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(54) **SYNCHRONIZATION OF VAGUS NERVE STIMULATION WITH THE CARDIAC CYCLE OF A PATIENT**

SYNCHRONISATION DER VAGUSNERV-STIMULATION MIT DEM HERZZYKLUS EINES PATIENTEN

SYNCHRONISATION DE STIMULATION DU NERF VAGUE AVEC LE CYCLE CARDIAQUE D'UN PATIENT

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Description

1. FIELD OF THE INVENTION

[0001] This invention relates generally to medical device systems and, more particularly, to medical device systems for applying electrical signals to a cranial nerve for the treatment of medical conditions, and for improved electrical signals in such systems.

2. DESCRIPTION OF THE RELATED ART

[0002] Many advancements have been made in treating diseases such as depression and epilepsy. Therapies using electrical signals for treating these diseases have been found to effective. Implantable medical devices have been effectively used to deliver therapeutic stimulation to various portions of the human body (e.g., the vagus nerve) for treating these diseases. As used herein, "stimulation" or "stimulation signal" refers to the application of an electrical, mechanical, magnetic, electro-magnetic, photonic, audio and/or chemical signal to a neural structure in the patient's body. The signal is an exogenous signal that is distinct from the endogenous electrical, mechanical, and chemical activity (e.g., afferent and/or efferent electrical action potentials) generated by the patient's body and environment. In other words, the stimulation signal (whether electrical, mechanical, magnetic, electro-magnetic, photonic, audio or chemical in nature) applied to the nerve is a signal applied from an artificial source, e.g., a neurostimulator.

[0003] A "therapeutic signal" refers to a stimulation signal delivered to a patient's body with the intent of treating a medical condition by providing a modulating effect to neural tissue. The effect of a stimulation signal on neuronal activity is termed "modulation"; however, for simplicity, the terms "stimulating" and "modulating", and variants thereof, are sometimes used interchangeably herein. In general, however, the delivery of an exogenous signal itself refers to "stimulation" of the neural structure, while the effects of that signal, if any, on the electrical activity of the neural structure are properly referred to as "modulation." The modulating effect of the stimulation signal upon the neural tissue may be excitatory or inhibitory, and may potentiate acute and/or long-term changes in neuronal activity. For example, the "modulating" effect of the stimulation signal to the neural tissue may comprise one more of the following effects: (a) initiation of an action potential (afferent and/or efferent action potentials); (b) inhibition or blocking of the conduction of action potentials, whether endogenous or exogenously induced, including hyperpolarizing and/or collision blocking, (c) affecting changes in neurotransmitter/neuromodulator release or uptake, and (d) changes in neuro-plasticity or neurogenesis of brain tissue.

[0004] Electrical neurostimulation may be provided by implanting an electrical device underneath the skin of a patient and delivering an electrical signal to a nerve such as a cranial nerve. The electrical neurostimulation involves sensing or detecting a body parameter, with the electrical signal being delivered in response to the sensed body parameter. This type of stimulation is generally referred to as "active," "feedback," or "triggered" stimulation. The system may operate without sensing or detecting a body parameter once the patient has been diagnosed with a medical condition that may be treated by neurostimulation. In this case, the system may apply a series of electrical pulses to the nerve (e.g., a cranial nerve such as a vagus nerve) periodically, intermittently, or continuously throughout the day, or over another predetermined time interval. This type of stimulation is generally referred to as "passive," "non-feedback," or "prophylactic," stimulation. The electrical signal may be applied by an IMD that is implanted within the patient's body. In other cases, the signal may be generated by an external pulse generator outside the patient's body, coupled by an RF or wireless link to an implanted electrode.

[0005] Generally, neurostimulation signals that perform neuromodulation are delivered by the IMD via one or more leads. The leads generally terminate at their distal ends in one or more electrodes, and the electrodes, in turn, are electrically coupled to tissue in the patient's body. For example, a number of electrodes may be attached to various points of a nerve or other tissue inside a human body for delivery of a neurostimulation signal.

[0006] While feedback stimulation schemes have been proposed, conventional vagus nerve stimulation (VNS) usually involves non-feedback stimulation characterized by a number of parameters. Specifically, convention vagus nerve stimulation usually involves a series of electrical pulses in bursts defined by an "on-time" and an "off-time." During the on-time, electrical pulses of a defined electrical current (e.g., 0.5 - 2.0 milliamps) and pulse width (e.g., 0.25 - 1.0 milliseconds) are delivered at a defined frequency (e.g., 20 - 30 Hz) for the on-time duration, usually a specific number of seconds, e.g., 10 - 100 seconds. The pulse bursts are separated from one another by the off-time, (e.g., 30 seconds - 5 minutes) in which no electrical signal is applied to the nerve. The on-time and off-time parameters together define a duty cycle, which is the ratio of the on-time to the combination of the on-time and off-time, and which describes the percentage of time that the electrical signal is applied to the nerve.

[0007] In conventional VNS, the on-time and off-time may be programmed to define an intermittent pattern in which a repeating series of electrical pulse bursts are generated and applied to the vagus nerve. Each sequence of pulses during an on-time may be referred to as a "pulse burst." The burst is followed by the off-time period in which no signals are applied to the nerve. The off-time is provided to allow the nerve to recover from the stimulation of the pulse burst, and to conserve power. If the off-time is set at zero, the electrical signal in conventional VNS may provide continuous stimulation to the vagus nerve. Alternatively, the idle time may be as long

as one day or more, in which case the pulse bursts are provided only once per day or at even longer intervals. Typically, however, the ratio of "off-time" to "on-time" may range from about 0.5 to about 10.

[0008] In addition to the on-time and off-time, the other parameters defining the electrical signal in conventional VNS may be programmed over a range of values. The pulse width for the pulses in a pulse burst of conventional VNS may be set to a value not greater than about 1 msec, such as about 250-500 μsec, and the number of pulses in a pulse burst is typically set by programming a frequency in a range of about 20-150 Hz (i.e., 20 pulses per second to 150 pulses per second). A non-uniform frequency may also be used. Frequency may be altered during a pulse burst by either a frequency sweep from a low frequency to a high frequency, or vice versa. Alternatively, the timing between adjacent individual signals within a burst may be randomly changed such that two adjacent signals may be generated at any frequency within a range of frequencies.

[0009] Various feedback stimulation schemes have been proposed. In US 5,928,272, the automatic activation of a neurostimulator such as a vagus nerve stimulator is described based on a detected increase in heart rate. The '272 patent notes that epilepsy attacks are sometimes preceded by increases in heart rate and proposes automatically applying an electrical signal to a vagus nerve if the patient's heart rate exceeds a certain level. The patent does not disclose initiating or synchronizing the therapeutic electrical signal with the patient's heart rhythms. Instead, detection of an abnormal heart rate is used to trigger otherwise conventional VNS. US2005267542 discloses a vagus nerve stimulating apparatus for treating heart failure, which has an implantable sensor sensing electrical parameter of a heart, and a control unit driving a multipolar electrode device to stimulate a vagus nerve.

[0010] A new type of stimulation has been proposed known as "microburst" stimulation, which provides enhanced evoked potentials in the brain (as more fully described in co-pending application Serial No._, "Microburst Electrical Stimulation Of Cranial Nerves For The Treatment Of Medical Conditions"). "Enhanced" in this context refers to electrical potentials evoked in the forebrain by neurostimulation that are higher than those produced by conventional neurostimulation. The electrical signal for this improved therapy is substantially different from the electrical signals in conventional VNS. In particular, electrical signals in microburst stimulation are characterized by very short bursts of a limited number of electrical pulses. These shorts bursts of less than 1 second are referred to hereinafter as "microbursts." By applying an electrical signal comprising a series of microbursts to, for example, a vagus nerve of a patient, enhanced vagal evoked potentials (eVEP) are produced in therapeutically significant areas of the brain. Significantly, eVEP are not produced by conventional vagus nerve stimulation.

[0011] As used herein, the term "microburst" refers to a portion of a therapeutic electrical signal comprising a limited plurality of pulses and a limited burst duration. More particularly, a microburst may comprise at least two but no more than 25 electrical pulses, and may last for no more than 1 second, and typically less than 100 milliseconds, more typically 10-80 msec. A therapeutic electrical signal may comprise a series of microbursts separated from one another by time intervals known as "interburst periods" which allow a refractory interval for the nervous system to recover from the microburst and again become receptive to eVEP stimulation by another microburst. The interburst period may be as long as or longer than the adjacent microbursts separated by the interburst period. The interburst period may comprise an absolute time period of at least 100 milliseconds and, up to 6 seconds. Adjacent pulses in a microburst are separated by a time interval known as an "interpulse interval," which may comprise a time period from 1 msec to 50 msec. The interpulse interval, together with the number of pulses and the pulse width of each pulse, determines a "microburst duration," which is the length of a microburst from the beginning of the first pulse to the end of the last pulse (and thus the beginning of a new interburst period). Microburst duration in microburst stimulation can be 1 second or less (i.e., microbursts can be no greater than 1 second), and more preferably is 100 msec or less, and still more preferably is in the range of 10-80 msec. The pulses in a microburst may be further characterized by a current amplitude and a pulse width. Microburst stimulation may optionally include an on-time and an off-time in which the microbursts are provided and not provided, respectively, to a cranial nerve. At least one of the interburst period, the number of pulses per burst, the interpulse interval, the microburst duration, the current amplitude, the pulse width, the on-time, or the off-time are selected to enhance cranial nerve evoked potentials.

[0012] The timing of neurostimulation signals has heretofore generally conformed to standard clock cycles, without regard to the efficacy of neurostimulation signals delivered at particular time-points. The present inventor is unaware of previous investigations of the efficacy of neurostimulation signals delivered at particular time-points of physiological cycles.

SUMMARY OF THE INVENTION

[0013] In accordance with a first aspect of the invention, there is provided a computer readable medium programmed with instructions to cause an apparatus (100) comprising:

- a controller (210) comprising a processor (215);
- at least one electrode (125) couplable to at least one vagus nerve (127) of a patient,
- an implantable device operatively coupled to the at least one electrode and comprising an electrical signal generator (110) configured to apply an electrical

signal to the at least one vagus nerve,

- a sensor configured to sense a body parameter that corresponds to a symptom of a medical condition, and
- a respiration cycle sensing element;

to apply an electrical signal to the at least one vagus nerve (127) in response to sensing the symptom of the medical condition of the patient in the apparatus (100), wherein the instructions, when executed by the processor (215), perform a method comprising:

- generating a first electrical signal with the electrical signal generator (110),
- sensing the symptom of the medical condition,
- detecting at least a portion of a physiological cycle of the patient selected from the cardiac cycle and the respiratory cycle of the patient, and
- applying the first electrical signal to the at least one vagus nerve (127) of the patient to treat the medical condition;

characterized in that the applying of the first electrical signal to the at least one vagus nerve (127) is performed during inspiration by the patient.

[0014] The disclosure describes, a method of treating a medical condition of a patient using an implantable medical device, comprising detecting said patient's cardiac cycle and applying an electrical signal to a portion of a vagus nerve of said patient through an electrode at a selected point in the cardiac cycle, to treat the medical condition.

[0015] The disclosure describes, is a method of treating a medical condition of a patient, comprising: coupling at least one electrode to at least one vagus nerve of the patient, providing a programmable electrical signal generator coupled to the electrode, detecting said patient's cardiac cycle, generating an electrical signal with the electrical signal generator, and applying the electrical signal to the electrode to treat the medical condition, and wherein the applying the electrical signal at a selected point in the cardiac cycle.

[0016] Applying an electrical signal at a selected point in a physiological cycle may be referred to herein as "synchronizing" the electrical signal with the physiological cycle. Synchronizing does not require modification of one or more electrical signal parameters to match one or more parameters of the physiological cycle.

[0017] The disclosure describes, is a computer readable program storage device encoded with instructions that, when executed by a computer, perform a method comprising: detecting said patient's cardiac cycle, generating an electrical signal with the electrical signal generator, and applying the electrical signal to an electrode coupled to at least one vagus nerve of the patient to treat the medical condition, and wherein applying the electrical signal to the vagus nerve occurs at a selected point in the cardiac cycle.

[0018] The disclosure describes, relates to a medical condition treatment system comprising at least one electrode coupled to at least one vagus nerve of a patient, an implantable device operatively coupled to the electrode and comprising an electrical signal generator capable of applying an electrical signal to the vagus nerve at a selected point in the patient's cardiac cycle, and a device operatively coupled to the electrode and capable of detecting said patient's cardiac cycle.

