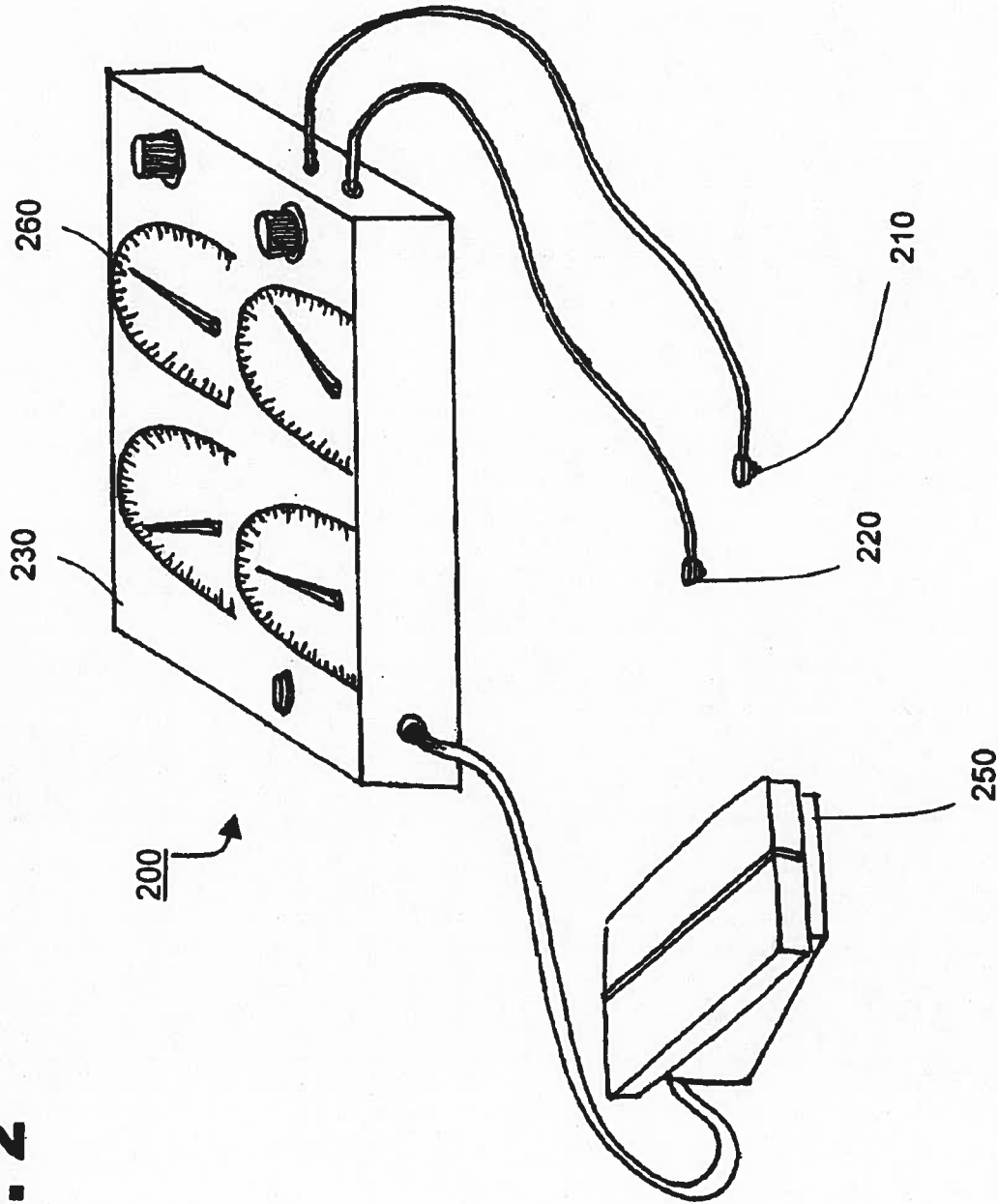
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**FIG. 2**

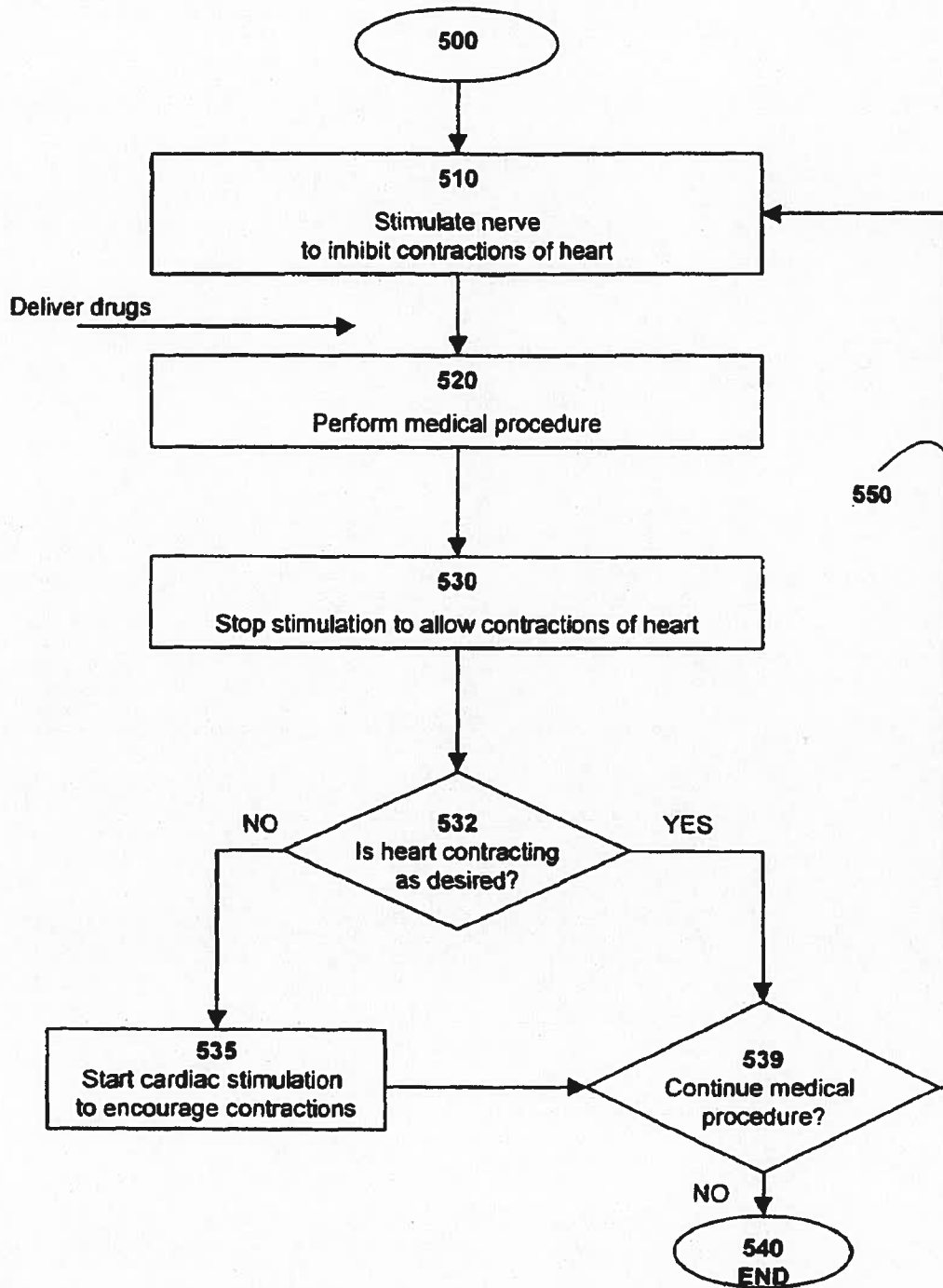


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**FIG. 3**



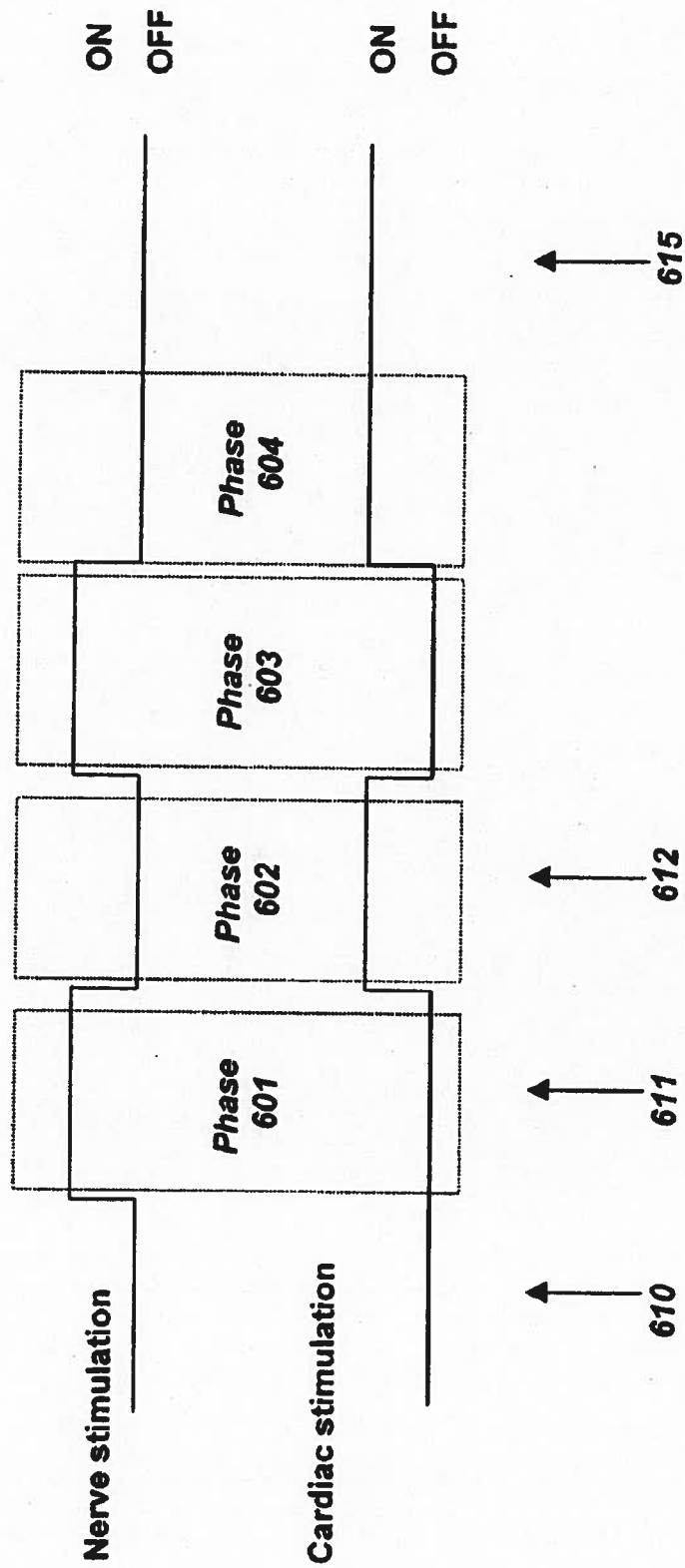
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**FIG. 4**



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# METHOD AND SYSTEM FOR NERVE STIMULATION PRIOR TO AND DURING A MEDICAL PROCEDURE

## CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 10/207,725, filed on Jul. 29, 2002, now U.S. Pat. No. 6,718,208 to inventors Hill, Jahns and Keogh, which is a continuation of U.S. patent application Ser. No. 09/670,441, filed on Sep. 26, 2000, now U.S. Pat. No. 6,449,507, to inventors Hill, Jahns and Keogh, which is a continuation-in-part of U.S. patent application Ser. No. 09/433,323, filed on Nov. 3, 1999, now U.S. Pat. No. 6,266,564, to inventors Hill and Jonkman, which is a continuation of U.S. patent application Ser. No. 09/070,506, filed on Apr. 30, 1998, now U.S. Pat. No. 6,006,134, to inventors Hill and Jonkman, which is a continuation-in-part of U.S. patent application Ser. No. 08/640,013, filed on Apr. 30, 1996, now abandoned.