[0019] The method may comprise alternating first and second time periods, wherein in the first time period a conventional vagus nerve stimulation electrical signal is applied to a vagus nerve of a patient, and a second time period in which microburst electrical signals are applied to a vagus nerve of a patient. The conventional vagus nerve stimulation signal may be defined by a current amplitude, a pulse width, a frequency, an on-time and an off-time. The first time period (in which the conventional VNS electrical signal is applied to the vagus nerve) may correspond to the on-time and the second time period (in which the microburst electrical signal is applied to the vagus nerve) may correspond to the off-time of the conventional vagus nerve signal.

[0020] The selected point in the cardiac cycle can be a point in the cardiac cycle correlated with increased afferent conduction on the vagus nerve, such as a point from about 10 msec to about 800 msec after an R-wave of the patient's ECG. The selected point in the cardiac cycle may occur from about 10 - 800 msec after an R-wave during inspiration by the patient. Alternatively, the selected point in the cardiac cycle may occur from about 10 - 800 msec after an R-wave during expiration by the patient. Alternatively, the selected point in the cardiac cycle may occur from about 10-500 msec after an R-wave of the patient's ECG, which may further occur during inspiration, expiration, or without regard to respiration. Alternatively, the selected point in the cardiac cycle can be a point in the cardiac cycle when said applying increases heart rate variability.

[0021] The disclosure provides a method of treating a medical condition of a patient, comprising: coupling at least one electrode to at least one vagus nerve of the patient, providing a programmable electrical signal generator coupled to the electrode, detecting said patient's respiratory cycle, generating an electrical signal with the electrical signal generator, and applying the electrical signal to the electrode to treat the medical condition, and wherein the applying the electrical signal at a selected point in the respiratory cycle.

[0022] The disclosure also provides a method of treating a medical condition of a patient, comprising: coupling at least one electrode to at least one vagus nerve of the patient, providing a programmable electrical signal generator coupled to the electrode, detecting said patient's respiratory cycle and cardiac cycle, generating an electrical signal with the electrical signal generator, and applying the electrical signal to the electrode to treat the medical condition, and wherein the applying the electrical

signal at a selected point in the respiratory cycle and/or cardiac cycle.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] The invention may be understood by reference to the following description taken in conjunction with the accompanying drawings, in which like reference numerals identify like elements, and in which:

Figure 1 provides a stylized diagram of an implantable medical device implanted into a patient's body for providing a therapeutic electrical signal to a neural structure of the patient's body;

Figure 2 is a block diagram of a medical device system that includes an implantable medical device and an external device for providing a patient management system for the implantable medical device;

Figure 3 illustrates an exemplary electrical signal of a firing neuron as a graph of voltage at a given location at particular times in response to application of an electrical signal to the nerve by the neurostimulator of Figure 2;

Figure 4A, 4B, and 4C illustrate exemplary waveforms for generating the electrical signals for stimulating the vagus nerve for treating a medical condition;

Figure 5 illustrates a flowchart depiction of a method for treating a medical condition;

Figure 6 illustrates a flowchart depiction of an alternative method for treating a medical condition;

Figure 7 depicts a more detailed flowchart depiction of the step of performing a detection process of Figure 6; and

Figure 8 illustrates synchronization of a vagal stimulus burst to the QRS wave of a patient's ECG.

DETAILED DESCRIPTION

[0024] Illustrative examples are described herein. In the interest of clarity, not all features of an actual implementation are described in this specification. In the development of any such actual example, numerous implementation-specific decisions must be made to achieve the design-specific goals, which will vary from one implementation to another. It will be appreciated that such a development effort, while possibly complex and time-consuming, would nevertheless be a routine undertaking for persons of ordinary skill in the art having the benefit of this disclosure.

[0025] This document does not intend to distinguish between components that differ in name but not function. In the following discussion and in the claims, the terms "including" and "includes" are used in an open-ended fashion, and thus should be interpreted to mean "including, but not limited to." Also, the term "couple" or "couples" is intended to mean either a direct or an indirect electrical connection. "Direct contact," "direct attachment," or providing a "direct coupling" indicates that a surface of a first element contacts the surface of a second element with no substantial attenuating medium there between. The presence of small quantities of substances, such as bodily fluids, that do not substantially attenuate electrical connections does not vitiate direct contact. The word "or" is used in the inclusive sense (i.e., "and/or") unless a specific use to the contrary is explicitly stated.

[0026] The term "electrode" or "electrodes" described herein may refer to one or more stimulation electrodes (i.e., electrodes for delivering an electrical signal generated by an IMD to a tissue), sensing electrodes (i.e., electrodes for sensing a physiological indication of a patient's body), and/or electrodes that are capable of delivering a stimulation signal, as well as performing a sensing function.

[0027] Cranial nerve stimulation has been proposed to treat a number of medical conditions pertaining to or mediated by one or more structures of the nervous system of the body, including epilepsy and other movement disorders, depression, anxiety disorders and other neuropsychiatric disorders, dementia, head trauma, coma, migraine headache, obesity, eating disorders, sleep disorders, cardiac disorders (such as congestive heart failure and atrial fibrillation), hypertension, endocrine disorders (such as diabetes and hypoglycemia), and pain, among others. See, e.g., U.S. Pats. Nos. 4,867,164; 5,299,569; 5,269,303; 5,571,150; 5,215,086; 5,188,104; 5,263,480; 6,587,719; 6,609,025; 5,335,657; 6,622,041; 5,916,239; 5,707,400; 5,231,988; and 5,330,515. Despite the numerous medical conditions for which cranial nerve stimulation has been proposed or suggested as a treatment option, the fact that detailed neural pathways for many (if not all) cranial nerves remain relatively unknown, makes predictions of efficacy for any given medical condition difficult or impossible. Moreover, even if such pathways were known, the precise stimulation parameters that would modulate particular pathways relevant to a particular medical condition generally cannot be predicted.

[0028] The disclosure describes a method of treating a medical condition selected from the group consisting of epilepsy, neuropsychiatric disorders (including but not limited to depression), eating disorders/obesity, traumatic brain injury/coma, addiction disorders, dementia, sleep disorders, pain, migraine, endocrine/pancreatic disorders (including but not limited to diabetes), motility disorders, hypertension, congestive heart failure/cardiac capillary growth, hearing disorders, angina, syncope, vocal cord disorders, thyroid disorders, pulmonary disorders, and reproductive endocrine disorders (including fertility) in a patient.

[0029] The disclosure describes synchronization of cranial nerve electrical stimulation to a physiological event, such as a specific point in the cardiac cycle and/or respiratory cycle. Synchronization of such electrical stimulation signals may be performed by an implantable medical device (IMD) system. An IMD system may comprise

an implantable medical device for delivering a therapeutic electrical signal and sensing/recording data, and an external device (ED) capable of programming and/or data transfer operations with the IMD.

[0030] The medical device system provides for software module(s) that are capable of acquiring, storing, and processing one or more forms of data, such as patient data/parameters (e.g., physiological data such as heart rate, cardiac cycle data and respiration cycle data, side-effects data, brain-activity data, disease progression or regression data, self-evaluation data, seizure characteristic data, quality of life data, etc.) and therapy parameter data. Therapy parameters may include, but are not limited to, electrical signal parameters that define the therapeutic electrical signals delivered by the medical device, medication parameters (e.g., dosages, frequency of medication provided to the patient, etc.) and/or any other therapeutic treatment parameter. Alternatively, the term "therapy parameters" may refer to electrical signal parameters defining the therapeutic electrical signals delivered by the medical device. Therapy parameters for a therapeutic electrical signal may also include, but are not limited to, an interburst period, a number of pulses per burst, an interpulse interval, a burst duration, a current amplitude, a pulse width, a pulse frequency, a signal on-time, a signal off-time, and/or a duty cycle.

[0031] Figure 1 depicts a stylized implantable medical device (IMD) 100. An electrical signal generator 110 is provided, having a main body 112 comprising a case or shell with a header 116 for connecting to an insulated, electrically conductive lead assembly 122. The generator 110 is implanted in the patient's chest in a pocket or cavity formed by the implanting surgeon just below the skin (indicated by a dotted line 145), similar to the implantation procedure for a pacemaker pulse generator.

[0032] A nerve electrode assembly 125, preferably comprising a plurality of electrodes having at least an electrode pair, is conductively connected to the distal end of the lead assembly 122, which preferably comprises a plurality of lead wires (one wire for each electrode). Each electrode in the electrode assembly 125 may operate independently or alternatively, may operate in conjunction with the other electrodes. The electrode assembly 125 may comprise at least a cathode and an anode. Alternatively, the electrode assembly may comprise one or more unipolar electrodes.

[0033] Lead assembly 122 is attached at its proximal end to connectors on the header 116 of generator 110. The electrode assembly 125 may be surgically coupled to a vagus nerve 127 in the patient's neck or at another location, e.g., near the patient's diaphragm or at the esophagus/stomach junction. Other (or additional) cranial nerves such as the trigeminal and/or glossopharyngeal nerves may also be used to deliver the electrical signal. The electrode assembly 125 may comprise a bipolar stimulating electrode pair 126, 128 (i.e., a cathode and an anode). Suitable electrode assemblies are available from Cyberonics, Inc., Houston, Texas, USA as the Model 302 electrode assembly. However, persons of skill in the art will appreciate that many electrode designs could be used. The two electrodes may be wrapped about the vagus nerve 127, and the electrode assembly 125 may be secured to the vagus nerve 127 by a spiral anchoring tether 130 such as that disclosed in U.S. Pat. No. 4,979,511 issued Dec. 25, 1990 to Reese S. Terry, Jr. and assigned to the same assignee as the instant application. Lead assembly 122 may be secured, while retaining the ability to flex with movement of the chest and neck, by a suture connection to nearby tissue (not shown).

[0034] The electrode assembly 125 may comprise temperature sensing elements, heart rate or cardiac cycle sensor elements, and/or respiration cycle sensing elements. The electrode assembly 125 may comprise a strain gauge that may be used to determine inspiration by identifying chest expansion. By detecting the onset of chest expansion, the strain gauge may detect the onset of inspiration. The strain gauge may also detect expiration by identifying when the chest is contracting. Other sensors for other body parameters may also be employed to trigger active stimulation. Both passive and active stimulation may be combined or delivered by a single IMD. Either or both modes may be appropriate to treat a specific patient under observation.

[0035] A sensor assembly 165, comprising a sensor lead assembly 162 and a sensor 160, may be employed to detect a body parameter of the patient, such as a parameter related to the patient's cardiac cycle. The sensor 160 may be one or more electrocardiogram leads or a heart rate monitor, among other sensing devices.

[0036] The electrical pulse generator 110 may be programmed with an external device (ED) such as computer 150 using programming software known in the art. A programming wand 155 may be coupled to the computer 150 as part of the ED to facilitate radio frequency (RF) communication between the computer 150 and the pulse generator 110. The programming wand 155 and computer 150 permit non-invasive communication with the generator 110 after the latter is implanted. In systems where the computer 150 uses one or more channels in the Medical Implant Communications Service (MICS) bandwidths, the programming wand 155 may be omitted to permit more convenient communication directly between the computer 150 and the pulse generator 110.

[0037] The IMD 100 may detect one or more portions of patient's cardiac cycle, e.g., P waves, R waves, R-R interval, QRS complex, T waves, etc., or the entire PQRST cycle. In response to detecting the one or more portions of the cardiac cycle, the IMD 100 may cause the pulse generator 110 to deliver an electrical signal via leads 122 to a cranial nerve such as vagus nerve 127 at a particular point during the cardiac cycle. For example, a sensor 160, such as a heart rate monitor or a set of electrocardiogram (ECG) leads, may be used to detect the one or more portions of the patient's cardiac cycle. The detected portion of the cardiac cycle may then be

used to trigger the pulse generator 110 to generate the therapeutic electrical signal and apply the signal to the vagus nerve 127.

[0038] A "cardiac cycle" herein refers to the electrical activity of a patient's heart that occurs in the period between the onset of consecutive P waves. This electrical activity may be measured and analyzed by an electrocardiogram (ECG). The cycle begins with the P wave, which corresponds to electrical depolarization of the atria of the heart. As is known, an electrocardiogram exhibits a P wave, a QRS complex, and a T wave, and in some patients it may also exhibit a U wave. An isoelectric baseline follows from the end of the T or U wave to the onset of the next P wave with the patient's next heartbeat.