## FIELD OF THE INVENTION

This invention relates to methods for performing a medical procedure, especially a procedure during which it is necessary to adjust the beating of the heart. More particularly, this invention relates to methods and systems of stimulating a nerve in order to modify the beating of a heart to allow a medical procedure to be performed or for blood flow to be controlled.

## BACKGROUND OF THE INVENTION

The current leading cause of death in the United States is coronary artery disease in which the coronary arteries are blocked by atherosclerotic plaques or deposits of fat. The typical treatment to relieve a partially or fully blocked coronary artery is coronary artery bypass graft (CABG) surgery.

CABG surgery, also known as "heart bypass" surgery, generally entails using a graft to bypass the coronary obstruction. The procedure is generally lengthy, traumatic and subject to patient risks. Among the risk factors involved is the use of a cardiopulmonary bypass (CPB) circuit, also known as a "heart-lung machine," to pump blood and oxygenate the blood so that the patient's heart may be stopped during the surgery.

Conventional CABG procedures are typically conducted on a stopped heart while the patient is on a (CPB) circuit. A stopped heart and a CPB circuit enables a surgeon to work in a bloodless, still operative field. However, there are a number of problems associated with CABG procedures performed while on CPB including the initiation of a systemic inflammatory response due to interactions of blood elements with the artificial material surfaces of the CPB circuit and global myocardial ischemia due to cardioplegic cardiac arrest. For these reasons, avoiding the use of CPB or cardioplegic cardiac arrest may help minimize post-operative complications.

One method, as disclosed in U.S. Pat. No. 5,651,378 to inventors Matheny and Taylor and in U.S. Pat. No. 5,913,876 to inventors Taylor et al., for facilitating coronary bypass surgery on a beating heart and thereby avoid the use of CPB and cardioplegic cardiac arrest includes stimulating the vagal nerve electrically in order to temporarily stop or

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substantially reduce the beating of the heart. This may be followed by pacing the heart to start its beating.

Another method, as disclosed in two published PCT applications, WO 99/09971 and WO 99/09973, both to inventor Puskas, involves stopping the beating of the heart during coronary bypass surgery using electrical stimulation of the vagal nerve in combination with administration of drugs. Another method, as disclosed in U.S. Pat. No. 6,060,454 to inventor Duhaylongsod, involves stopping the beating of the heart during coronary bypass surgery via the local delivery of drugs to the heart.

Although it is desirable to stop the heart for a period of time in order to allow the surgeon to accomplish a required task without interference from heart movement, i.e. a motionless operative field, it is undesirable to have the heart stopped for too long a period of time since the body needs, among other things, a constant supply of oxygen. In fact, it is particularly important to maintain sufficient blood flow, and therefore oxygen flow, to the brain. Stopping the heart for prolonged periods of time may cause damage to the patient.

It would be desirable therefore to provide a method for controllably stopping or slowing the heart intermittently for diagnostic purposes.

Additionally, it would be desirable to provide a method for controllably stopping or slowing the heart intermittently for therapeutic purposes.

Additionally, it would be desirable to provide a method for controllably stopping or slowing the heart intermittently in order to control blood flow.

Additionally, it would be desirable to provide a method for controllably stopping or slowing the heart intermittently in order to perform a medical procedure on the heart or another organ.

## SUMMARY OF THE INVENTION

One aspect of the present invention provides a method of performing a medical procedure. The method includes stimulating a nerve to adjust the beating of a heart to a first condition. A medical procedure is then performed the medical procedure on an organ. Stimulation of the nerve is then reduced to adjust the beating of a heart to a second condition. The nerve is then stimulated a subsequent time in order to re-adjust the beating of the heart to the first condition and then the medical procedure is continued.

The nerve may be stimulated using transvascular stimulation. The stimulation may be stopped to achieve the second condition. The first condition may be a stopped or a slowed condition. The second condition may be a beating condition. The heart may also be stimulated to adjust the beating of the heart to the second condition. The heart may be stimulated by pacing.

Drugs, such as a beta-blocker, a cholinergic agent, a cholinesterase inhibitor, a calcium channel blocker, a sodium channel blocker, a potassium channel agent, adenosine, an adenosine receptor agonist, an adenosine deaminase inhibitor, dipyridamole, a monoamine oxidase inhibitor, digoxin, digitalis, lignocaine, a bradykinin agent, a serotonergic agonist, an antiarrhythmic agent, a cardiac glycoside, a local anesthetic, atropine, a calcium solution, an agent that promotes heart rate, an agent that promotes heart contractions, dopamine, a catecholamine, an inotrope glucagon, a hormone, forskolin, epinephrine, norepinephrine, thyroid hormone, a phosphodiesterase inhibitor, prostacyclin, prostaglandin and a methylxanthine, may be delivered

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during the medical procedure. These drugs may be naturally occurring or chemically synthesized.

The nerve being stimulated may be vagus nerve fibers, hypoglossal nerve fibers, phrenic nerve fibers, parasympathetic nerve fibers, and sympathetic nerve fibers, a vagal nerve, a carotid sinus nerve, a fat pad. The organ may be the heart.

The medical procedure may be surgical procedures, non-surgical procedures, endoscopic procedures, fluoroscopic procedures, stent delivery procedures, aortic aneurysm repairs, cranial aneurysm repairs, delivery of drugs, delivery of biological agents, cardiac surgery with cardiopulmonary bypass circuits, cardiac surgery without cardiopulmonary bypass circuits, brain surgery, cardiograms, heart valve repair, heart valve replacement, MAZE procedures, transmyocardial revascularization, CABG procedures, beating heart surgery, vascular surgery, neurosurgery, electrophysiology procedures, diagnostic ablation of arrhythmias, therapeutic ablation of arrhythmias, endovascular procedures, treatment of injuries to the liver, treatment of the spleen, treatment of the heart, treatment of the lungs, treatment of major blood vessels, non-invasive procedures, invasive procedures, and port-access procedures.

Another aspect of the present invention provides a system for performing a medical procedure. The system includes a transvenous nerve stimulator to inhibit beating of the heart and a cardiac stimulator in communication with the transvenous nerve stimulator to stimulate beating of the heart. The system may also include drug delivery means for delivering at least one drug during the medical procedure such as a spray, a cream, an ointment, a medicament, a pill, a patch, a catheter, a cannula, a needle and syringe, a pump, and an iontophoretic drug delivery device. The transvenous nerve stimulator may stimulate vagus nerve fibers, hypoglossal nerve fibers, phrenic nerve fibers, parasympathetic nerve fibers, and sympathetic nerve fibers, a vagal nerve, a carotid sinus nerve, a fat pad. The transvenous nerve stimulator comprises one or more electrodes such as nerve stimulation electrodes, endotracheal electrodes, endoesophageal electrodes, intravascular electrodes, transcutaneous electrodes, intracutaneous electrodes, balloon-type electrodes, basket-type electrodes, umbrella-type electrodes, tape-type electrodes, suction-type electrodes, screw-type electrodes, barb-type electrodes, bipolar electrodes, monopolar electrodes, metal electrodes, wire electrodes, patch electrodes, cuff electrodes, clip electrodes, needle electrodes and probe electrodes. The cardiac stimulator also comprises one or more electrodes such as cardiac stimulation electrodes, clip electrodes, needle electrodes, probe electrodes, pacing electrodes, epicardial electrodes, patch electrodes, intravascular electrodes, balloon-type electrodes, basket-type electrodes, tape-type electrodes, umbrella-type electrodes, suction-type electrodes, endotracheal electrodes, endoesophageal electrodes, transcutaneous electrodes, intracutaneous electrodes, screw-type electrodes, barb-type electrodes, bipolar electrodes, monopolar electrodes, metal electrodes, wire electrodes and cuff electrodes. The system may also include a respiratory controller for controlling respiration.

Another aspect of the present invention provides a method of performing heart surgery. A nerve is stimulated transvenously to reduce the beating of a heart. The heart is operated upon. Stimulation of the nerve is then reduced or stopped. The heart is stimulated to cause beating of the heart. The nerve is then restimulated to re-inhibit beating of the heart and surgery is continued.

Another aspect of the present invention provides a device for performing a medical procedure. The device includes a

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processor connected to a transvenous nerve stimulation electrode and a cardiac stimulation electrode. The processor processes output from the nerve stimulation electrode and adjusts output from the cardiac stimulation electrode based on output from the nerve stimulation electrode. Stimulation from the nerve stimulation electrode may occur in an inverse relationship to stimulation from the cardiac stimulation electrode.

The foregoing, and other, features and advantages of the invention will become further apparent from the following detailed description of the presently preferred embodiments, read in conjunction with the accompanying drawings. The detailed description and drawings are merely illustrative of the invention rather than limiting, the scope of the invention being defined by the appended claims in equivalence thereof.

#### BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a schematic view of one embodiment of a system for performing a medical procedure in accordance with the present invention;

FIG. 2 is a schematic view of one embodiment of a medical device in accordance with the present invention;

FIG. 3 is a flow diagram of one embodiment of a method of performing a medical procedure in accordance with the present invention; and

FIG. 4 is a timeline view of one embodiment of a system for controllably stopping or slowing the heart intermittently in a patient monitoring blood flow in the brain during a medical procedure in accordance with the present invention.

#### DETAILED DESCRIPTION OF THE PRESENTLY PREFERRED EMBODIMENTS

FIG. 1 shows a schematic view of one embodiment of a system for performing a medical procedure in accordance with the present invention at 100. System 100 comprises a nerve stimulator 10, and a cardiac stimulator 20. System 100 may also feature a controller 30 and a breathing regulator 40.

System 100 may also include a nerve stimulator 10. In one embodiment, the nerve stimulator 10 may be used to electrically manipulate cardiac rhythm by stimulating the vagus nerve. This vagal stimulation may produce asystole (slowing or stopping of the heart's beating.) Once this induced asystole is stopped, i.e. once the vagal stimulation is stopped, the heart may be allowed to return to its usual cardiac rhythm. Alternatively, the heart may be paced with an electrical pacing system, thereby maintaining a normal cardiac output. Vagal stimulation, alone or in combination with electrical pacing, may be used selectively and intermittently to allow a surgeon to perform a medical procedure during intermittent periods of asystole.

It is known that stimulation of the vagus nerve can reduce the sinus rate, as well as prolong AV conduction time or, if stimulation energies are high enough, induce AV node block. Use of vagal nerve stimulation to treat supraventricular arrhythmias and angina pectoris is disclosed in the article "Vagal Tuning" by Bilgutay et al., Journal of Thoracic and Cardiovascular Surgery, Vol. 56, No. 1, July, 1968, pp. 71-82. It is also known that stimulation of the carotid sinus nerve produces a similar result, as disclosed in the article "Carotid Sinus Nerve Stimulation in the Treatment of Angina Pectoris and Supraventricular Tachycardia" by Braunwald et al., published in California Medicine, Vol. 112, pp. 41-50, March, 1970.