[0039] Conventional bursts and/or microbursts of electrical pulses comprising an electrical signal may be applied to the vagus nerve in synchronization with one or more portions of the cardiac cycle. The electrical signal may be synchronized with the R wave of a patient's cardiac cycle. The signal may be synchronized with the QRS complex. The signal may be further synchronized with the respiration cycle of the patient. The therapeutic electrical signal may be synchronized with both a portion of the patient's cardiac cycle and the respiration cycle of the patient. Synchronization of the application of the therapeutic electrical signal with the patient's cardiac and/or respiration cycles enables the IMD to augment endogenous cardiac-related and/or respiration-related vagal afferent activity with the exogenous electrical signal. As illustrated in FIG. 8, the neurostimulation burst may be triggered by the R-wave of the ECG after a delay period, which comprises a predetermined or random time interval that may range, e.g., from -10-800 msec following detection of the R-wave. The therapeutic electrical signal may be applied to the vagus nerve after a predetermined or random time interval, e.g. -10-1000 msec following the beginning of inspiration by the patient. Alternatively, the IMD 100 may apply an electrical signal to a cranial nerve, such as vagus nerve 127, beginning at a point from about 10 msec to about 800 msec after an R-wave of the patient's ECG when the patient is inspiring. Without being bound by theory, it is believed that synchronizing the application of the exogenous therapeutic electrical signal to the vagus nerve with the detection of the R-wave of the patient's cardiac cycle and/or the beginning of inspiration by the patient may increase the efficacy of neurostimulation therapy by entraining the exogenous signal with the endogenous cyclic facilitation of central vagal afferent pathways.

[0040] A first electrical signal may be applied in synchrony with the patient's cardiac and/or respiratory cycles, as described above, and a second electrical signal is applied without reference to the patient's physiological cycle, wherein the second electrical signal differs from the first in at least one parameter selected from the group consisting of a burst duration, a number of pulses per burst, an interpulse interval, an interburst period, a current magnitude, a pulse frequency, a signal width, an on-time, and an off-time.

[0041] The synchronization of the exogenous electrical signal may further comprise not providing the exogenous signal during periods in the opposite half of the cardiac and/or respiratory duty cycles, when the central pathways are inhibited. Again without being bound by theory, it is believed that asynchronously-applied neurostimulation signals in other portions of the cardiac and/or respiratory cycles may be less effective because endogenous signals in those portions of the cardiac and/or respiratory cycles are less significant, in terms of their information content, for modulating those portions of the brain relevant to homeostasis mechanisms implicated in medical conditions such as epilepsy and depression, among others. Thus, at least a portion of the exogenous electrical signal in conventional stimulation algorithms may be therapeutically irrelevant, or even counterproductive.

[0042] Accordingly, the therapeutic electrical signal burst or microburst may be applied to the cranial nerve, such as the vagus nerve 127, after a delay period of, e.g., -10-800 msec following detection of the R-wave, and no signal is applied during the remaining portions of one or more subsequent cardiac cycles. The therapeutic electrical signal may be applied to the vagus nerve after a delay period of -10-1000 msec following the beginning of inspiration by the patient, and no signal is applied to the nerve during the remaining portions of the respiration cycle. Alternatively, the therapeutic electrical signal may be applied to the vagus nerve after a delay period following detection of the R-wave only if the patient is inspiring, and otherwise no signal is applied to the vagus nerve.

[0043] A patient's heart rate can vary due to a number of reasons, including variations in activity level (e.g., exercise or other exertion), variations in emotional state, or variations in breathing, among others. In generally healthy patients, heart rate variability (HRV) of about 0.15 Hz to about 0.4 Hz is observed with respiration (breathing), with heart rate increasing during inspiration (inhalation) and decreasing during expiration (exhaling). HRV can decrease or increase greatly during meditation, and can increase by the practice of slow, paced breathing. Observers have noted a correlation between respiration-related HRV of about 0.15 Hz to about 0.4 Hz and physical health, including greater immune function, lower incidence of cardiac arrhythmia, and a greater prevalence of commonly-preferred emotional states (e.g., more "happiness" and less "sadness") relative to persons having respiration-related HRV below 0.15 Hz. Consequently, it may be beneficial for the patient to begin paced breathing during the pulse burst. Further, it may improve the efficacy of the exogenous electrical signal if the pulses are triggered while the patient is performing paced breathing. The beneficial effects of the paced breathing coupled with the therapeutic effects of the microbursts may increase the efficacy of the stimulation. Respiration-related HRV can be determined by monitoring heart rate or electrocardiography and calculating intervals between heart beats or particular points in consecutive cardiac

cycles, such as consecutive R-waves. The variations in HRV can be used to indicate periods when the R-R interval is decreasing (corresponding to inspiration as the heart rate accelerates, thus reducing the duration of R-R interval relative to the prior R-R interval) or increasing (corresponding to expiration as the heart rate decelerates, thus increasing the R-R interval duration relative to the prior R-R interval). Alternatively, the IMD system 100 may detect the high frequency (0.18-0.4 Hz) component of the HRV power spectrum to determine when inspiration occurs. It will be appreciated that different techniques to detect cardiac cycles and respiration may be used, including separate sensors for heart rate and breathing.

[0044] The IMD 100 may apply a therapeutic electrical signal to the cranial nerve, such as the vagus nerve 127, at a point in the cardiac cycle correlated with increased afferent conduction on the cranial nerve, such as the vagus nerve 127. This may be done by sensing electrical activity on the vagus nerve and initiating the therapeutic electrical signal when the electrical activity increases. Without being bound by theory, since it is believed that increased electrical activity corresponds with inspiration and/or appropriate portions of the cardiac cycle, such a technique could result in supplementing the endogenous central vagal activity relevant to the patient's medical condition with the therapeutic, exogenous electrical signal.

[0045] The IMD 100 may apply an electrical signal to the cranial nerve, such as the vagus nerve 127, at a point in the cardiac cycle when applying the signal increases heart rate variability. The IMD 100 may apply an electrical signal to the cranial nerve, such as the vagus nerve 127, beginning at a point from about 10 msec to about 800 msec after an R-wave of the patient's ECG during expiration (exhalation) by the patient.

[0046] The IMD 100 may not apply an electrical signal to the cranial nerve, such as the vagus nerve 127, at a point during the cardiac cycle correlated with increased efferent conduction on the cranial nerve.

[0047] Stimulation may be applied to generate efferent electrical activity on the nerve, which refers to signals traveling on a nerve in a direction away from the central nervous system. A "blocking" type of electrical signal may be employed using the IMD 100, such that both afferent and efferent electrical activity on the nerve is prevented from traveling further. Thus, the IMD 100 may operate to "silence" the vagus nerve.

[0048] Further, or alternatively, afferent stimulation may also be performed, wherein afferent fibers are stimulated while efferent fibers are not stimulated or are blocked. Afferent stimulation may be especially potent at times when the nerve conducts a relatively large number of afferent signals. For the vagus nerve, an example of such a time is about 10 msec to about 800 msec after the R-wave of the cardiac cycle.

[0049] In addition to electrical signals to generate efferent or afferent electrical activity on the nerve, the blocking type of stimulation described above may also be applied to the nerve. Efferent blocking may be realized by enhancing the hyper polarization of a stimulation signal, as described below. Examples may employ the IMD 100 to perform afferent or efferent stimulation in combination with signal blocking, in order to treat medical conditions. Using the stimulation from the IMD 100, cranial nerve portions may be inhibited such that blocking of action potentials is achieved, wherein the various portions of the cranial nerve may also be stimulated to affect a mechanism in the patients' body.

[0050] The electrical stimulation treatment described herein may be used to treat a medical condition separately, or in combination with another type of treatment. For example, electrical stimulation treatment may be applied in combination with a chemical agent, such as various drugs, to treat various medical conditions. Therefore, various drugs may be taken by a patient, wherein the effects of these drugs may be enhanced by providing electrical stimulation to various portions of the nerves described herein to treat medical conditions. Further, the electrical stimulation may be performed in combination with treatment(s) relating to a biological or chemical agent. Therefore, drug therapy may be enhanced by the application of the stimulation provided by the IMD 100. The electrical stimulation treatment may also be performed in combination with other types of treatment, such as transcranial magnetic stimulation (TMS) treatment. Combining the electrical stimulation with the chemical, magnetic, or biological treatments, side effects associated with certain drugs or biological agents may be reduced.

[0051] Turning now to Figure 2, a block diagram depiction of the IMD 200 is provided. The IMD 200 (such as generator 110 from Figure 1) may comprise a controller 210 capable of controlling various aspects of the operation of the IMD 200. The controller 210 is capable of receiving internal data or external data and causing a stimulation unit 220 to generate and deliver an electrical signal to target tissues of the patient's body for treating a medical condition. For example, the controller 210 may receive manual instructions from an operator externally, or may cause the electrical signal to be generated and delivered based on internal calculations and programming. The controller 210 is capable of affecting substantially all functions of the IMD 200.

[0052] The controller 210 may comprise various components, such as a processor 215, a memory 217, etc. The processor 215 may comprise one or more microcontrollers, microprocessors, etc., capable of performing various executions of software components. The memory 217 may comprise various memory portions where a number of types of data (e.g., internal data, external data instructions, software codes, status data, diagnostic data, etc.) may be stored. The memory 217 may comprise one or more of random access memory (RAM) dynamic random access memory (DRAM), electrically erasable programmable read-only memory (EEPROM), flash memory, etc.

[0053] The IMD 200 may also comprise a stimulation unit 220 capable of generating and delivering electrical signals to one or more electrodes via leads. A lead assembly such as lead assembly 122 (Figure 1) may be coupled to the IMD 200. Therapy may be delivered to the leads comprising the lead assembly 122 by the stimulation unit 220 based upon instructions from the controller 210. The stimulation unit 220 may comprise various circuitry, such as electrical signal generators, impedance control circuitry to control the impedance "seen" by the leads, and other circuitry that receives instructions relating to the delivery of the electrical signal to tissue. The stimulation unit 220 is capable of delivering an electrical signal over the leads comprising the lead assembly 122.

[0054] The IMD 200 may also comprise a power supply 230. The power supply 230 may comprise a battery, voltage regulators, capacitors, etc., to provide power for the operation of the IMD 200, including delivering the therapeutic electrical signal. The power supply 230 comprises a power source that may be rechargeable. Alternatively, a non-rechargeable power source may be used. The power supply 230 provides power for the operation of the IMD 200, including electronic operations and the electrical signal generation and delivery functions. The power supply 230 may comprise a lithium/thionyl chloride cell or a lithium/carbon monofluoride (LiCFx) cell. Other battery types known in the art of implantable medical devices may also be used.

[0055] The IMD 200 may also comprise a communication unit 260 capable of facilitating communications between the IMD 200 and various devices. In particular, the communication unit 260 is capable of providing transmission and reception of electronic signals to and from an external unit 270, such as computer 150 and wand 155 that may comprise an ED (Figure 1). The communication unit 260 may include hardware, software, firmware, or any combination thereof.

[0056] The IMD 200 also comprises a detection unit 295 that is capable of detecting various patient parameters. For example, the detection unit 295 may comprise hardware, software, or firmware that is capable of obtaining and/or analyzing data relating to one or more body parameters of the patient, such as heart rate, cardiac cycle data, and/or respiratory cycle data. Based upon the data obtained by the detection unit 295, the IMD 200 may deliver the electrical signal to a portion of the vagus nerve to treat epilepsy, depression or other medical conditions. The detection unit 295 may be capable of detecting a feedback response from the patient. The feedback response may include a magnetic signal input, a tap input, a wireless data input to the IMD 200, etc. The feedback may be indicative of a pain and/or noxious threshold, wherein the threshold may be the limit of tolerance of discomfort for a particular patient. The term "patient parameters" may refer to, but is not limited to, various body parameters, which may involve sensors coupled to the IMD 200.

[0057] The detection unit 295 may comprise hardware, software, or firmware that is capable of obtaining and/or analyzing data relating to one or more body parameters of the patient's cardiac cycle. Based upon the data obtained by the detection unit 295, the IMD 200 may deliver the electrical signal to a portion of the vagus nerve at one or more particular points in the cardiac cycle to treat epilepsy, depression or other medical conditions.