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As set forth in "Functional Anatomy of the Cardiac Efferent Innervation" by Randall et al., in *Neurocardiology*, edited by Kulbertus et al, Futura Publishing Co., 1988, direct surgical excision of the fat pad associated with the SA node affects the functioning of the SA node without significantly affecting the AV node. Similarly, excision of the fat pad associated with the AV node affects functioning of the AV node without significantly affecting the SA node.

As set forth in the article "Parasympathetic Postganglionic Pathways to the Sinoatrial Node", Bluemel et al., *Am. J. Physiol.* 259, (Heart Circ. Physiol. 28) H1504-H1510, 1990, stimulation of the fat pad associated with the SA node results in slowing of the sinus rate without the accompanying prolongation of AV conduction time which normally results from vagal nerve stimulation. The article also indicates that stimulation of the fat pad associated with the AV node is believed to produce corresponding effects limited to the AV node, i.e., extension of the AV conduction time without concurrent slowing of the sinus rate.

As set forth in the article "Neural Effects on Sinus Rate and Atrial Ventricular Conduction Produced by Electrical Stimulation From a Transvenous Electrode Catheter in the Canine Right Pulmonary Artery" by Cooper et al., published in *Circulation Research*, Vol. 46, No. 1, January, 1980, pp. 48-57, the fat pads associated with both the AV node and the SA node may be stimulated by means of electrodes located in the right pulmonary artery. The results obtained include both a depression of the sinus rate and a prolongation of the AV conduction time in response to continuous stimulation at 2-80 Hz at up to 50 ma.

Generally in healthy individuals, the SA node functions as the pacemaker. Normal heart rhythm associated with the SA node is typically referred to as sinus rhythm. When the SA node fails, the AV node generally takes over creating a heart rate of approximately 35 to 60 beats per minute. Heart rhythm associated with the AV node is typically referred to as nodal rhythm. When the AV node itself is blocked or injured, a new even slower pacemaker site may form at the junction of the AV node and the His bundle. Heart rhythm associated with this junction is typically referred to as junctional escape rhythm. When this junction site is inhibited, the Purkinje fibers in the His bundle or below may act as a pacemaker creating a heart rate of approximately 30 beats per minute. Heart rhythm associated with the Purkinje fibers is typically referred to as idioventricular rhythm.

In one embodiment of the present invention, nerve stimulator 10 may be used to electrically manipulate cardiac rhythm by stimulating the carotid sinus nerve, the fat pad associated with the SA node, the fat pad associated with the AV node, the junction of the AV node and the His bundle and/or the Purkinje fibers.

In one embodiment of the present invention, nerve stimulator 10 is used alone or in combination with other heart rate inhibiting agents to temporarily stop or slow the beating heart, thereby eliminating or reducing heart motion and/or blood flow during a medical procedure. For example, the present invention may be used to eliminate or reduce motion in the anastomosis field during CABG procedures such that a facilitated anastomosis procedure may be performed safely and effectively. The number of occasions that the vagal nerve may be stimulated depends on the type of medical procedure to be performed. Likewise, the type of medical procedure to be performed will dictate the duration of the individual electrical stimulations.

Nerve stimulator 10 may be powered by AC current, DC current or it may be battery powered either by a disposable or re-chargeable battery. Nerve stimulator 10 may be con-

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figured to synchronize activation and deactivation of breathing regulator 40 with vagal stimulation, thereby minimizing or eliminating unwanted heart and chest motion associated with the patient's breathing. Nerve stimulator 10 may comprise a surgeon controlled switch box. A switch may be incorporated in or on one of the surgeon's instruments, such as surgical site retractor, or any other location easily and quickly accessed by the surgeon for regulation of the nerve stimulator 10 by the surgeon. The switch may be, for example, a hand switch, a foot switch, or a voice-activated switch comprising voice-recognition technologies.

A visual and/or audible signal used to alert a surgeon to the completion or resumption of vagal nerve stimulation may be incorporated into nerve stimulator 10. For example, a beeping tone or flashing light that increases in frequency as the nerve stimulation period should end or begin may be used.

Nerve stimulator 10 may be slaved to cardiac stimulator 20 or cardiac stimulator 20 may be slaved to nerve stimulator 10. For example, the output of cardiac stimulator 20 may be off whenever the output of nerve stimulator 10 is on. Software controlling cardiac stimulator 20 may be designed to automatically commence cardiac pacing if the heart does not resume beating within a pre-determined interval after cessation of vagal nerve stimulation. In addition, the software controlling nerve stimulator 10 may be designed to automatically stop vagal nerve stimulation if the heart has been stopped for too long.

System 100 may also include cardiac stimulator 20 which may be used to stimulate the heart as desired. As with nerve stimulator 10, cardiac stimulator 20 may be intermittently stopped and started to allow the surgeon to perform individual steps of a medical procedure.

Cardiac stimulator 20 may be a conventional ventricular demand pacer or dual chamber (atrial-ventricular) pacer. Cardiac stimulator 20 may be powered by AC current, DC current or it may be battery powered either by a disposable or re-chargeable battery. Cardiac stimulator 20 may be configured to synchronize activation and deactivation of breathing regulator 40 with pacing, thereby minimizing or eliminating unwanted heart and chest motion associated with the patient's breathing. Cardiac stimulator 20 may be any conventional pacing device suitable for ventricular demand pacing and having leads electrically coupled to a switch box. Cardiac stimulator 20 may be combined in a single unit with a switch box. Cardiac stimulator 20 may comprise a surgeon controlled switch box. A switch may be incorporated in or on one of the surgeon's instruments, such as surgical site retractor, or any other location easily and quickly accessed by the surgeon for regulation of the cardiac stimulator by the surgeon. The switch may be, for example, a hand switch, a foot switch, or a voice-activated switch comprising voice-recognition technologies. A single switch may be used to regulate both cardiac stimulator 20 and nerve stimulator 10.

A visual and/or audible signal used to prepare a surgeon for the resumption of pacing may be incorporated into cardiac stimulator 20. For example, a beeping tone or flashing light that increases in frequency as the pacing period ends may be used. A single signaling method or device may be used for both cardiac stimulator 20 and nerve stimulator 10.

Nerve stimulator 10 and/or cardiac stimulator 20 may be slaved to a robotic system or a robotic system may be slaved to nerve stimulator 10 and/or cardiac stimulator 20. Breathing regulator 40 and other components may also be slaved to such a system. Computer- and voice-controlled robotic

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systems that position and maneuver endoscopes and/or other surgical instruments for performing microsurgical procedures such as anastomoses through small incisions may be used by a surgeon to perform precise and delicate maneuvers. These robotic systems may allow a surgeon to perform a variety of microsurgical procedures including endoscopic CABG. Endoscopic CABG may allow multiple occluded coronary arteries to be bypassed without a thoracotomy or mini-thoracotomy. Heart valve repair and replacement may also be other surgical applications for these robotic systems. In general, robotic systems may include head-mounted displays which integrate 3-D visualization of surgical anatomy and related diagnostic and monitoring data, miniature high resolution 2-D and 3-D digital cameras, a computer, a high power light source and a standard video monitor.

System 100 may also include a breathing regulator 40. In one embodiment, the breathing regulator 40 may be used to stimulate the phrenic nerve in order to provide a diaphragmatic pacemaker. Breathing regulator 40 may comprise one or more electrodes for supplying electrical current to the phrenic nerve to control breathing during vagal and/or cardiac stimulation and/or destimulation. Electrodes used to stimulate the phrenic nerve may be, for example, non-invasive, e.g., clips, or invasive, e.g., needles or probes. The application of an electrical stimulus to the phrenic nerve may include, but is not limited to bipolar and/or monopolar techniques. Different electrode positions are accessible through various access openings, for example, in the cervical or thorax regions. Nerve stimulation electrodes may be positioned through a thoracotomy, sternotomy, endoscopically through a percutaneous port, through a stab wound or puncture, through a small incision, placed on the skin or in combinations thereof. The present invention may include various electrodes, catheters and electrode catheters suitable for phrenic nerve stimulation to control breathing.

Phrenic nerve stimulation electrodes may be intravascular, patch-type, balloon-type, basket-type, umbrella-type, tape-type, cuff-type, suction-type, screw-type, barb-type, bipolar, monopolar, metal, wire, endotracheal, endoesophageal, intravascular, transcutaneous or intracutaneous electrodes. Guided or steerable catheter devices comprising electrodes may be used alone or in combination with the nerve stimulation electrodes. For example, a catheter comprising one or more wire, metal strips or metal foil electrodes or electrode arrays may be used. The catheter may comprise, for example, a balloon which may be inflated with air or liquid to press the electrodes firmly against a vessel wall that lays adjacent the phrenic nerve.

Phrenic nerve stimulation electrodes may be oriented in any fashion along the catheter device, including longitudinally or transversely. Various techniques such as ultrasound, fluoroscopy and echocardiography may be used to facilitate positioning of the electrodes. If desired or necessary, avoidance of obstruction of blood flow may be achieved with notched catheter designs or with catheters which incorporate one or more tunnels or passageways.

In another embodiment, the breathing regulator 40 may comprise a connector which interfaces with a patient's respirator, and sends a logic signal to activate or deactivate the respirator to control breathing during vagal and/or cardiac stimulation and/or destimulation.

FIG. 2 shows one embodiment of the present invention at 200. In this embodiment, the elements named above may be combined or connected to a control unit along with other

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components. The unit 200 may be used to coordinate the various elements. Unit 200 may incorporate a controller or any suitable processor 230.

Unit 200 may incorporate a nerve stimulator. For example, FIG. 2 shows an electrode for nerve stimulation at 210. Electrodes used to stimulate a nerve such as the vagal nerve may be, for example, non-invasive, e.g., clips, or invasive, e.g., needles or probes. The application of an electrical stimulus to the right or left vagal nerve may include, but is not limited to bipolar and/or monopolar techniques. Different electrode positions are accessible through various access openings, for example, in the cervical or thorax regions. Nerve stimulation electrodes 210 may be positioned through a thoracotomy, sternotomy, endoscopically through a percutaneous port, through a stab wound or puncture, through a small incision in the neck or chest, through the internal jugular vein, the esophagus, the trachea, placed on the skin or in combinations thereof. Electrical stimulation may be carried out on the right vagal nerve, the left vagal nerve or to both nerves simultaneously or sequentially. The present invention may include various electrodes, catheters and electrode catheters suitable for vagal nerve stimulation to temporarily stop or slow the beating heart alone or in combination with other heart rate inhibiting agents.

Nerve stimulation electrodes 210 may be endotracheal, endoesophageal, intravascular, transcutaneous, intracutaneous, patch-type, balloon-type, cuff-type, basket-type, umbrella-type, tape-type, screw-type, barb-type, metal, wire or suction-type electrodes. Guided or steerable catheter devices comprising electrodes may be used alone or in combination with the nerve stimulation electrodes 210. For example, a catheter comprising one or more wire, metal strips or metal foil electrodes or electrode arrays may be inserted into the internal jugular vein to make electrical contact with the wall of the internal jugular vein, and thus stimulate the vagal nerve adjacent to the internal jugular vein. Access to the internal jugular vein may be via, for example, the right atrium, the right atrial appendage, the inferior vena cava or the superior vena cava. The catheter may comprise, for example, a balloon which may be inflated with air or liquid to press the electrodes firmly against the vessel wall. Similar techniques may be performed by insertion of a catheter-type device into the trachea or esophagus. Additionally, tracheal tubes and esophageal tubes comprising electrodes may be used.

Nerve stimulation electrodes 210 may be oriented in any fashion along the catheter device, including longitudinally or transversely. Various techniques such as ultrasound, fluoroscopy and echocardiography may be used to facilitate positioning of the electrodes. If desired or necessary, avoidance of obstruction of blood flow may be achieved with notched catheter designs or with catheters which incorporate one or more tunnels or passageways.

In one embodiment of the present invention, the location of the electrodes 210 is chosen to elicit maximum bradycardia effectiveness while minimizing current spread to adjacent tissues and vessels and to prevent the induction of post stimulation tachycardia. Furthermore, a non-conductive material such as plastic may be employed to sufficiently enclose the electrodes of all the configurations to shield them from the surrounding tissues and vessels, while exposing their confronting edges and surfaces for positive contact with the vagal nerve or selected tissues.

Unit 200 may also incorporate a cardiac stimulator. For example, FIG. 2 shows an electrode for stimulation of the heart at 220. Cardiac electrodes 220 used to stimulate the



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heart may be, for example, non-invasive, e.g., clips, or invasive, e.g., needles or probes. Electrodes 220 may be positioned through a thoracotomy, sternotomy, endoscopically through a percutaneous port, through a stab wound or puncture, through a small incision in the chest, placed on the chest or in combinations thereof. The present invention may also use various electrodes, catheters and electrode catheters suitable for pacing the heart, e.g., epicardial, patch-type, intravascular, balloon-type, basket-type, umbrella-type, tape-type electrodes, suction-type, pacing electrodes, endotracheal electrodes, endoesophageal electrodes, transcutaneous electrodes, intracutaneous electrodes, screw-type electrodes, barb-type electrodes, bipolar electrodes, monopolar electrodes, metal electrodes, wire electrodes and cuff electrodes. Guided or steerable catheter devices comprising electrodes may be used alone or in combination with the electrodes.

Controller 230 may be used to gather information from nerve stimulation electrodes 210 and cardiac stimulation electrodes 220. Controller 230 may also be used to control the stimulation levels and stimulation duration of nerve stimulation electrodes 210 and cardiac stimulation electrodes 220. Controller 230 may also gather and process information from the various components of system 100. This information may be used to adjust stimulation levels and stimulation times of nerve stimulation electrodes 210 and cardiac stimulation electrodes 220.

Unit 200 may incorporate one or more switches to facilitate regulation of the various components by the surgeon. One example of such a switch is shown as foot pedal 250. The switch may also be, for example, a hand switch, or a voice-activated switch comprising voice-recognition technologies. The switch may be incorporated in or on one of the surgeon's instruments, such as surgical site retractor, or any other location easily and quickly accessed by the surgeon.

Unit 200 may also include a display 260. Unit 200 may also include other means of indicating the status of various components to the surgeon such as a numerical display, gauges, a monitor display or audio feedback. Unit 200 may also include one or more visual and/or audible signals used to prepare a surgeon for the start or stop of nerve stimulation and/or cardiac stimulation.

FIG. 3 shows a flow diagram of one embodiment of the present invention. The patient is prepared for a medical procedure at 500.

At block 510, a nerve that controls the beating of the heart is stimulated. Such a nerve may be for example a vagal nerve. The nerve may be stimulated to slow, inhibit or stop the contractions of the heart.

Also at block 510, one or more of a variety of pharmacological agents or drugs may be delivered. These drugs may produce reversible asystole of a heart while maintaining the ability of the heart to be electrically paced.

A variety of pharmacological agents or drugs may also be delivered at other times during the procedure 500. These drugs may also produce reversible asystole of a heart while maintaining the ability of the heart to be electrically paced. Other drugs may be administered for a variety of functions and purposes as described below. Drugs may be delivered at any appropriate time during the medical procedure, for example, at the beginning of the procedure, intermittently during the procedure, continuously during the procedure, or following the procedure.

Drugs, drug formulations or compositions suitable for administration to a patient during a medical procedure may include a pharmaceutically acceptable carrier or solution in an appropriate dosage. There are a number of pharmaceu-

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tically acceptable carriers that may be used for delivery of various drugs, for example, via direct injection, oral delivery, suppository delivery, transdermal delivery, epicardial delivery and/or inhalation delivery. Pharmaceutically acceptable carriers include a number of solutions, preferably sterile, for example, water, saline, Ringer's solution and/or sugar solutions such as dextrose in water or saline. Other possible carriers that may be used include sodium citrate, citric acid, amino acids, lactate, mannitol, maltose, glycerol, sucrose, ammonium chloride, sodium chloride, potassium chloride, calcium chloride, sodium lactate, and/or sodium bicarbonate. Carrier solutions may or may not be buffered.

Drug formulations or compositions may include antioxidants or preservatives such as ascorbic acid. They may also be in a pharmaceutically acceptable form for parenteral administration, for example to the cardiovascular system, or directly to the heart, such as intracoronary infusion or injection. Drug formulations or compositions may comprise agents that provide a synergistic effect when administered together. A synergistic effect between two or more drugs or agents may reduce the amount that normally is required for therapeutic delivery of an individual drug or agent. Two or more drugs may be administered, for example, sequentially or simultaneously. Drugs may be administered via one or more bolus injections and/or infusions or combinations thereof. The injections and/or infusions may be continuous or intermittent. Drugs may be administered, for example, systemically or locally, for example, to the heart, to a coronary artery and/or vein, to a pulmonary artery and/or vein, to the right atrium and/or ventricle, to the left atrium and/or ventricle, to the aorta, to the AV node, to the SA node, to a nerve and/or to the coronary sinus. Drugs may be administered or delivered via intravenous, intracoronary and/or intraventricular administration in a suitable carrier. Examples of arteries that may be used to deliver drugs to the AV node include the AV node artery, the right coronary artery, the right descending coronary artery, the left coronary artery, the left anterior descending coronary artery and Kugel's artery. Drugs may be delivered systemically, for example, via oral, transdermal, intranasal, suppository or inhalation methods. Drugs also may be delivered via a pill, a spray, a cream, an ointment or a medicament formulation.

Drugs may be delivered via a drug delivery device that may comprise a catheter, such as a drug delivery catheter or a guide catheter, a patch, such as a transepical patch that slowly releases drugs directly into the myocardium, a cannula, a pump and/or a hypodermic needle and syringe assembly. A drug delivery catheter may include an expandable member, e.g., a low-pressure balloon, and a shaft having a distal portion, wherein the expandable member is disposed along the distal portion. A catheter for drug delivery may comprise one or more lumens and may be delivered endovascularly via insertion into a blood vessel, e.g., an artery such as a femoral, radial, subclavian or coronary artery. The catheter can be guided into a desired position using various guidance techniques, e.g., fluoroscopic guidance and/or a guiding catheter or guide wire techniques.

Drugs may be delivered via an iontophoretic drug delivery device placed on the heart. In general, the delivery of ionized drugs may be enhanced via a small current applied across two electrodes. Positive ions may be introduced into the tissues from the positive pole, or negative ions from the negative pole. The use of iontophoresis may markedly facilitate the transport of certain ionized drug molecules. For example, lidocaine hydrochloride may be applied to the heart via a drug patch comprising the drug. A positive electrode could be placed over the patch and current passed.



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The negative electrode would contact the heart or other body part at some desired distance point to complete the circuit. One or more of the electrodes may also be used as nerve stimulation electrodes 210 or as cardiac stimulation electrodes 220.

The two divisions of the autonomic nervous system that regulate the heart have opposite functions. First, the adrenergic or sympathetic nervous system increases heart rate by releasing epinephrine and norepinephrine. Second, the parasympathetic system also known as the cholinergic nervous system or the vagal nervous system decreases heart rate by releasing acetylcholine. Catecholamines such as norepinephrine (also called noradrenaline) and epinephrine (also called adrenaline) are agonists for beta-adrenergic receptors. An agonist is a stimulant biomolecule or agent that binds to a receptor.

Beta-adrenergic receptor blocking agents compete with beta-adrenergic receptor stimulating agents for available beta-receptor sites. When access to beta-receptor sites are blocked by receptor blocking agents, also known as beta-adrenergic blockade, the chronotropic or heart rate, inotropic or contractility, and vasodilator responses to receptor stimulating agents are decreased proportionately. Therefore, beta-adrenergic receptor blocking agents are agents that are capable of blocking beta-adrenergic receptor sites.

Since beta-adrenergic receptors are concerned with contractility and heart rate, stimulation of beta-adrenergic receptors, in general, increases heart rate, the contractility of the heart and the rate of conduction of electrical impulses through the AV node and the conduction system.

Drugs, drug formulations and/or drug compositions that may be used according to this invention may include any naturally occurring or chemically synthesized (synthetic analogues) beta-adrenergic receptor blocking agents. Beta-adrenergic receptor blocking agents or  $\beta$ -adrenergic blocking agents are also known as  $\beta$ -blockers or  $\beta$ -blockers and as class II antiarrhythmics.

The term "beta-blocker" appearing herein may refer to one or more agents that antagonize the effects of beta-stimulating catecholamines by blocking the catecholamines from binding to the beta-receptors. Examples of beta-blockers include, but are not limited to, acebutolol, alprenolol, atenolol, betantolol, betaxolol, bevantolol, bisoprolol, cartersol, celiprolol, chlorthalidone, esmolol, labetalol, metoprolol, nadolol, penbutolol, pindolol, propranolol, oxprenolol, sotalol, teratolo, timolol and combinations, mixtures and/or salts thereof.

The effects of administered beta-blockers may be reversed by administration of beta-receptor agonists, e.g., dobutamine or isoproterenol.

The parasympathetic or cholinergic system participates in control of heart rate via the sinoatrial (SA) node, where it reduces heart rate. Other cholinergic effects include inhibition of the AV node and an inhibitory effect on contractile force. The cholinergic system acts through the vagal nerve to release acetylcholine, which, in turn, stimulates cholinergic receptors. Cholinergic receptors are also known as muscarinic receptors. Stimulation of the cholinergic receptors decreases the formation of cAMP. Stimulation of cholinergic receptors generally has an opposite effect on heart rate compared to stimulation of beta-adrenergic receptors. For example, beta-adrenergic stimulation increases heart rate, whereas cholinergic stimulation decreases it. When vagal tone is high and adrenergic tone is low, there is a marked slowing of the heart (sinus bradycardia). Acetylcholine effectively reduces the amplitude, rate of increase and duration of the SA node action potential. During vagal nerve

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stimulation, the SA node does not arrest. Rather, pacemaker function may shift to cells that fire at a slower rate. In addition, acetylcholine may help open certain potassium channels thereby creating an outward flow of potassium ions and hyperpolarization. Acetylcholine also slows conduction through the AV node.

Drugs, drug formulations and/or drug compositions that may be used according to this invention may include any naturally occurring or chemically synthesized (synthetic analogues) cholinergic agent. The term "cholinergic agent" appearing herein may refer to one or more cholinergic receptor modulators or agonists. Examples of cholinergic agents include, but are not limited to, acetylcholine, carbachol (carbaryl choline chloride), bethanechol, methacholine, arecoline, norepinephrine and combinations, mixtures and/or salts thereof.