[0058] The external unit 270 may be an ED that is capable of programming electrical signal parameters of the IMD 200. The external unit 270 is a computer system capable of executing a data-acquisition program. The external unit 270 may be controlled by a healthcare provider, such as a physician, at a base station in, for example, a doctor's office. The external unit 270 may be controlled by a patient in a system providing less control over the operation of the IMD 200 than another external unit 270 controlled by a healthcare provider. Whether controlled by the patient or by a healthcare provider, the external unit 270 may be a computer, preferably a handheld computer or PDA, but may alternatively comprise any other device that is capable of electronic communications and programming, e.g., hand-held computer system, a PC computer system, a laptop computer system, a server, a personal digital assistant (PDA), an Apple-based computer system, etc. The external unit 270 may download various parameters and program software into the IMD 200 for programming the operation of the IMD, and may also receive and upload various status conditions and other data from the IMD 200. Communications between the external unit 270 and the communication unit 260 in the IMD 200 may occur via a wireless or other type of communication, represented generally by line 277 in Figures 2A and 2B. This may occur using, e.g., wand 155 (Figure 1) to communicate by RF energy with a generator 110. Alternatively, the wand may be omitted in some systems, e.g., systems in which external unit 270 operates in the MICS bandwidths.

[0059] The external unit 270 may comprise a local database unit 255. Optionally or alternatively, the external unit 270 may also be coupled to a database unit 250, which may be separate from external unit 270 (e.g., a centralized database wirelessly linked to a handheld external unit 270). The database unit 250 and/or the local database unit 255 are capable of storing various patient data. This data may comprise patient parameter data acquired from a patient's body and/or therapy parameter data. The database unit 250 and/or the local database unit 255 may comprise data for a plurality of patients, and may be organized and stored in a variety of manners, such as in date format, severity of disease format, etc. The database unit 250 and/or the local database unit 255 may be relational databases. A physician may perform various patient management functions using the external unit 270, which may include obtaining and/or analyzing data from the IMD 200 and/or data from the database unit 250 and/or the local database unit 255. The database unit 250 and/or the local database unit 255 may store various patient data such as heart rate data, cardiac cycle

data (such as R-R interval data), respiratory cycle information, etc.

[0060] One or more of the blocks illustrated in the block diagram of the IMD 200 in Figure 2, may comprise hardware units, software units, firmware units, or any combination thereof. Additionally, one or more blocks illustrated in Figure 2 may be combined with other blocks, which may represent circuit hardware units, software algorithms, etc. Additionally, any number of the circuitry or software units associated with the various blocks illustrated in Figure 2 may be combined into a programmable device, such as a field programmable gate array, an ASIC device, etc.

[0061] Figure 3 provides a stylized depiction of an exemplary electrical signal of a firing neuron as a graph of voltage at a given point on the nerve at particular times during the propagation of an action potential along the nerve. A typical neuron has a resting membrane potential of about -70 mV, maintained by transmembrane ion channel proteins. When a portion of the neuron reaches a firing threshold of about -55 mV, the ion channel proteins in the locality allow the rapid ingress of extracellular sodium ions, which depolarizes the membrane to about +30 mV. The wave of depolarization then propagates along the neuron. After depolarization at a given location, potassium ion channels open to allow intracellular potassium ions to exit the cell, lowering the membrane potential to about -80 mV (hyperpolarization). About 1 msec is required for transmembrane proteins to return sodium and potassium ions to their starting intra- and extracellular concentrations and allow a subsequent action potential to occur.

[0062] Referring again to Figure 1, the IMD 100 may generate a pulsed electrical signal for application to a cranial nerve such as vagus nerve 127 according to one or more programmed parameters. The electrical signal may be a conventional vagus nerve therapeutic electrical signal defined by a plurality of parameters such as current magnitude, pulse width, frequency, on-time and off-time. The electrical signal may be a microburst signal defined by a plurality of parameters such as an interburst period, a number of a number of pulses per burst, an interpulse interval, a burst duration, a current magnitude, a pulse width, an on-time, and an off-time. The electrical signal may comprise a first time period in which conventional vagus nerve therapeutic electrical signals are applied to the nerve, and a second time period in which microburst electrical signals are applied to the nerve. Conventional and microburst signals may be alternated with a defined off-time in a conventional on-time and a microburst on-time. Thus a 30 second burst of a conventional VNS signal may be followed by 5 minutes off-time, followed by a 1 minute period of microburst stimulation, followed by a 5 minute off-time, after which the process repeats itself.

[0063] Exemplary pulse waveforms are shown in Figures 4A-4C. Pulse shapes in electrical signals may include a variety of shapes known in the art including square waves, biphasic pulses (including active and passive charge-balanced biphasic pulses), triphasic waveforms, etc. The pulses may comprise a square, biphasic waveform in which the second phase is a charge-balancing phase of the opposite polarity to the first phase.

[0064] In addition to conventional programmed or random off-time periods (and whether conventional or microburst stimulation is applied), the duration of a period of "off-time" may be varied with changes in the patient's cardiac cycle. The "off-time" may begin about 10 msec to about 800 msec after the onset of the R-wave of a patient's cardiac cycle and ends at the onset of the R-wave of a later cardiac cycle of the patient, such as the next cardiac cycle.

[0065] One example may include coupling of at least one electrode to each of two or more cranial nerves. (In this context, two or more cranial nerves mean two or more nerves having different names or numerical designations, and do not refer to the left and right versions of a particular nerve). At least one electrode may be coupled to each of the vagus nerves 127 or a branch of either vagus nerve. The term "operatively" coupled may include directly or indirectly coupling. Each of the nerves may be stimulated according to particular activation modalities that may be independent between the two nerves.

[0066] Another activation modality for stimulation is to program the output of the IMD 100 to the maximum amplitude which the patient may tolerate. The stimulation may be cycled on and off for a predetermined period of time followed by a relatively long interval without stimulation. Where the cranial nerve stimulation system is completely external to the patient's body, higher current amplitudes may be needed to overcome the attenuation resulting from the absence of direct contact with the cranial nerve and the additional impedance of the skin of the patient. Although external systems typically require greater power consumption than implantable ones, they have an advantage in that their batteries may be replaced without surgery.

[0067] Returning to systems for providing cranial nerve stimulation, such as that shown in Figures 1 and 2, stimulation may be provided in either non-feedback or feedback modalities. Where cranial nerve stimulation is provided based solely on programmed off-times and on-times, the stimulation may be referred to as passive, inactive, or non-feedback stimulation. In contrast, stimulation may be triggered by one or more feedback loops according to changes in the body or mind of the patient. This stimulation may be referred to as active or feedback-loop stimulation. Feedback-loop stimulation may be manually-triggered stimulation, in which the patient manually causes the activation of a pulse burst outside of the programmed on-time/off-time cycle. The patient may manually activate the IMD 100 to stimulate the vagus nerve 127 to treat an acute episode of a medical condition. The patient may also be permitted to alter the intensity of the signals applied to the cranial nerve within limits established by the physician.

[0068] Patient activation of an IMD 100 may involve

use of an external control magnet for operating a reed switch in an implanted device, for example. Certain other techniques of manual and automatic activation of implantable medical devices are disclosed in U.S. Pat. No. 5,304,206 to Baker, Jr., et al., assigned to the same assignee as the present application ("the '206 patent"). According to the '206 patent, means for manually activating or deactivating the electrical signal generator 110 may include a sensor such as piezoelectric element mounted to the inner surface of the generator case and adapted to detect light taps by the patient on the implant site. One or more taps applied in fast sequence to the skin above the location of the electrical signal generator 110 in the patient's body may be programmed into the implanted medical device 100 as a signal for activation of the electrical signal generator 110. Two taps spaced apart by a slightly longer duration of time may be programmed into the IMD 100 to indicate a desire to deactivate the electrical signal generator 110, for example. The patient may be given limited control over operation of the device to an extent which may be determined by the program dictated or entered by the attending physician. The patient may also activate the IMD 100 using other suitable techniques or apparatus.

[0069] Feedback stimulation systems other than manually-initiated stimulation may be used. A cranial nerve stimulation system may include a sensing lead coupled at its proximal end to a header along with a stimulation lead and electrode assemblies. A sensor may be coupled to the distal end of the sensing lead. The sensor may include a cardiac cycle sensor. The sensor may also include a nerve sensor for sensing activity on a nerve, such as a cranial nerve, such as the vagus nerve 127.

[0070] The sensor may sense a body parameter that corresponds to a symptom of a medical condition. If the sensor is to be used to detect a symptom of the medical condition, a signal analysis circuit may be incorporated into the IMD 100 for processing and analyzing signals from the sensor. Upon detection of the symptom of the medical condition, the processed digital signal may be supplied to a microprocessor in the IMD 100 to trigger application of the electrical signal to the cranial nerve, such as the vagus nerve 127. The detection of a symptom of interest may trigger a stimulation program including different stimulation parameters from a passive stimulation program. This may entail providing a higher current stimulation signal or providing a higher ratio of on-time to off-time.

[0071] Turning now to Figure 5, a flowchart depiction of a method for treating a medical condition. An electrode may be coupled to a portion of a cranial nerve to perform a stimulation function or a blocking function to treat a medical condition. One or more electrodes may be positioned in electrical contact or proximate to a portion of the cranial nerve to deliver a stimulation signal to the portion of the cranial nerve (block 710). The electrodes may be operatively coupled to at least one of main trunk of the right or left vagus nerve, or any branch thereof. The IMD 100 may then generate a controlled electrical signal, based upon one or more characteristics relating to the medical condition(s) of the patient (block 720). This may include a predetermined electrical signal that is pre-programmed based upon a particular condition of a patient. The term "medical condition" may include epilepsy or depression, among others. For example, a physician may pre-program the type of stimulation to provide (e.g., conventional stimulation, microburst stimulation, or combination conventional/microburst stimulation) in order to treat the patient based upon the medical condition of the patient. The IMD 100 may then generate a signal, such as a controlled-current pulse signal, to affect one or more portions of the neurological system of a patient.

[0072] The IMD 100 may then deliver the stimulation signal to the portion of the cranial nerve (block 730). The application of the electrical signal may be delivered to the main trunk of the right or left vagus nerve, or any branch thereof. Application of the stimulation signal may be designed to generate afferent electrical activity on the vagus nerve 127. Further, the stimulation by the IMD 100 may reduce incidents or symptoms relating to a medical condition. Application of the stimulation signal may be controlled so that the signal is applied during periods of the cardiac cycle correlated with increased afferent traffic on the cranial nerve.

[0073] Application of the stimulation signal may be designed to promote a blocking effect relating to a signal that is being sent from the brain, to treat the medical condition. This may be accomplished by delivering a particular type of controlled electrical signal, such as a controlled current signal to the cranial nerve. Afferent fibers may also be stimulated in combination with an efferent blocking to treat a medical condition.

[0074] Additional functions, such as a detection process, may be alternatively employed. The detection process may be employed such that an external detection or an internal detection of a bodily function may be used to adjust the operation of the IMD 100.

[0075] Turning now to Figure 6, a block diagram depiction of a method is illustrated. The IMD 100 may perform a detection process, which may include checking a database for physiological data, such as data indicative of the patient's cardiac cycle (block 810). Data from the database may be used for determining the timing of the delivery of stimulation signals, e.g. timing delivery based on the patient's cardiac cycle. The detection process may encompass detecting a variety of types of characteristics of the cardiac cycle of the patient. A more detailed depiction of the steps for performing the detection process is provided in Figure 7, and accompanying description below. Upon performing the detection process, the IMD 100 may determine whether an appropriate point in the cardiac cycle has been reached (block 820). Upon a determination that an appropriate point in the cardiac cycle has not been reached, the detection process is continued (block 830).

[0076] Upon a determination that an appropriate time

in the cardiac cycle has been reached, a determination as to the type of stimulation based upon data relating to the medical condition is made (block 840). The type of stimulation may be determined in a variety of manners, such as performing a look-up in a look-up table that may be stored in the memory 217. Alternatively, the type of stimulation may be determined by an input from an external source, such as the external unit 270 or an input from the patient. Further, determination of the type of stimulation may also include determining the location as to where the stimulation is to be delivered. Accordingly, the selection of particular electrodes, which may be used to deliver the stimulation signal, is made.

[0077] Upon determining the type of stimulation to be delivered, the IMD 100 performs the stimulation by applying the electrical signal to one or more selected electrodes (block 850). Upon delivery of the stimulation, the IMD 100 may monitor, store, or compute the results of the stimulation (block 860). For example, based upon the calculation, a determination may be made that adjustment(s) to the type of signal to be delivered for stimulation, may be performed. Further, the calculations may reflect the need to deliver additional stimulation. Additionally, data relating to the results of stimulation may be stored in memory 217 for later extraction or further analysis. Also, real time or near real time communications may be provided to communicate the stimulation result or the stimulation log to an external unit 270.