Drugs, drug formulations and/or drug compositions that may be used according to this invention may include any naturally occurring or chemically synthesized cholinesterase inhibitor. The term "cholinesterase inhibitor" appearing herein may refer to one or more agents that prolong the action of acetylcholine by inhibiting its destruction or hydrolysis by cholinesterase. Cholinesterase inhibitors are also known as acetylcholinesterase inhibitors. Examples of cholinesterase inhibitors include, but are not limited to, edrophonium, neostigmine, neostigmine methylsulfate, pyridostigmine, tacrine and combinations, mixtures and/or salts thereof.

There are ion-selective channels within certain cell membranes. These ion selective channels include calcium channels, sodium channels and/or potassium channels. Therefore, other drugs, drug formulations and/or drug compositions that may be used according to this invention may include any naturally occurring or chemically synthesized calcium channel blocker. Calcium channel blockers inhibit the inward flux of calcium ions across cell membranes of arterial smooth muscle cells and myocardial cells. Therefore, the term "calcium channel blocker" appearing herein may refer to one or more agents that inhibit or block the flow of calcium ions across a cell membrane. The calcium channel is generally concerned with the triggering of the contractile cycle. Calcium channel blockers are also known as calcium ion influx inhibitors, slow channel blockers, calcium ion antagonists, calcium channel antagonist drugs and as class IV antiarrhythmics. A commonly used calcium channel blocker is verapamil.

Administration of a calcium channel blocker, e.g., verapamil, generally prolongs the effective refractory period within the AV node and slows AV conduction in a rate-related manner, since the electrical activity through the AV node depends significantly upon the influx of calcium ions through the slow channel. A calcium channel blocker has the ability to slow a patient's heart rate, as well as produce AV block. Examples of calcium channel blockers include, but are not limited to, amiloride, amlodipine, bepridil, diltiazem, felodipine, isradipine, mibefradil, nicardipine, nifedipine (dihydropyridines), nickel, nimodipine, nisoldipine, nitric oxide (NO), norverapamil and verapamil and combinations, mixtures and/or salts thereof. Verapamil and diltiazem are very effective at inhibiting the AV node, whereas drugs of the nifedipine family have a lesser inhibitory effect on the AV node. Nitric oxide (NO) indirectly promotes calcium channel closure. NO may be used to inhibit contraction. NO may also be used to inhibit sympathetic outflow, lessen the release of norepinephrine, cause vasodilation, decrease heart rate and decrease contractility. In the SA node, cholinergic stimulation leads to formation of NO.

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Other drugs, drug formulations and/or drug compositions that may be used according to this invention may include any naturally occurring or chemically synthesized sodium channel blocker. Sodium channel blockers are also known as sodium channel inhibitors, sodium channel blocking agents, rapid channel blockers or rapid channel inhibitors. Antiarrhythmic agents that inhibit or block the sodium channel are known as class I antiarrhythmics, examples include, but are not limited to, quinidine and quinidine-like agents, lidocaine and lidocaine-like agents, tetrodotoxin, encainide, flecainide and combinations, mixtures and/or salts thereof. Therefore, the term "sodium channel blocker" appearing herein may refer to one or more agents that inhibit or block the flow of sodium ions across a cell membrane or remove the potential difference across a cell membrane. For example, the sodium channel may also be totally inhibited by increasing the extracellular potassium levels to depolarizing hyperkalemic values, which remove the potential difference across the cell membrane. The result is inhibition of cardiac contraction with cardiac arrest (cardioplegia). The opening of the sodium channel (influx of sodium) is for swift conduction of the electrical impulse throughout the heart.

Other drugs, drug formulations and/or drug compositions that may be used according to this invention may include any naturally occurring or chemically synthesized potassium channel agent. The term "potassium channel agent" appearing herein may refer to one or more agents that impact the flow of potassium ions across the cell membrane. There are two major types of potassium channels. The first type of channel is voltage-gated and the second type is ligand-gated. Acetylcholine-activated potassium channels, which are ligand-gated channels, open in response to vagal stimulation and the release of acetylcholine. Opening of the potassium channel causes hyperpolarization which decreases the rate at which the activation threshold is reached. Adenosine is one example of a potassium channel opener. Adenosine slows conduction through the AV node. Adenosine, a breakdown product of adenosine triphosphate, inhibits the AV node and atria. In atrial tissue, adenosine causes the shortening of the action potential duration and causes hyperpolarization. In the AV node, adenosine has similar effects and also decreases the action potential amplitude and the rate of increase of the action potential. Adenosine is also a direct vasodilator by its actions on the adenosine receptor on vascular smooth muscle cells. In addition, adenosine acts as a negative neuromodulator, thereby inhibiting release of norepinephrine. Class III antiarrhythmic agents also known as potassium channel inhibitors lengthen the action potential duration and refractoriness by blocking the outward potassium channel to prolong the action potential. Amiodarone and d-sotalol are both examples of class III antiarrhythmic agents.

Potassium is the most common component in cardioplegic solutions. High extracellular potassium levels reduce the membrane resting potential. Opening of the sodium channel, which normally allows rapid sodium influx during the upstroke of the action potential, is therefore inactivated because of a reduction in the membrane resting potential. The present invention may be combined with conventional CPB, the induced asystole as described by this invention may serve as a substitute for conventional cardioplegic arrest. For example, the combination of drugs and vagal stimulation may be used as a cardioplegic agent in a variety of medical procedures.

Drugs, drug formulations and/or drug compositions that may be used during according to this invention may comprise one or more of any naturally occurring or chemically

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synthesized beta-blocker, cholinergic agent, cholinesterase inhibitor, calcium channel blocker, sodium channel blocker, potassium channel agent, adenosine, adenosine receptor agonist, adenosine deaminase inhibitor, dipyridamole, monoamine oxidase inhibitor, digoxin, digitalis, lignocaine, bradykinin agents, serotonergic agonist, antiarrhythmic agents, cardiac glycosides, local anesthetics and combinations or mixtures thereof. Digitalis and digoxin both inhibit the sodium pump. Digitalis is a natural inotrope derived from plant material, while digoxin is a synthesized inotrope. Dipyridamole inhibits adenosine deaminase which breaks down adenosine. Drugs, drug formulations and/or drug compositions capable of reversibly suppressing autonomous electrical conduction at the SA and/or AV node, while still allowing the heart to be electrically paced to maintain cardiac output may be used according to this invention.

In one embodiment, the cardiac asystole produced in accordance with the present invention is reversible, e.g., chemically such as by the administration of atropine or by natural forces. Beta-adrenergic stimulation or administration of calcium solutions may be used to reverse the effects of a calcium channel blocker such as verapamil. Agents that promote heart rate and/or contraction may be used in a preferred embodiment of the present invention. For example, dopamine, a natural catecholamine, is known to increase contractility. Positive inotropes are agents that specifically increase the force of contraction of the heart. Glucagon, a naturally occurring hormone, is known to increase heart rate and contractility. Glucagon may be used to reverse the effects of a beta-blocker since its effects bypass the beta receptor. Forskolin is known to increase heart rate and contractility. As mentioned earlier, epinephrine and norepinephrine naturally increase heart rate and contractility. Thyroid hormone, phosphodiesterase inhibitors and prostacyclin, a prostaglandin, are also known to increase heart rate and contractility. In addition, methylxanthines are known to prevent adenosine from interacting with its cell receptors.

Typically, vagal nerve stimulation prevents the heart from contracting. This non-contraction must then be followed by periods without vagal nerve stimulation during which the heart is allowed to contract.

At Block 520, a medical procedure may be performed or begun. Such a procedure may be, for example, surgery on the heart. Alternatively, the procedure may be surgery performed on another organ of the body.

The term "medical procedure" may mean any one or more medical or surgical procedures such as, for example cardiac surgery, performed with or without cardiopulmonary bypass (CPB) circuits, heart valve repair, heart valve replacement, MAZE procedures, revascularization procedures, transmyocardial revascularization (IMR) procedures, percutaneous myocardial revascularization (PMR) procedures, CABG procedures, anastomosis procedures, non-surgical procedures, fluoroscopic procedures, beating heart surgery, vascular surgery, neurosurgery, brain surgery, electrophysiology procedures, diagnostic and therapeutic procedures, ablation procedures, ablation of arrhythmias, endovascular procedures, treatment of the liver, spleen, heart, lungs, and major blood vessels, aneurysm repair, imaging procedures of the heart and great vessels, CAT scans or MRI procedures, pharmacological therapies, drug delivery procedures, gene therapies, cellular therapies, cancer therapies, radiation therapies, genetic, cellular, tissue and/or organ manipulation or transplantation procedures, coronary angioplasty procedures, placement or delivery of coated or noncoated stents, atherectomy procedures, atherosclerotic plaque manipula-



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tion and/or removal procedures, procedures where bleeding needs to be precisely controlled, procedures that require precise control of cardiac motion and/or bleeding.

When the medical procedure comprises one or more medical devices, e.g., coated stents, these devices may be coated with one or more radioactive materials and/or biological agents such as, for example, an anticoagulant agent, an antithrombotic agent, a clotting agent, a platelet agent, an anti-inflammatory agent, an antibody, an antigen, an immunoglobulin, a defense agent, an enzyme, a hormone, a growth factor, a neurotransmitter, a cytokine, a blood agent, a regulatory agent, a transport agent, a fibrous agent, a protein, a peptide, a proteoglycan, a toxin, an antibiotic agent, an antibacterial agent, an antimicrobial agent, a bacterial agent or component, hyaluronic acid, a polysaccharide, a carbohydrate, a fatty acid, a catalyst, a drug, a vitamin, a DNA segment, a RNA segment, a nucleic acid, a lectin, an antiviral agent, a viral agent or component, a genetic agent, a ligand and a dye (which acts as a biological ligand). Biological agents may be found in nature (naturally occurring) or may be chemically synthesized.

The medical procedure may be non-invasive, minimally invasive and/or invasive. The medical procedure may entail a port-access approach, a partially or totally endoscopic approach, a sternotomy approach or a thoracotomy approach. The medical procedure may include the use of various mechanical stabilization devices or techniques as well as various robotic or imaging systems.

In one method, the heart may be temporarily slowed or intermittently stopped for short periods of time to permit the surgeon to accomplish the required surgical task and yet still allow the heart itself to supply blood circulation to the body. For example, stimulation of the vagus nerve in order to temporarily and intermittently slow or stop the heart is described in U.S. Pat. No. 6,006,134 entitled "Method and Device for Electronically Controlling the Beating of a Heart Using Venous Electrical Stimulation of Nerve Fibers," Dec. 21, 1999, to inventors Hill and Junkman. This patent is assigned to Medtronic, Inc. and is incorporated herein by reference.

After a time, the medical procedure or one phase of the medical procedure is completed at 520. As seen at Block 530, after all or some phase of the medical procedure is performed, cardiac contractions are allowed to occur. Cardiac contractions may be allowed to occur intermittently during the procedure to ensure adequate blood flow. In one embodiment, the stimulation from the nerve stimulator 10 is stopped or slowed enough to allow the heart to contract. For example, the vagal nerve stimulation is removed, thereby allowing cardiac contractions to occur.

As seen at Block 532, it may be evaluated if the cardiac contractions are occurring as desired.