[0078] Turning now to Figure 7, a more detailed block diagram depiction of the step of performing the detection process of block 810 in Figure 6, is illustrated. The system 100 may monitor one or more signals relating to the cardiac cycle of the patient (block 910). This detection may be made by sensors residing inside the human body, which may be operatively coupled to the IMD 100. The sensors may be located in the IMD 100. These signals may be detected by external means and may be provided to the IMD 100 from an external device via the communication unit 260.

[0079] Upon acquisition of various signals, a comparison may be performed comparing the data relating to the real-time signals or stored physiological data to predetermined and/or stored data (block 920). For example, an ECG may be compared to various benchmark ECGs to determine whether a portion of the cardiac cycle correlated with increased afferent vagus nerve conduction has been reached. Based upon the comparison of the collected data with theoretical, stored thresholds, the IMD 100 may determine whether an appropriate time to commence an on-time (i.e., a time to apply the electrical signal to the cranial nerve) has been reached (block 930). Based upon the determination described in Figure 7, the IMD 100 may continue to determine whether the medical condition is sufficiently significant to perform treatment, as described in Figure 6.

[0080] Additionally, external devices may perform such calculation and communicate the results or accompanying instructions to the IMD 100. The IMD 100 may also determine the specific cranial nerve(s), or the location or branch of the nerve(s), to stimulate. The IMD 100 may also indicate the type of treatment to be delivered. For example, an electrical treatment alone or in combination with another type of treatment may be provided based upon the quantifiable parameter(s) that are detected. For example, a determination may be made that an electrical signal by itself is to be delivered. Alternatively, based upon a particular type of medical condition, a determination may be made that an electrical signal, in combination with a magnetic signal, such as transcranial magnetic stimulation (TMS) may be performed. Stimulation can be induced by light such as from a laser.

[0081] In addition to electrical or magnetic stimulation, a determination may be made whether to deliver a chemical, biological, or other type of treatment(s) in combination with the electrical stimulation provided by the IMD 100. In one example, electrical stimulation may be used to enhance the effectiveness of a chemical agent. Therefore, various drugs or other compounds may be delivered in combination with an electrical stimulation or a magnetic stimulation. Based upon the type of stimulation to be performed, the IMD 100 delivers the stimulation to treat various medical conditions. The invention is set out in the appended claims.

Claims

1. A computer readable medium programmed with instructions to cause an apparatus (100) comprising:

- a controller (210) comprising a processor (215);
- at least one electrode (125) couplable to at least one vagus nerve (127) of a patient,
- an implantable device operatively coupled to the at least one electrode and comprising an electrical signal generator (110) configured to apply an electrical signal to the at least one vagus nerve,
- a sensor configured to sense a body parameter that corresponds to a symptom of a medical condition, and
- a respiration cycle sensing element;

to apply an electrical signal to the at least one vagus nerve (127) in response to sensing the symptom of the medical condition of the patient in the apparatus (100), wherein the instructions, when executed by the processor (215), perform a method comprising:

- generating a first electrical signal with the electrical signal generator (110),
- sensing the symptom of the medical condition,
- detecting at least a portion of a physiological cycle of the patient selected from the cardiac cycle and the respiratory cycle of the patient, and

- applying the first electrical signal to the at least one vagus nerve (127) of the patient to treat the medical condition;

characterized in that the applying of the first electrical signal to the at least one vagus nerve (127) is performed during inspiration by the patient.

2. The computer readable medium of claim 1, wherein the first electrical signal is a controlled current electrical signal, the method further comprising programming the electrical signal generator (110) to define the first electrical signal by at least one signal parameter selected from a group consisting of a microburst duration, a number of pulses per microburst interpulse interval, an interburst period, a current magnitude, a pulse frequency, a signal width, an on-time, and an off-time and wherein the at least one signal parameter is selected to treat the medical condition.

3. The computer readable medium of claim 1 or 2, wherein the electrical signal is applied at a point in a physiological cycle of the patient which is correlated with increased afferent conduction on the at least one vagus nerve (127).

4. The computer readable medium of any one of claims 1-3, wherein the electrical signal is applied at a point in the physiological cycle of the patient which is from about 10 msec to about 800 msec after an R-wave detected in the patient's ECG.

5. The computer readable medium of any one of claims 1-4, wherein the method further comprises applying a second electrical signal to the at least one vagus nerve (127) of the patient through the electrical signal generator (110).

6. The computer readable medium of claim 5, wherein the second electrical signal is different from the first electrical signal with respect to at least one parameter selected from a second group consisting of a second microburst duration, a second number of pulses per microburst, a second interpulse interval, a second interburst period, a second current magnitude, a second pulse frequency, a second signal width, a second on-time, and a second off-time.

7. The computer readable medium of claims 5 or claim 6, wherein the second electrical signal is configured to block electrical activity on the at least one vagus nerve (127).

Patentansprüche

1. Computerlesbares Medium, das mit Anweisungen programmiert ist, die eine Vorrichtung (100), die Folgendes umfasst:

- eine Steuerung (210), die einen Prozessor (215) umfasst;
- mindestens eine Elektrode (125), die an mindestens einen Vagusnerv (127) eines Patienten gekoppelt werden kann,
- eine implantierbare Vorrichtung, die mit der mindestens einen Elektrode wirkgekoppelt ist und einen Generator (110) für elektrische Signale umfasst, der dazu konfiguriert ist, ein elektrisches Signal an den mindestens einen Vagusnerv anzulegen,
- einen Sensor, der dazu konfiguriert ist, einen Körperparameter zu erfassen, der einem Symptom einer Erkrankung entspricht, und
- ein Atemzykluserfassungselement;

dazu veranlassen, als Reaktion darauf, dass das Symptom der Erkrankung des Patienten in der Vorrichtung (100) erfasst wird, ein elektrisches Signal an den mindestens einen Vagusnerv (127) anzulegen, wobei die Anweisungen bei Ausführung durch den Prozessor (215) ein Verfahren durchführen, das Folgendes umfasst:

- Generieren eines ersten elektrischen Signals mithilfe des Generators (110) für elektrische Signale,
- Erfassen des Symptoms der Erkrankung,
- Detektieren zumindest eines Teils eines physiologischen Zyklus des Patienten, ausgewählt aus dem Herzzyklus und dem Atemzyklus des Patienten, und
- Anlegen des ersten elektrischen Signals an den mindestens einen Vagusnerv (127) des Patienten zum Behandeln der Erkrankung;

dadurch gekennzeichnet, dass das Anlegen des ersten elektrischen Signals an den mindestens einen Vagusnerv (127) während eines Einatmens des Patienten durchgeführt wird.

2. Computerlesbares Medium nach Anspruch 1, wobei das erste elektrische Signal ein gesteuertes elektrisches Stromsignal ist, wobei das Verfahren außerdem ein Programmieren des Generators (110) für elektrische Signale zum Definieren des ersten elektrischen Signals durch mindestens einen Signalparameter umfasst, der aus einer Gruppe bestehend aus einer Dauer von Mikrostromstößen, einer Anzahl von Impulsen pro Mikrostromstoß-Zwischenimpulsintervall, einem Zeitraum zwischen Stromstößen, einer Stromgröße, einer Impulsfrequenz, einer Signalbreite, einer Einschaltzeit und einer Ausschaltzeit ausgewählt ist, und wobei der mindestens eine Signalparameter zum Behandeln der Erkran-

kung ausgewählt ist.

3. Computerlesbares Medium nach Anspruch 1 oder 2, wobei das elektrische Signal an einem Punkt in einem physiologischen Zyklus des Patienten angelegt wird, der mit einer erhöhten afferenten Leitung an dem mindestens einem Vagusnerv (127) korreliert ist.

4. Computerlesbares Medium nach einem der Ansprüche 1-3, wobei das elektrische Signal an einem Punkt in dem physiologischen Zyklus des Patienten angelegt wird, der etwa 10 msec bis etwa 800 msec nach dem Detektieren einer R-Zacke im EKG des Patienten liegt.

5. Computerlesbares Medium nach einem der Ansprüche 1-4, wobei das Verfahren außerdem ein Anlegen eines zweiten elektrischen Signals an den mindestens einen Vagusnerv (127) des Patienten durch den Generator (110) für elektrische Signale umfasst.

6. Computerlesbares Medium nach Anspruch 5, wobei sich das zweite elektrische Signal in Bezug auf mindestens einen Parameter von dem ersten elektrischen Signal unterscheidet, der aus einer zweiten Gruppe bestehend aus einer zweiten Dauer von Mikrostromstößen, einer zweiten Anzahl von Impulsen pro Mikrostromstoß, einem zweiten Zwischenimpulsintervall, einem zweiten Zeitraum zwischen Stromstößen, einer zweiten Stromgröße, einer zweiten Impulsfrequenz, einer zweiten Signalbreite, einer zweiten Einschaltzeit und einer zweiten Ausschaltzeit ausgewählt ist.

7. Computerlesbares Medium nach Anspruch 5 oder Anspruch 6, wobei das zweite elektrische Signal dazu konfiguriert ist, die elektrische Aktivität an dem mindestens einen Vagusnerv (127) zu blockieren.

Revendications

1. Support lisible par un ordinateur programmé avec des instructions pour amener un appareil (100) comprenant :

   - une unité de commande (210) comprenant un processeur (215) ;
   - au moins une électrode (125) couplable à au moins un nerf vague (127) d'un patient,
   - un dispositif implantable couplé de manière opérationnelle à l'au moins une électrode et comprenant un générateur de signal électrique (110) configuré pour appliquer un signal électrique à l'au moins un nerf vague,
   - un capteur configuré pour détecter un paramètre corporel qui correspond à un symptôme d'une condition médicale, et
   - un élément de détection de cycle de respiration ;

   à appliquer un signal électrique à l'au moins un nerf vague (127) en réponse à la détection du symptôme de la condition médicale du patient dans l'appareil (100), dans lequel les instructions, lorsqu'elles sont exécutées par le processeur (215), exécutent un procédé comprenant :

   - la génération d'un premier signal électrique avec le générateur de signal électrique (110),
   - la détection du symptôme de la condition médicale,
   - la détection d'au moins une partie d'un cycle physiologique du patient sélectionné parmi le cycle cardiaque et le cycle respiratoire du patient, et
   - l'application du premier signal électrique à l'au moins un nerf vague (127) du patient pour traiter la condition médicale ;

   caractérisé en ce que l'application du premier signal électrique à l'au moins un nerf vague (127) est exécutée pendant une inspiration du patient.

2. Support lisible par un ordinateur selon la revendication 1, dans lequel le premier signal électrique est un signal électrique de courant régulé, le procédé comprenant en outre la programmation du générateur de signal électrique (110) pour définir le premier signal électrique par au moins un paramètre de signal sélectionné parmi un groupe constitué d'une durée de microrafale, un nombre d'impulsions par intervalle inter-impulsion de microrafale, une période inter-rafale, une magnitude de courant, une fréquence d'impulsion, une largeur de signal, un temps d'activation et un temps de désactivation et dans lequel l'au moins un paramètre de signal est sélectionné pour traiter la condition médicale.

3. Support lisible par un ordinateur selon la revendication 1 ou 2, dans lequel le signal électrique est appliqué à un point dans un cycle physiologique du patient qui est corrélé à une conduction afférente augmentée sur l'au moins un nerf vague (127).

4. Support lisible par un ordinateur selon l'une quelconque des revendications 1 à 3, dans lequel le signal électrique est appliqué à un point dans le cycle physiologique du patient qui est d'environ 10 ms à environ 800 ms après la détection d'une onde R dans l'ECG du patient.

5. Support lisible par un ordinateur selon l'une quelconque des revendication 1 à 4, dans lequel le procédé comprend en outre l'application d'un deuxième si-

gnal électrique à l'au moins un nerf vague (127) du patient par le biais du générateur de signal électrique (110).

6. Support lisible par un ordinateur selon la revendication 5, dans lequel le deuxième signal électrique est différent du premier signal électrique par rapport à au moins un paramètre sélectionné parmi un deuxième groupe constitué d'une deuxième durée de microrafale, un deuxième nombre d'impulsions par microrafale, un deuxième intervalle inter-impulsion, une deuxième période inter-rafale, une deuxième magnitude de courant, une deuxième fréquence d'impulsion, une deuxième largeur de signal, un deuxième temps d'activation, et un deuxième temps de désactivation.

7. Support lisible par un ordinateur selon la revendication 5 ou 6, dans lequel le deuxième signal électrique est configuré pour bloquer une activité électrique sur l'au moins un nerf vague (127).

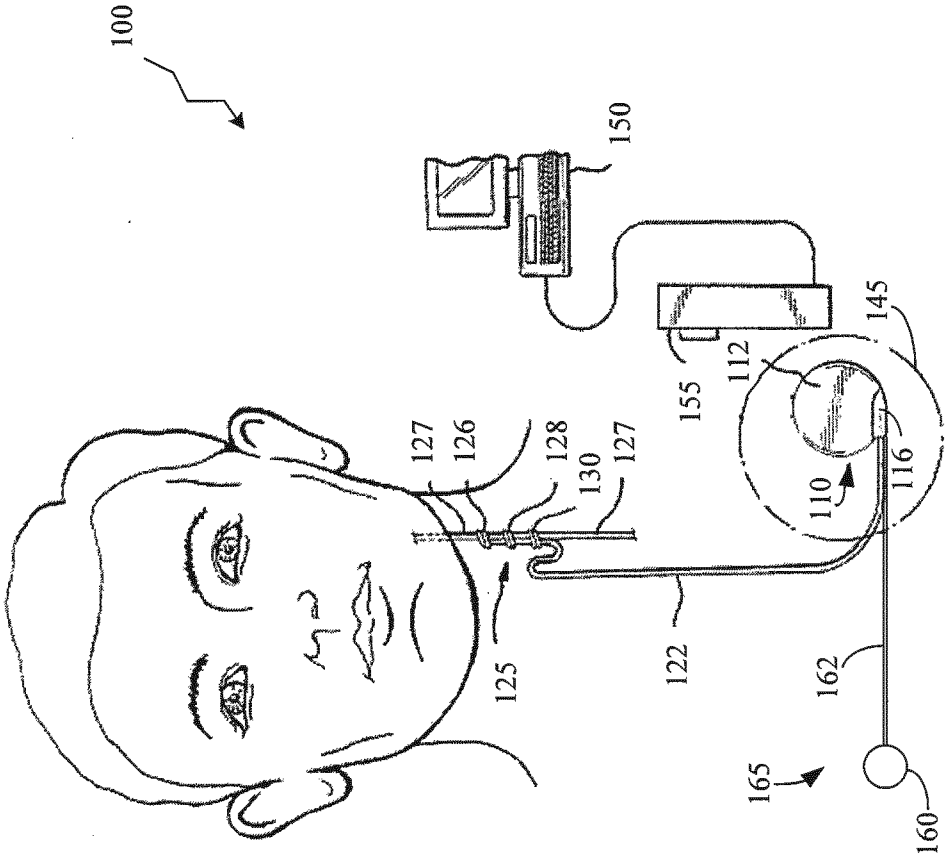

100
150
145
112
155
127
126
128
130
127
110
116
125
122
162
165
160

FIGURE 1

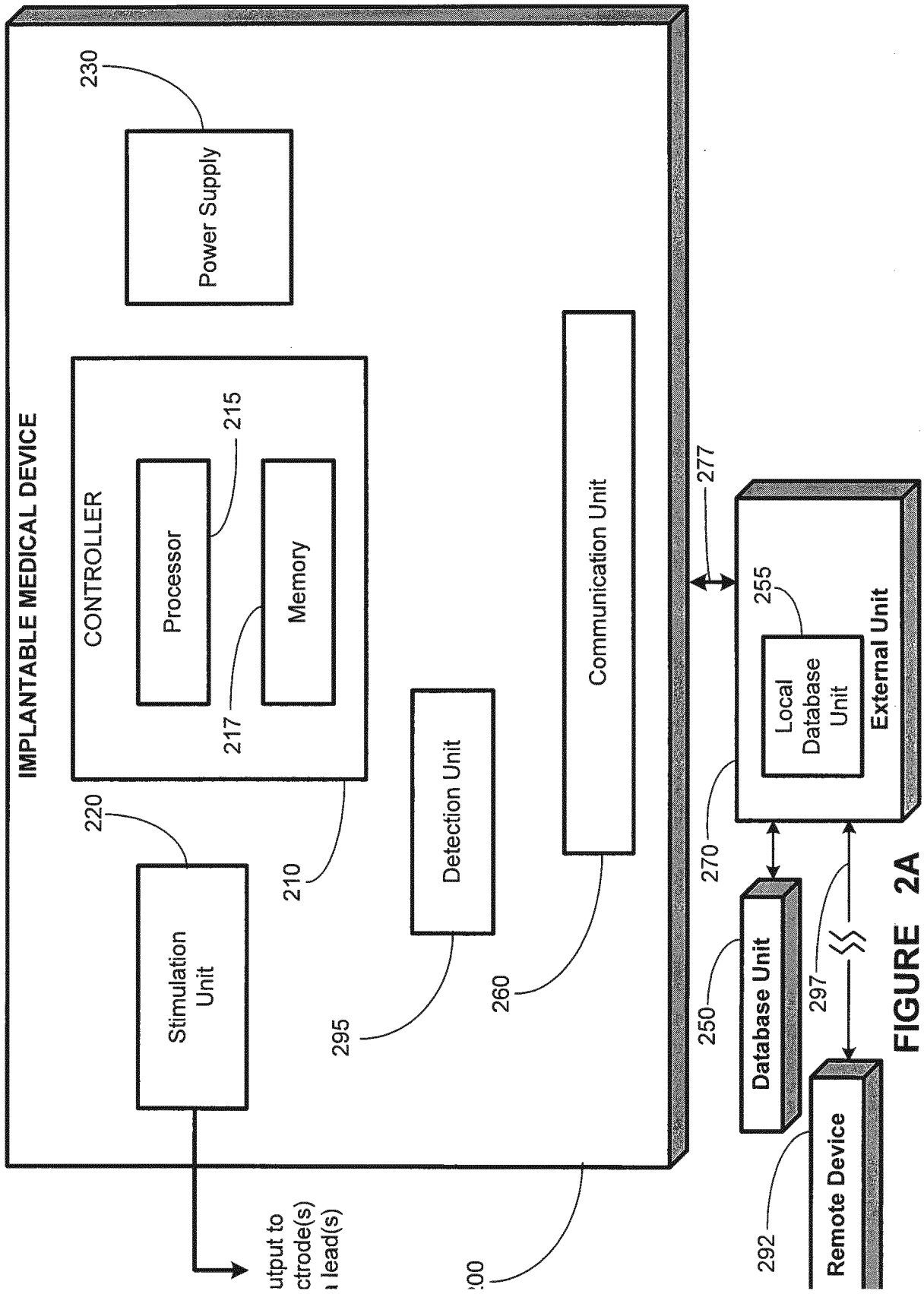

IMPLANTABLE MEDICAL DEVICE
230
Power Supply
CONTROLLER
215
Processor
Memory
217
210
220
Stimulation Unit
utput to
ctrode(s)
lead(s)
295
Detection Unit
260
Communication Unit
277
255
Local Database Unit
External Unit
270
250
Database Unit
297
292
Remote Device

FIGURE 2A

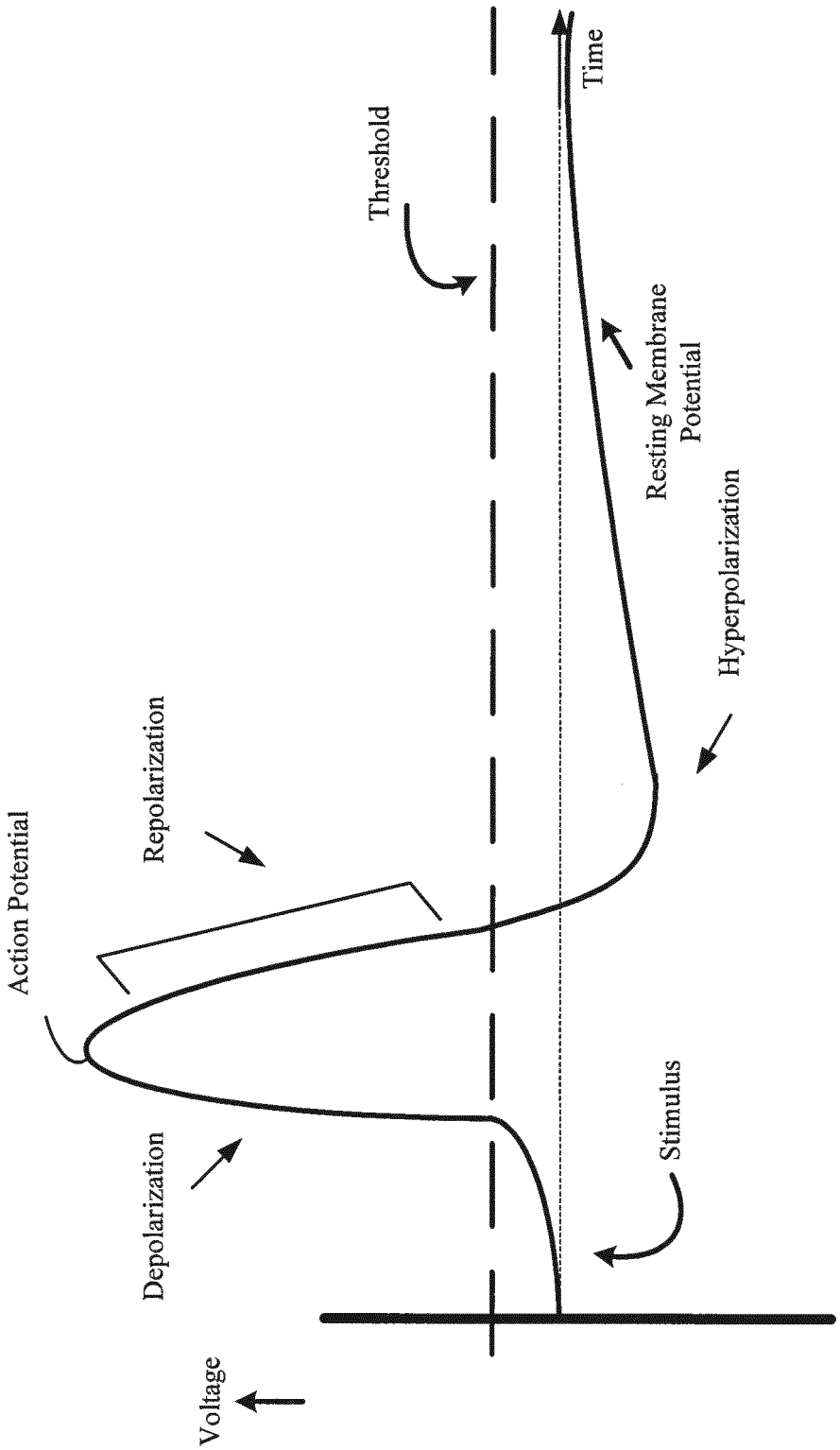

Action Potential
Repolarization
Depolarization
Voltage
Threshold
Time
Resting Membrane Potential
Hyperpolarization
Stimulus