As seen at Block 535, if the contractions are not occur as desired, the heart may be stimulated to ensure that cardiac contractions occur. For example, cardiac stimulator 20 may be used to apply pacing pulses to the heart to encourage the heart to contract normally. In particular, the pacing pulses may be applied to the ventricle as is well known in the field. Once the heart is contracting as desired, the method may proceed to Block 539.

The present invention permits the heart to be stilled for selected and controllable periods of time in order to permit cardiac or other medical procedure to be performed. While such a period of stillness is desired, it must not last too long, otherwise insufficient blood and oxygen is delivered to organs. Thus, it is necessary to have the periods when the heart is beating (by stopping stimulation to allow contrac-

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tions as seen at Block 530 and/or by starting cardiac stimulation to encourage contractions as seen at Block 535).

As seen at Block 539, if the heart is contracting as desired, it may be determined if additional medical procedures or additional stages of the current medical procedure need to be performed. If not, the method may end as seen at Block 540. If it is determined that the procedure should continue, the heart may again be stilled using the methods of stilling the heart described above. Thus, as seen at 550, the method of the present invention may return to Block 510 and be repeated. For example, the heart may again be prevented from contracting by stimulation of the vagal nerve (Block 510). Additional drugs may be delivered or the drugs previously administered may continue to be administered.

Additional surgery, additional steps in the medical procedure or additional medical procedures may again be performed (Block 520) while the heart is still. Then, this stage of stillness may be followed by another stage when the stimulation is removed (Block 530) and the heart is allowed to contract. Again, the heart may be stimulated to encourage contractions (Block 535).

This cycle may be repeated until the procedure, such as the surgery, is completed. After the procedure is completed, step 535 may be performed until the heart is beating normally. At the procedure's end, one or more of a variety of pharmacological agents or drugs may be delivered or may continue to be delivered for example to alleviate pain or aid in recuperation. Other drugs may be administered for a variety of functions and purposes as described above.

For example, a surgical procedure at 520 may require several stitches to be made by the surgeon. The surgeon may stimulate the vagal nerve at 510 to stop the heart. Then the surgeon may make the first stitch at 520. The surgeon may then reduce or halt stimulation at 530 and allow the heart to contract. The surgeon may also pace the heart at 535. Then at 540, the surgeon may return to 510 to inhibit contractions of the heart. At 520, the surgeon will then make the second stitch. This process may be repeated (the loop designated by 540 may be repeated) until all the required stitches have been made.

FIG. 4 is a timeline showing the relation of the vagal nerve stimulation to the cardiac stimulation in one embodiment of the present invention.

Point 610 indicates a point before the medical procedure has begun. At this point 610, both nerve stimulation and cardiac stimulation are off. At point 610, the heart is beating regularly. Then nerve stimulation is turned on to inhibit beating of the heart. During phase 601, the vagal nerve stimulation is on and the cardiac stimulation is off. This is the condition of the two types of stimulation at step 520 described above. Point 611 is a representative point during phase 601. At point 611, the contractions of the heart are stilled or substantially slowed. Then during phase 602 the vagal stimulation is turned off (as described at step 530) and the cardiac stimulation may be turned on (as described at 535). Point 612 is a representative point during phase 602. At point 612, the contractions are allowed and/or may be induced. During phase 603, the vagal nerve stimulation is again turned on and the cardiac stimulation is turned off. Then during phase 604 the vagal stimulation is again turned off and the cardiac stimulation may again be turned on. The method of the present invention may be repeated as necessary until a point is reached, represented by point 615, when the necessary medical procedures are completed. At this point 615, nerve stimulation is off although cardiac stimulation may be left on in order to pace the heart to its normal rhythm.



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It will be appreciated by those skilled in the art that while the invention has been described above in connection with particular embodiments and examples, the invention is not necessarily so limited, and that numerous other embodiments, examples, uses, modifications and departures from the embodiments, examples and uses are intended to be encompassed by the claims attached hereto. The entire disclosure of each patent and publication cited herein is incorporated by reference, as if each such patent or publication were individually incorporated by reference herein.

We claim:

1. A method for controllably stopping or slowing a heart intermittently during a medical procedure, comprising:
  - providing a controllable nerve stimulator capable of automatically stopping stimulation of a vagal nerve, the nerve stimulator comprising a nerve stimulation electrode;
  - positioning the nerve stimulation electrode in a position suitable for stimulating a vagal nerve to stop or slow the heart;
  - controllably starting stimulation of the vagal nerve; automatically stopping stimulation of the vagal nerve; continuing to start and stop stimulation of the vagal nerve in order to stop or slow the heart intermittently during the medical procedure.
2. The method of claim 1 wherein the vagal nerve is stimulated using transvascular stimulation.
3. The method of claim 1 wherein the vagal nerve is stimulated using endotracheal stimulation.
4. The method of claim 1 wherein the vagal nerve is stimulated using esophageal stimulation.
5. The method of claim 1 wherein the vagal nerve is stimulated using transcutaneous stimulation.
6. The method of claim 1 wherein the vagal nerve is stimulated using intracutaneous stimulation.
7. The method of claim 1 further comprising delivering at least one drug during the medical procedure.
8. The method of claim 7 wherein the drug is selected from the group consisting of: a beta-blocker, a cholinergic agent, a cholinesterase inhibitor, a calcium channel blocker, a sodium channel blocker, a potassium channel agent, adenosine, an adenosine receptor agonist, an adenosine deaminase inhibitor, dipyridamole, a monoamine oxidase inhibitor, digoxin, digitalis, lignocaine, a bradykinin agent, a serotonergic agonist, an antiarrhythmic agent, a cardiac glycoside a local anesthetic, atropine, a calcium solution, an agent that promotes heart rate, an agent that promotes heart contractions, dopamine, a catecholamine, an inotrope glucagon, a hormone, forskolin, epinephrine, norepinephrine, thyroid hormone, a phosphodiesterase inhibitor, prostacyclin, prostaglandin and a methylxanthine.
9. The method of claim 7 wherein the drug is naturally occurring.
10. The method of claim 7 wherein the drug is chemically synthesized.
11. The method of claim 1 further comprising stimulating the heart.
12. The method of claim 11 wherein stimulation of the vagal nerve occurs in an inverse relationship to stimulation of the heart.
13. The method of claim 11 wherein the heart is stimulated by pacing.
14. The method of claim 1 wherein the medical procedure is selected from the group consisting of: surgical procedures, non-surgical procedures, endoscopic procedures, fluoroscopic procedures, stent delivery procedures, aortic aneurysm repairs, cranial aneurysm repairs, delivery of drugs,

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delivery of biological agents, cardiac surgery with cardiopulmonary bypass circuits, cardiac surgery without cardiopulmonary bypass circuits, brain surgery, cardiograms, heart valve repair, heart valve replacement, MAZE procedures, transmyocardial revascularization, CABG procedures, beating heart surgery, vascular surgery, neurosurgery, electrophysiology procedures, diagnostic ablation of arrhythmias, therapeutic ablation of arrhythmias, endovascular procedures, treatment of injuries to the liver, treatment of the spleen, treatment of the heart, treatment of the lungs, treatment of major blood vessels, non-invasive procedures, invasive procedures, and port-access procedures.

15. A method of performing a medical procedure, comprising:

- providing a nerve stimulator capable of automatically stopping stimulation of a vagal nerve;
- stimulating the vagal nerve to reduce heart rate;
- automatically stopping stimulation of the vagal nerve; and
- stimulating the vagal nerve a subsequent time in order to reduce heart rate a subsequent time.

16. The method of claim 15 wherein the vagal nerve is stimulated using transvascular stimulation.

17. The method of claim 15 wherein the vagal nerve is stimulated using endotracheal stimulation.

18. The method of claim 15 wherein the vagal nerve is stimulated using esophageal stimulation.

19. The method of claim 15 wherein the vagal nerve is stimulated using transcutaneous stimulation.

20. The method of claim 15 wherein the vagal nerve is stimulated using intracutaneous stimulation.

21. The method of claim 15 further comprising delivering at least one drug during the medical procedure.

22. The method of claim 21 wherein the drug is selected from the group consisting of: a beta-blocker, a cholinergic agent, a cholinesterase inhibitor, a calcium channel blocker, a sodium channel blocker, a potassium channel agent, adenosine, an adenosine receptor agonist, an adenosine deaminase inhibitor, dipyridamole, a monoamine oxidase inhibitor, digoxin, digitalis, lignocaine, a bradykinin agent, a serotonergic agonist, an antiarrhythmic agent, a cardiac glycoside a local anesthetic, atropine, a calcium solution, an agent that promotes heart rate, an agent that promotes heart contractions, dopamine, a catecholamine, an inotrope glucagon, a hormone, forskolin, epinephrine, norepinephrine, thyroid hormone, a phosphodiesterase inhibitor, prostacyclin, prostaglandin and a methylxanthine.

23. The method of claim 21 wherein the drug is naturally occurring.

24. The method of claim 21 wherein the drug is chemically synthesized.

25. The method of claim 15 further comprising stimulating the heart.

26. The method of claim 25 wherein stimulation of the vagal nerve occurs in an inverse relationship to stimulation of the heart.

27. The method of claim 25 wherein the heart is stimulated by pacing.

28. The method of claim 25 wherein the medical procedure is selected from the group consisting of: surgical procedures, non-surgical procedures, endoscopic procedures, fluoroscopic procedures, stent delivery procedures, aortic aneurysm repairs, cranial aneurysm repairs, delivery of drugs, delivery of biological agents, cardiac surgery with cardiopulmonary bypass circuits, cardiac surgery without cardiopulmonary bypass circuits, brain surgery, cardiograms, heart valve repair, heart valve replacement, MAZE procedures, transmyocardial revascularization, CABG pro-

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cedures, heating heart surgery, vascular surgery, neurosurgery, electrophysiology procedures, diagnostic ablation of arrhythmias, therapeutic ablation of arrhythmias, endovascular procedures, treatment of injuries to the liver, treatment of the spleen, treatment of the heart, treatment of the lungs, treatment of major blood vessels, non-invasive procedures, invasive procedures, and port-access procedures.

29. A method of electrically manipulating heart rhythm during therapeutic treatment of a heart, comprising:

providing a nerve stimulator, the nerve stimulator comprising a nerve stimulation electrode;

positioning the nerve stimulation electrode in a position suitable for electrically stimulating a vagal nerve to manipulate heart rhythm; and

intermittently starting and automatically stopping electrical stimulation of the vagal nerve subsequent times in order to manipulate heart rhythm during therapeutic treatment of the heart.

30. The method of claim 29 wherein the nerve stimulation electrode is positioned in a transvascular position.

31. The method of claim 29 wherein the nerve stimulation electrode is positioned in a transcutaneous position.

32. The method of claim 29 wherein the nerve stimulation electrode is positioned in an intracutaneous position.

33. The method of claim 29 further comprising delivering at least one drug during treatment of the heart.

34. The method of claim 33 wherein the drug is chemically synthesized.

35. The method of claim 29 further comprising stimulating the heart.

36. The method of claim 35 wherein stimulation of the vagal nerve occurs in an inverse relationship to stimulation of the heart.

37. The method of claim 35 wherein the heart is stimulated by pacing.

38. A method of electrically manipulating heart rhythm during therapeutic treatment of a heart, comprising:

providing a nerve stimulator, the nerve stimulator comprising a nerve stimulation electrode;

positioning the nerve stimulation electrode in a position suitable for electrically stimulating a vagal nerve to manipulate heart rhythm; and

intermittently starting and stopping electrical stimulation of the vagal nerve subsequent times in order to manipulate heart rhythm during therapeutic treatment of the heart;

the nerve stimulation electrode being positioned in an endotracheal position.