FIGURE 3

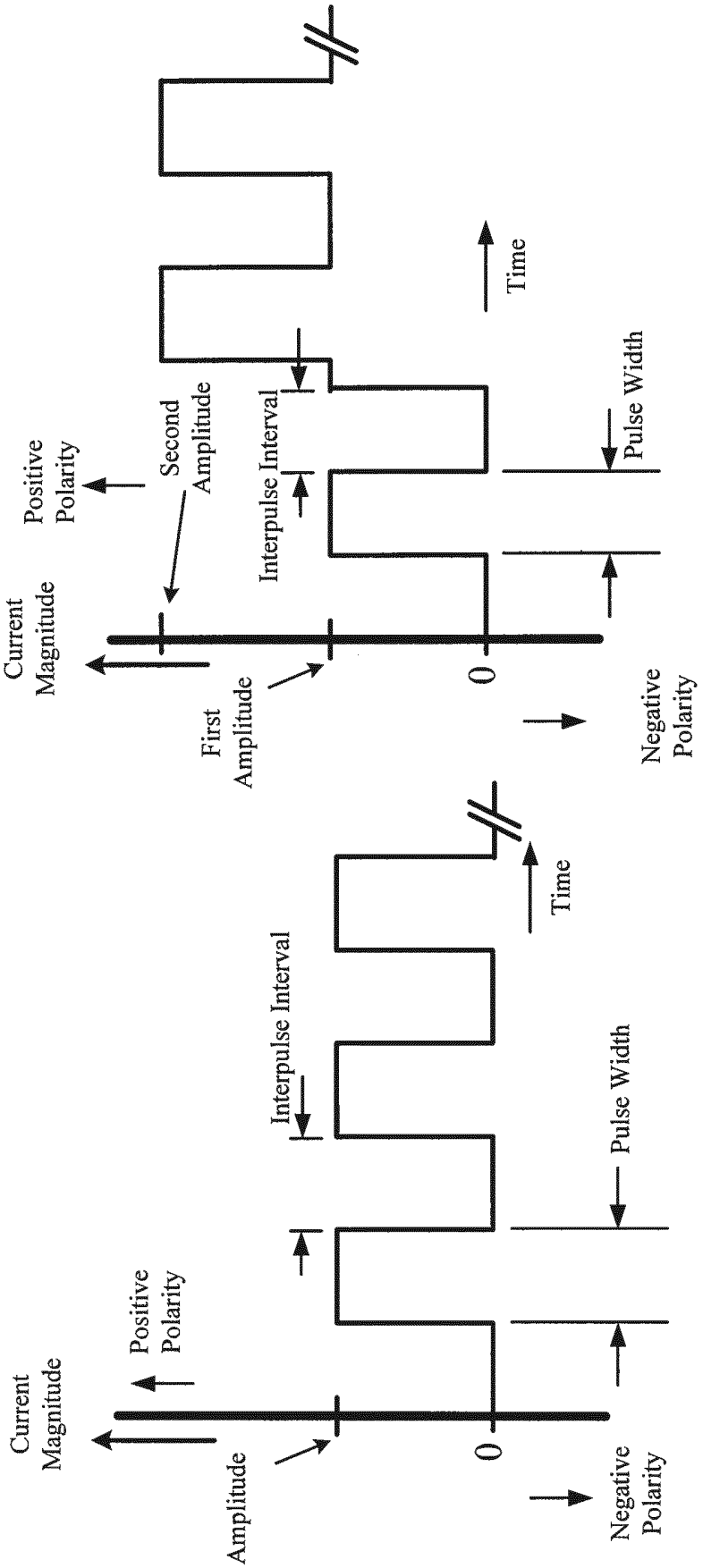


FIGURE 4A

FIGURE 4B

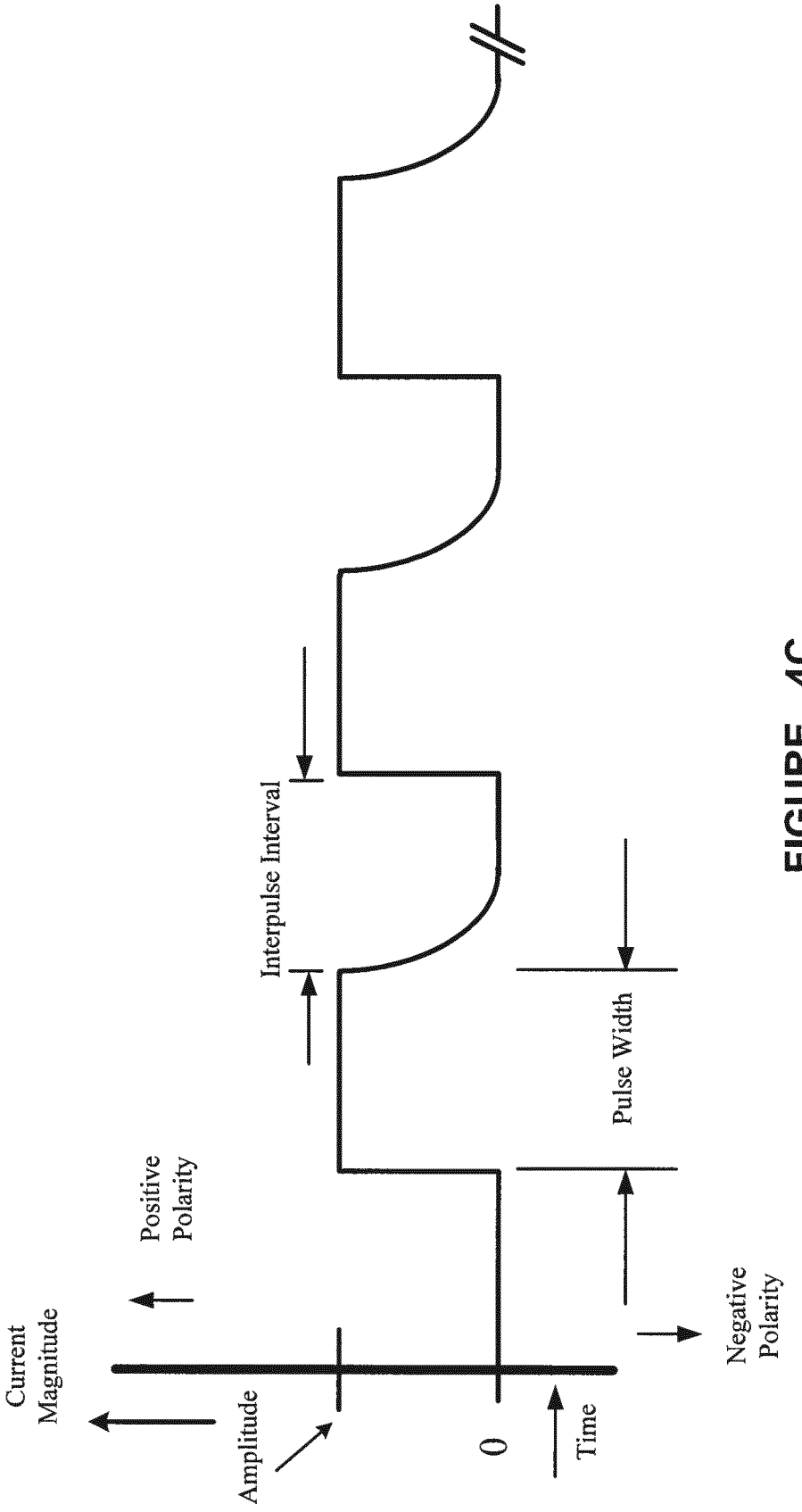

Current Magnitude
Positive Polarity
Amplitude
Interpulse Interval
0
Time
Pulse Width
Negative Polarity

FIGURE 4C

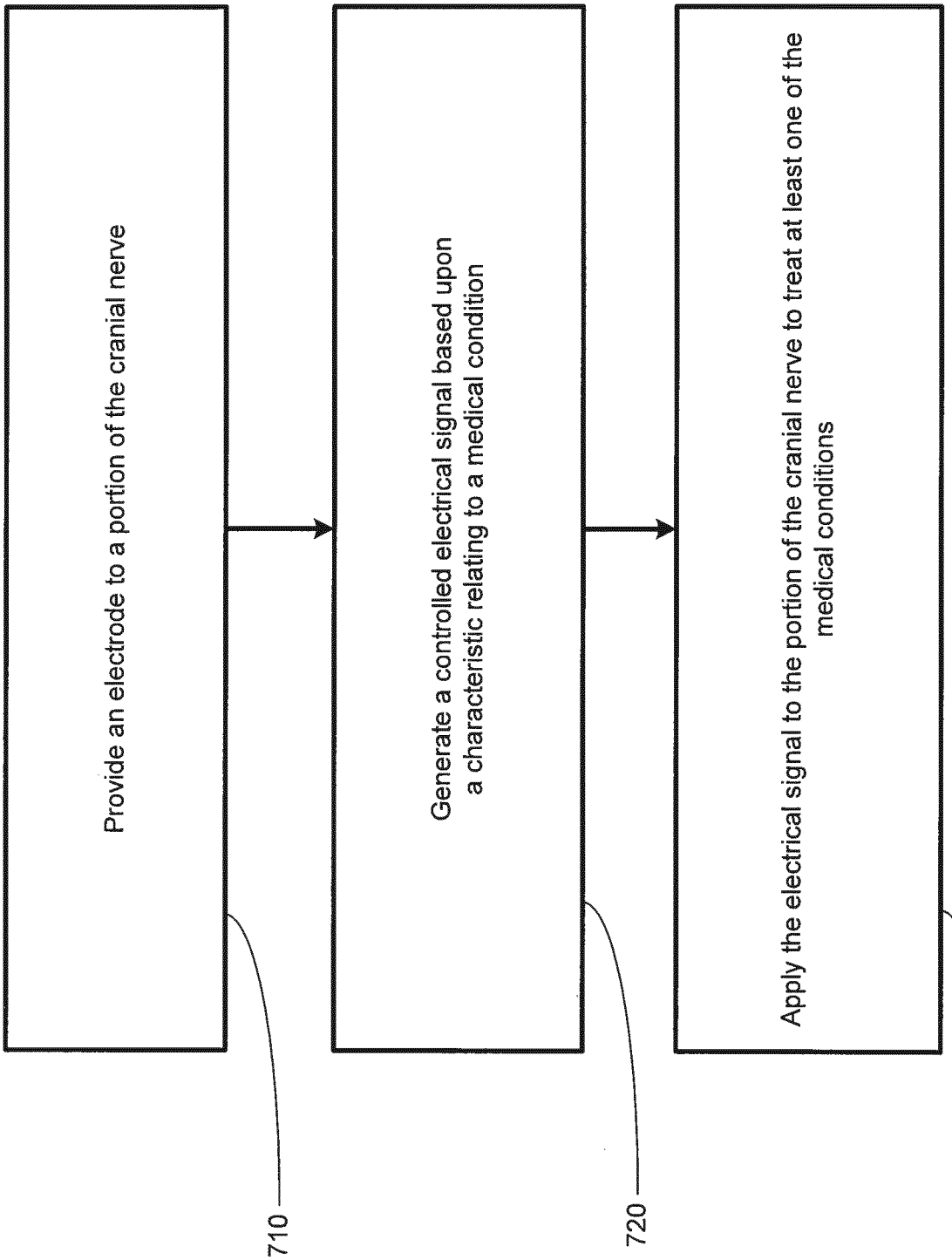

Provide an electrode to a portion of the cranial nerve
Generate a controlled electrical signal based upon a characteristic relating to a medical condition
Apply the electrical signal to the portion of the cranial nerve to treat at least one of the medical conditions
710
720
730

FIGURE 5

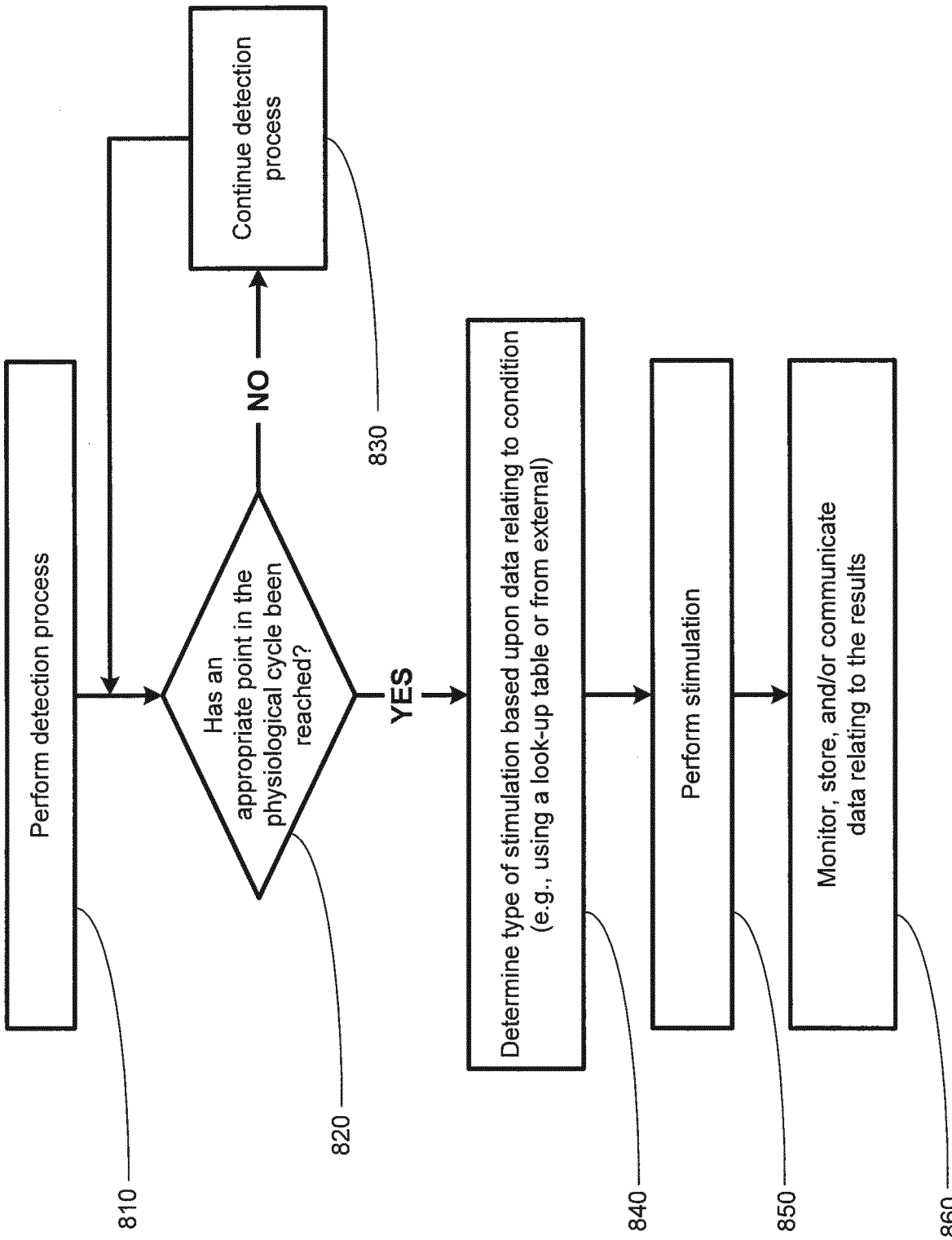

Perform detection process
Has an appropriate point in the physiological cycle been reached?
NO
YES
Continue detection process
Determine type of stimulation based upon data relating to condition (e.g., using a look-up table or from external)
Perform stimulation
Monitor, store, and/or communicate data relating to the results
810
820
830
840
850
860

FIGURE 6

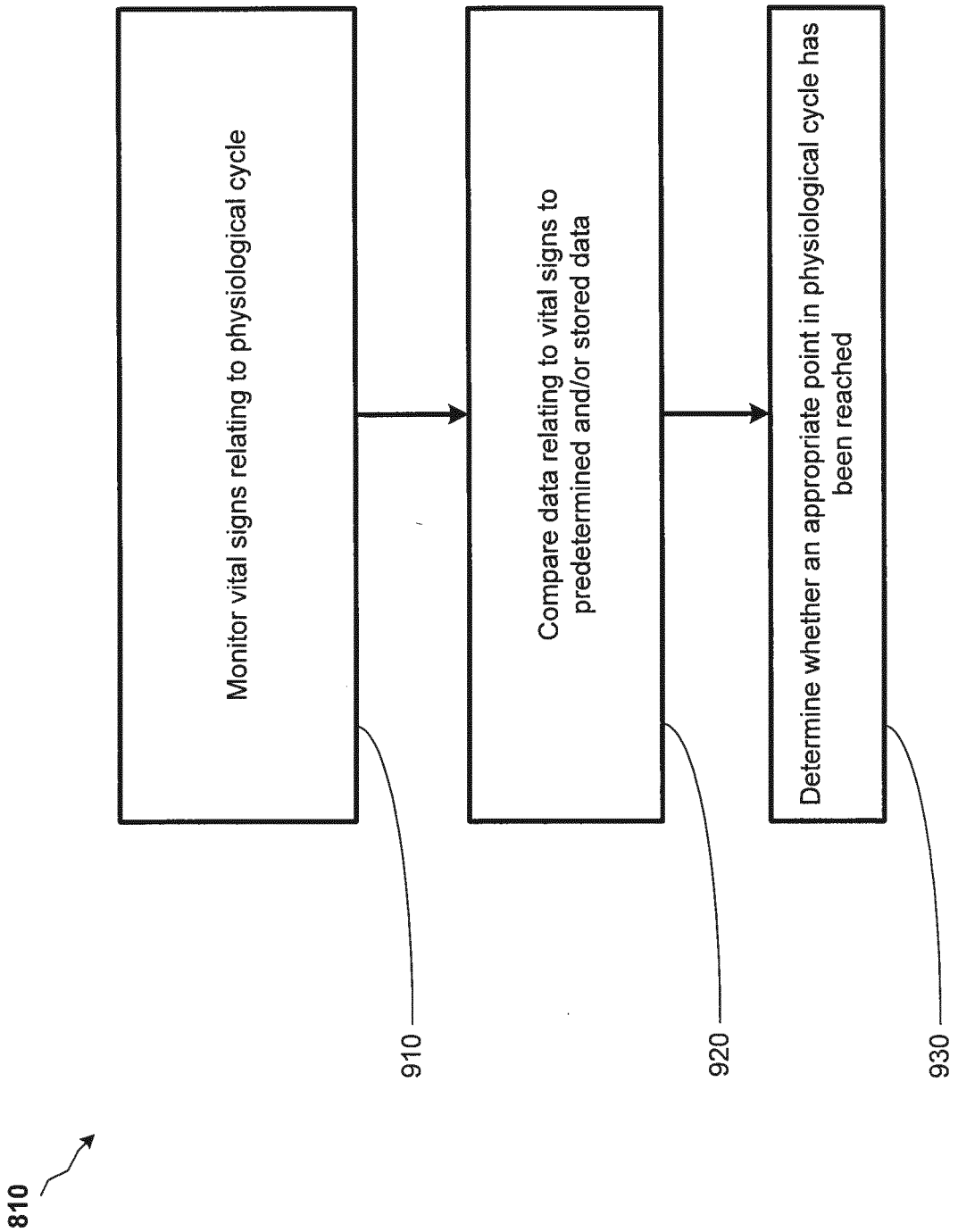
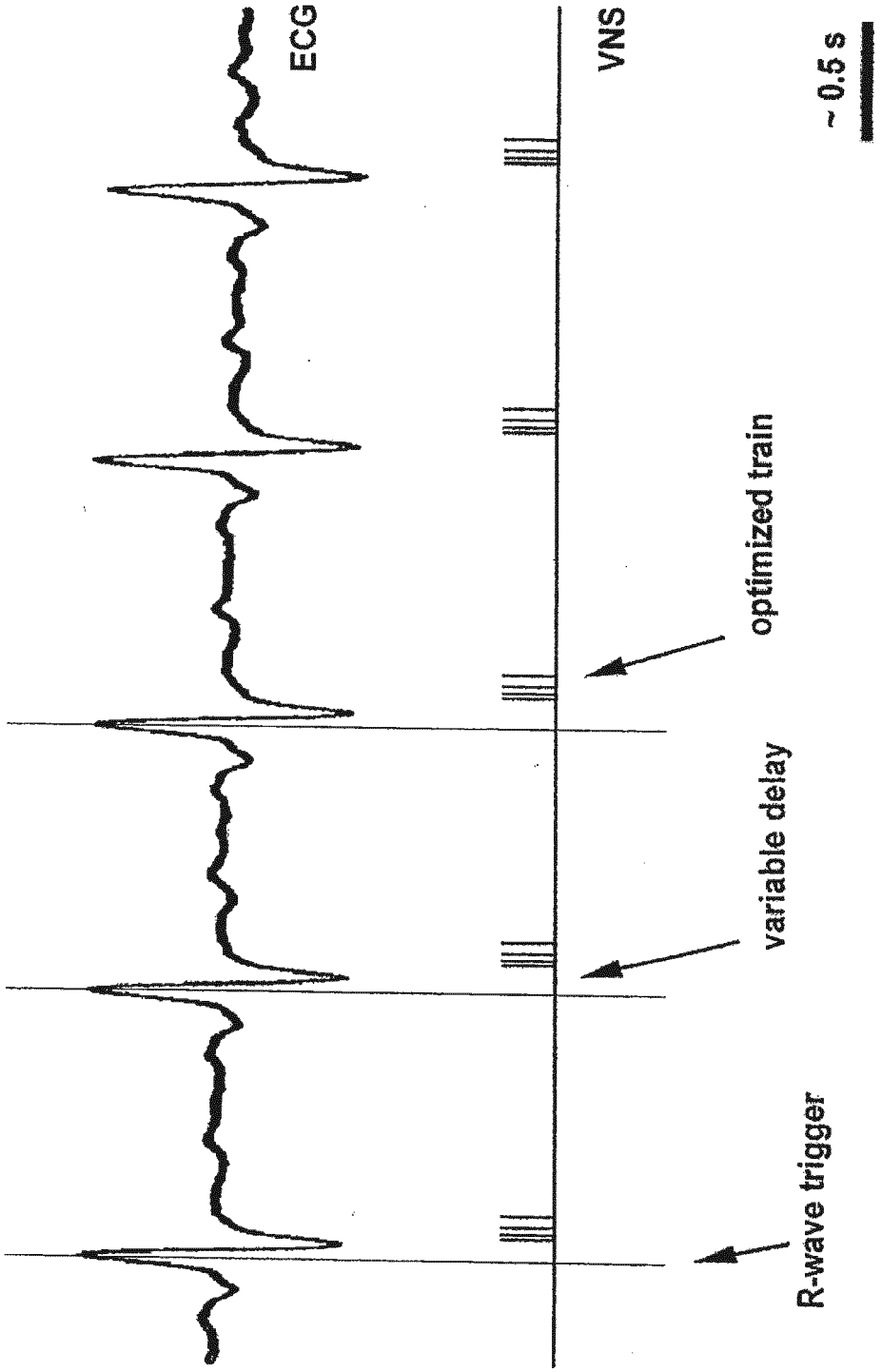

Monitor vital signs relating to physiological cycle
Compare data relating to vital signs to predetermined and/or stored data
Determine whether an appropriate point in physiological cycle has been reached
910
920
930
810

FIGURE 7

FIGURE 8



REFERENCES CITED IN THE DESCRIPTION

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专利名称(译)	迷走神经刺激与患者的心动周期同步		
公开(公告)号	EP2965781B1	公开(公告)日	2019-06-05
申请号	EP2015168839	申请日	2007-03-29
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当前申请(专利权)人(译)	卫生尊严		
[标]发明人	CRAIG ARTHUR		
发明人	CRAIG, ARTHUR		
IPC分类号	A61N1/36 A61B5/0476 A61B5/00 A61N1/05		
CPC分类号	A61N1/36139 A61B5/0476 A61B5/4094 A61N1/0551 A61N1/3605 A61N1/36053 A61N1/36064 A61N1/36082 A61N1/36114 A61N1/36178		
代理机构(译)	HUTTER，ANTON		
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其他公开文献	EP2965781A1		
外部链接	Espacenet		

摘要(译)

植入的电信号发生器向患者的迷走神经递送新的外源电信号。迷走神经将源自心脏和肺的动作电位传导到大脑的各种结构，从而在这些结构中引起迷走神经诱发电位。外源电信号模拟和/或增强源自患者心脏和/或肺的内源传入活动，从而增强脑的各种结构中的迷走神经诱发电位。外源电信号包括一系列电脉冲，这些电脉冲被组织或图案化成一系列微爆，每个微爆包括2到20个脉冲。在微爆流之间不发送脉冲。每个微爆流可以与ECG的QRS波部分同步。在各种脑结构中增强的迷走神经诱发电位可用于治疗各种医学病症，包括癫痫和抑郁症。

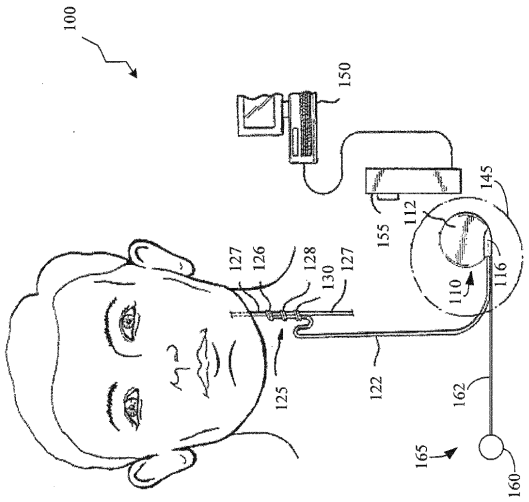

FIGURE 1