39. A method of electrically manipulating heart rhythm during therapeutic treatment of a heart, comprising:

providing a nerve stimulator, the nerve stimulator comprising a nerve stimulation electrode;

positioning the nerve stimulation electrode in a position suitable for electrically stimulating a vagal nerve to manipulate heart rhythm; and

intermittently starting and stopping electrical stimulation of the vagal nerve subsequent times in order to manipulate heart rhythm during therapeutic treatment of the heart;

the nerve stimulation electrode being positioned in an esophageal position.

40. A method of electrically manipulating heart rhythm during therapeutic treatment of a heart, comprising:

providing a nerve stimulator, the nerve stimulator comprising a nerve stimulation electrode;

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positioning the nerve stimulation electrode in a position suitable for electrically stimulating a vagal nerve to manipulate heart rhythm;

intermittently starting and stopping electrical stimulation of the vagal nerve subsequent times in order to manipulate heart rhythm during therapeutic treatment of the heart; and

delivering at least one drug during treatment of the heart; the drug being selected from the group consisting of: a beta-blocker, a cholinergic agent, a cholinesterase inhibitor, a calcium channel blocker, a sodium channel blocker, a potassium channel agent, adenosine, an adenosine receptor agonist, an adenosine deaminase inhibitor, dipyridamole, a monoamine oxidase inhibitor, digoxin, digitalis, lignocaine, a bradykinin agent, a serotonergic agonist, an antiarrhythmic agent, a cardiac glycoside, a local anesthetic, atropine, a calcium solution, an agent that promotes heart rate, an agent that promotes heart contractions, dopamine, a catecholamine, an inotrope, glucagon, a hormone, forskolin, epinephrine, norepinephrine, thyroid hormone, a phosphodiesterase inhibitor, prostacyclin, prostaglandin and a methylxanthine.

41. A method of electrically manipulating heart rhythm during therapeutic treatment of a heart, comprising:

providing a nerve stimulator, the nerve stimulator comprising a nerve stimulation electrode;

positioning the nerve stimulation electrode in a position suitable for electrically stimulating a vagal nerve to manipulate heart rhythm;

intermittently starting and stopping electrical stimulation of the vagal nerve subsequent times in order to manipulate heart rhythm during therapeutic treatment of the heart; and

delivering at least one drug during treatment of the heart; the drug being naturally occurring.

42. A method of electrically manipulating cardiac rhythm during a medical procedure, comprising:

providing a nerve stimulator, the nerve stimulator comprising a stimulation electrode;

positioning the stimulation electrode in a position suitable for stimulating a carotid sinus nerve to manipulate cardiac rhythm;

intermittently starting and stopping stimulation of the carotid sinus nerve multiple times in order to manipulate cardiac rhythm during a medical procedure.

43. A method of electrically manipulating cardiac rhythm during a medical procedure, comprising:

providing a stimulator, the stimulator comprising a stimulation electrode;

positioning the stimulation electrode in a position suitable for stimulating Purkinje fibers to stop or slow cardiac rhythm;

intermittently starting and stopping stimulation of the Purkinje fibers multiple times in order to manipulate cardiac rhythm during a medical procedure.

44. A method of electrically manipulating cardiac rhythm during a medical procedure, comprising:

providing a stimulator, the stimulator comprising a stimulation electrode;

positioning the stimulation electrode in a position suitable for stimulating a junction of an AV node and a His bundle to manipulate cardiac rhythm;

intermittently starting and stopping stimulation of the junction of the AV node and the His bundle multiple times in order to manipulate cardiac rhythm during a medical procedure.

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45. A method of electrically manipulating cardiac rhythm  
during a medical procedure, comprising:  
providing a stimulator, the stimulator comprising a stimu-  
lation electrode;  
positioning the stimulation electrode in a position suitable 5  
for stimulating a fat pad associated with AV node to  
manipulate cardiac rhythm; and  
intermittently starting and stopping stimulation of the fat  
pad associated with the AV node multiple times in order  
to manipulate cardiac rhythm during a medical proce- 10  
dure.  
46. A method of electrically manipulating cardiac rhythm  
during a medical procedure, comprising:

22

providing a stimulator, the stimulator comprising a stimu-  
lation electrode;  
positioning the stimulation electrode in a position suitable  
for stimulating a fat pad associated with a SA node to  
manipulate cardiac rhythm; and  
intermittently starting and stopping stimulation of the fat  
pad associated with the SA node multiple times in order  
to manipulate cardiac rhythm during a medical proce-  
dure.

\* \* \* \* \*



**UNITED STATES DISTRICT COURT  
CENTRAL DISTRICT OF CALIFORNIA**

**NOTICE OF ASSIGNMENT TO UNITED STATES MAGISTRATE JUDGE FOR DISCOVERY**

This case has been assigned to District Judge Cormac J. Carney and the assigned discovery Magistrate Judge is Marc Goldman.

The case number on all documents filed with the Court should read as follows:

**SACV12- 327 CJC (MLGx)**

Pursuant to General Order 05-07 of the United States District Court for the Central District of California, the Magistrate Judge has been designated to hear discovery related motions.

All discovery related motions should be noticed on the calendar of the Magistrate Judge

=====

**NOTICE TO COUNSEL**

*A copy of this notice must be served with the summons and complaint on all defendants (if a removal action is filed, a copy of this notice must be served on all plaintiffs).*

Subsequent documents must be filed at the following location:

☐ **Western Division**  
312 N. Spring St., Rm. G-8  
Los Angeles, CA 90012

☒ **Southern Division**  
411 West Fourth St., Rm. 1-053  
Santa Ana, CA 92701-4516

☐ **Eastern Division**  
3470 Twelfth St., Rm. 134  
Riverside, CA 92501

Failure to file at the proper location will result in your documents being returned to you.

## Name &amp; Address:

David Martinez, Bar No. 193183

Lauren E. Wood, Bar No. 280096

Robins, Kaplan, Miller &amp; Ciresi L.L.P.

2049 Century Park East, Suite 3400

Los Angeles, CA 90067

UNITED STATES DISTRICT COURT  
CENTRAL DISTRICT OF CALIFORNIA

Medtronic, Inc.,

PLAINTIFF(S)

v.

Edwards Lifesciences Corporation, Edwards  
Lifesciences LLC, and Edwards Lifesciences (U.S.)  
Inc.,

DEFENDANT(S).

CASE NUMBER

SACV12-00327 CJC (MLGx)

SUMMONS

TO: DEFENDANT(S):

A lawsuit has been filed against you.

Within 21 days after service of this summons on you (not counting the day you received it), you must serve on the plaintiff an answer to the attached ☒ complaint ☐ amended complaint ☐ counterclaim ☐ cross-claim or a motion under Rule 12 of the Federal Rules of Civil Procedure. The answer or motion must be served on the plaintiff's attorney, Robins, Kaplan, Miller & Ciresi L.L.P., whose address is 2049 Century Park East, Suite 3400, Los Angeles, CA 90067-3208. If you fail to do so, judgment by default will be entered against you for the relief demanded in the complaint. You also must file your answer or motion with the court.

Clerk, U.S. District Court

Dated: MAR 2 - 2012By: AMY DeAVILA

Deputy Clerk

(Seal of the Court)

[Use 60 days if the defendant is the United States or a United States agency, or is an officer or employee of the United States. Allowed 60 days by Rule 12(a)(3)].

**UNITED STATES DISTRICT COURT, CENTRAL DISTRICT OF CALIFORNIA**  
**CIVIL COVER SHEET**

<b>I (a) PLAINTIFFS</b> (Check box if you are representing yourself <input type="checkbox"/> ) MEDTRONIC, INC.	<b>DEFENDANTS</b> EDWARDS LIFESCIENCES CORPORATION, EDWARDS LIFESCIENCES LLC, and EDWARDS LIFESCIENCES (U.S.) INC.
<b>(b) Attorneys</b> (Firm Name, Address and Telephone Number. If you are representing yourself, provide same.)  David Martinez and Lauren E. Wood (310) 552-0130 ROBINS, KAPLAN, MILLER & CIRESI L.L.P. 2049 Century Park East, Suite 3400, Los Angeles, CA 90067-3208	<b>Attorneys (If Known)</b>

<b>II. BASIS OF JURISDICTION</b> (Place an X in one box only.)  <input type="checkbox"/> 1 U.S. Government Plaintiff <input checked="" type="checkbox"/> 3 Federal Question (U.S. Government Not a Party)  <input type="checkbox"/> 2 U.S. Government Defendant <input type="checkbox"/> 4 Diversity (Indicate Citizenship of Parties in Item III)	<b>III. CITIZENSHIP OF PRINCIPAL PARTIES - For Diversity Cases Only</b> (Place an X in one box for plaintiff and one for defendant.) <table style="width:100%; border: none;"> <tr> <td style="width:33%;"></td> <td style="width:10%; text-align: center;"><b>PTF</b></td> <td style="width:10%; text-align: center;"><b>DEF</b></td> <td style="width:47%;"></td> <td style="width:10%; text-align: center;"><b>PTF</b></td> <td style="width:10%; text-align: center;"><b>DEF</b></td> </tr> <tr> <td>Citizen of This State</td> <td align="center"><input type="checkbox"/> 1</td> <td align="center"><input type="checkbox"/> 1</td> <td>Incorporated or Principal Place of Business in this State</td> <td align="center"><input type="checkbox"/> 4</td> <td align="center"><input type="checkbox"/> 4</td> </tr> <tr> <td>Citizen of Another State</td> <td align="center"><input type="checkbox"/> 2</td> <td align="center"><input type="checkbox"/> 2</td> <td>Incorporated and Principal Place of Business in Another State</td> <td align="center"><input type="checkbox"/> 5</td> <td align="center"><input type="checkbox"/> 5</td> </tr> <tr> <td>Citizen or Subject of a Foreign Country</td> <td align="center"><input type="checkbox"/> 3</td> <td align="center"><input type="checkbox"/> 3</td> <td>Foreign Nation</td> <td align="center"><input type="checkbox"/> 6</td> <td align="center"><input type="checkbox"/> 6</td> </tr> </table>		<b>PTF</b>	<b>DEF</b>		<b>PTF</b>	<b>DEF</b>	Citizen of This State	<input type="checkbox"/> 1	<input type="checkbox"/> 1	Incorporated or Principal Place of Business in this State	<input type="checkbox"/> 4	<input type="checkbox"/> 4	Citizen of Another State	<input type="checkbox"/> 2	<input type="checkbox"/> 2	Incorporated and Principal Place of Business in Another State	<input type="checkbox"/> 5	<input type="checkbox"/> 5	Citizen or Subject of a Foreign Country	<input type="checkbox"/> 3	<input type="checkbox"/> 3	Foreign Nation	<input type="checkbox"/> 6	<input type="checkbox"/> 6
	<b>PTF</b>	<b>DEF</b>		<b>PTF</b>	<b>DEF</b>																				
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Citizen of Another State	<input type="checkbox"/> 2	<input type="checkbox"/> 2	Incorporated and Principal Place of Business in Another State	<input type="checkbox"/> 5	<input type="checkbox"/> 5																				
Citizen or Subject of a Foreign Country	<input type="checkbox"/> 3	<input type="checkbox"/> 3	Foreign Nation	<input type="checkbox"/> 6	<input type="checkbox"/> 6																				

  
**IV. ORIGIN** (Place an X in one box only.)  
☒ 1 Original Proceeding     ☐ 2 Removed from State Court     ☐ 3 Remanded from Appellate Court     ☐ 4 Reinstated or Reopened     ☐ 5 Transferred from another district (specify):     ☐ 6 Multi-District Litigation     ☐ 7 Appeal to District Judge from Magistrate Judge
   
  
**V. REQUESTED IN COMPLAINT:** JURY DEMAND: ☒ Yes     ☐ No (Check 'Yes' only if demanded in complaint.)  
**CLASS ACTION** under F.R.C.P. 23: ☐ Yes     ☒ No     **MONEY DEMANDED IN COMPLAINT:** \$ \_\_\_\_\_
   
  
**VI. CAUSE OF ACTION** (Cite the U.S. Civil Statute under which you are filing and write a brief statement of cause. Do not cite jurisdictional statutes unless diversity.)  
 35 U.S.C. sec. 271; action for infringement of a United States patent
   
  
**VII. NATURE OF SUIT** (Place an X in one box only.)
 

<b>OTHER STATUTES</b> <input type="checkbox"/> 400 State Reapportionment <input type="checkbox"/> 410 Antitrust <input type="checkbox"/> 430 Banks and Banking <input type="checkbox"/> 450 Commerce/ICC Rates/etc. <input type="checkbox"/> 460 Deportation <input type="checkbox"/> 470 Racketeer Influenced and Corrupt Organizations <input type="checkbox"/> 480 Consumer Credit <input type="checkbox"/> 490 Cable/Sat TV <input type="checkbox"/> 810 Selective Service <input type="checkbox"/> 850 Securities/Commodities/Exchange <input type="checkbox"/> 875 Customer Challenge 12 USC 3410 <input type="checkbox"/> 890 Other Statutory Actions <input type="checkbox"/> 891 Agricultural Act <input type="checkbox"/> 892 Economic Stabilization Act <input type="checkbox"/> 893 Environmental Matters <input type="checkbox"/> 894 Energy Allocation Act <input type="checkbox"/> 895 Freedom of Info. Act <input type="checkbox"/> 900 Appeal of Fee Determination Under Equal Access to Justice <input type="checkbox"/> 950 Constitutionality of State Statutes	<b>CONTRACT</b> <input type="checkbox"/> 110 Insurance <input type="checkbox"/> 120 Marine <input type="checkbox"/> 130 Miller Act <input type="checkbox"/> 140 Negotiable Instrument <input type="checkbox"/> 150 Recovery of Overpayment & Enforcement of Judgment <input type="checkbox"/> 151 Medicare Act <input type="checkbox"/> 152 Recovery of Defaulted Student Loan (Excl. Veterans) <input type="checkbox"/> 153 Recovery of Overpayment of Veteran's Benefits <input type="checkbox"/> 160 Stockholders' Suits <input type="checkbox"/> 190 Other Contract <input type="checkbox"/> 195 Contract Product Liability <input type="checkbox"/> 196 Franchise <b>REAL PROPERTY</b> <input type="checkbox"/> 210 Land Condemnation <input type="checkbox"/> 220 Foreclosure <input type="checkbox"/> 230 Rent Lease & Ejectment <input type="checkbox"/> 240 Torts to Land <input type="checkbox"/> 245 Tort Product Liability <input type="checkbox"/> 290 All Other Real Property	<b>TORTS</b> <b>PERSONAL INJURY</b> <input type="checkbox"/> 310 Airplane <input type="checkbox"/> 315 Airplane Product Liability <input type="checkbox"/> 320 Assault, Libel & Slander <input type="checkbox"/> 330 Fed. Employers' Liability <input type="checkbox"/> 340 Marine <input type="checkbox"/> 345 Marine Product Liability <input type="checkbox"/> 350 Motor Vehicle <input type="checkbox"/> 355 Motor Vehicle Product Liability <input type="checkbox"/> 360 Other Personal Injury <input type="checkbox"/> 362 Personal Injury-Med Malpractice <input type="checkbox"/> 365 Personal Injury-Product Liability <input type="checkbox"/> 368 Asbestos Personal Injury Product Liability <b>IMMIGRATION</b> <input type="checkbox"/> 462 Naturalization Application <input type="checkbox"/> 463 Habeas Corpus-Alien Detainee <input type="checkbox"/> 465 Other Immigration Actions	<b>TORTS</b> <b>PERSONAL PROPERTY</b> <input type="checkbox"/> 370 Other Fraud <input type="checkbox"/> 371 Truth in Lending <input type="checkbox"/> 380 Other Personal Property Damage <input type="checkbox"/> 385 Property Damage-Product Liability <b>BANKRUPTCY</b> <input type="checkbox"/> 422 Appeal 28 USC 158 <input type="checkbox"/> 423 Withdrawal 28 USC 157 <b>CIVIL RIGHTS</b> <input type="checkbox"/> 441 Voting <input type="checkbox"/> 442 Employment <input type="checkbox"/> 443 Housing/Accommodations <input type="checkbox"/> 444 Welfare <input type="checkbox"/> 445 American with Disabilities - Employment <input type="checkbox"/> 446 American with Disabilities - Other <input type="checkbox"/> 440 Other Civil Rights	<b>PRISONER PETITIONS</b> <input type="checkbox"/> 510 Motions to Vacate Sentence <input type="checkbox"/> 530 General Habeas Corpus <input type="checkbox"/> 535 Death Penalty <input type="checkbox"/> 540 Mandamus/Other <input type="checkbox"/> 550 Civil Rights <input type="checkbox"/> 555 Prison Condition <b>FORFEITURE / PENALTY</b> <input type="checkbox"/> 610 Agriculture <input type="checkbox"/> 620 Other Food & Drug <input type="checkbox"/> 625 Drug Related Seizure of Property 21 USC 881 <input type="checkbox"/> 630 Liquor Laws <input type="checkbox"/> 640 R.R. & Truck <input type="checkbox"/> 650 Airline Regs <input type="checkbox"/> 660 Occupational Safety /Health <input type="checkbox"/> 690 Other	<b>LABOR</b> <input type="checkbox"/> 710 Fair Labor Standards Act <input type="checkbox"/> 720 Labor/Mgmt. Relations <input type="checkbox"/> 730 Labor/Mgmt. Reporting & Disclosure Act <input type="checkbox"/> 740 Railway Labor Act <input type="checkbox"/> 790 Other Labor Litigation <input type="checkbox"/> 791 Empl. Ret. Inc. Security Act <b>PROPERTY RIGHTS</b> <input type="checkbox"/> 820 Copyrights <input checked="" type="checkbox"/> 830 Patent <input type="checkbox"/> 840 Trademark <b>SOCIAL SECURITY</b> <input type="checkbox"/> 861 HIA (1395ff) <input type="checkbox"/> 862 Black Lung (923) <input type="checkbox"/> 863 DIWC/DIWW (405(g)) <input type="checkbox"/> 864 SSID Title XVI <input type="checkbox"/> 865 RSI (405(g)) <b>FEDERAL TAX SUITS</b> <input type="checkbox"/> 870 Taxes (U.S. Plaintiff or Defendant) <input type="checkbox"/> 871 IRS-Third Party 26 USC 7609
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**FOR OFFICE USE ONLY:** Case Number: SACV12-00327 CJC (MLGx)

AFTER COMPLETING THE FRONT SIDE OF FORM CV-71, COMPLETE THE INFORMATION REQUESTED BELOW.



**UNITED STATES DISTRICT COURT, CENTRAL DISTRICT OF CALIFORNIA  
CIVIL COVER SHEET**

**VIII(a). IDENTICAL CASES:** Has this action been previously filed in this court and dismissed, remanded or closed? ☒ No ☐ Yes

If yes, list case number(s): \_\_\_\_\_

**VIII(b). RELATED CASES:** Have any cases been previously filed in this court that are related to the present case? ☐ No ☒ Yes

If yes, list case number(s): Case No. SACV 11-00961 JVS (MLGx)

**Civil cases are deemed related if a previously filed case and the present case:**

(Check all boxes that apply) ☒ A. Arise from the same or closely related transactions, happenings, or events; or

☒ B. Call for determination of the same or substantially related or similar questions of law and fact; or

☐ C. For other reasons would entail substantial duplication of labor if heard by different judges; or

☐ D. Involve the same patent, trademark or copyright, and one of the factors identified above in a, b or c also is present.

**IX. VENUE:** (When completing the following information, use an additional sheet if necessary.)

(a) List the County in this District; California County outside of this District; State if other than California; or Foreign Country, in which **EACH** named plaintiff resides.

☐ Check here if the government, its agencies or employees is a named plaintiff. If this box is checked, go to item (b).

County in this District:*	California County outside of this District; State, if other than California; or Foreign Country
	Medtronic Inc.: Minnesota

(b) List the County in this District; California County outside of this District; State if other than California; or Foreign Country, in which **EACH** named defendant resides.

☐ Check here if the government, its agencies or employees is a named defendant. If this box is checked, go to item (c).

County in this District:*	California County outside of this District; State, if other than California; or Foreign Country
Edwards Lifesciences Corporation, Edwards Lifesciences LLC, and Edwards Lifesciences (U.S.) Inc.: Orange County	

(c) List the County in this District; California County outside of this District; State if other than California; or Foreign Country, in which **EACH** claim arose.

**Note:** In land condemnation cases, use the location of the tract of land involved.

County in this District:*	California County outside of this District; State, if other than California; or Foreign Country
Orange County	

\* Los Angeles, Orange, San Bernardino, Riverside, Ventura, Santa Barbara, or San Luis Obispo Counties

**Note:** In land condemnation cases, use the location of the tract of land involved

**X. SIGNATURE OF ATTORNEY (OR PRO PER):**

Lauren E. Wood

Date March 2, 2012

**Notice to Counsel/Parties:** The CV-71 (JS-44) Civil Cover Sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law. This form, approved by the Judicial Conference of the United States in September 1974, is required pursuant to Local Rule 3-1 is not filed but is used by the Clerk of the Court for the purpose of statistics, venue and initiating the civil docket sheet. (For more detailed instructions, see separate instructions sheet.)

**Key to Statistical codes relating to Social Security Cases:**

Nature of Suit Code	Abbreviation	Substantive Statement of Cause of Action
861	HIA	All claims for health insurance benefits (Medicare) under Title 18, Part A, of the Social Security Act, as amended. Also, include claims by hospitals, skilled nursing facilities, etc., for certification as providers of services under the program. (42 U.S.C. 1935FF(b))
862	BL	All claims for "Black Lung" benefits under Title 4, Part B, of the Federal Coal Mine Health and Safety Act of 1969. (30 U.S.C. 923)
863	DIWC	All claims filed by insured workers for disability insurance benefits under Title 2 of the Social Security Act, as amended; plus all claims filed for child's insurance benefits based on disability. (42 U.S.C. 405(g))
863	DIWW	All claims filed for widows or widowers insurance benefits based on disability under Title 2 of the Social Security Act, as amended. (42 U.S.C. 405(g))
864	SSID	All claims for supplemental security income payments based upon disability filed under Title 16 of the Social Security Act, as amended.
865	RSI	All claims for retirement (old age) and survivors benefits under Title 2 of the Social Security Act, as amended. (42 U.S.C. (g))