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(54) IMPLANTABLE DEVICE FOR EVALUATING AUTONOMIC CARDIOVASCULAR DRIVE IN A PATIENT SUFFERING FROM CHRONIC CARDIAC DYSFUNCTION

IMPLANTIERBARE VORRICHTUNG ZUR BEURTEILUNG DER AUTONOMEN KARDIOVASKULÄREN ANSTEUERUNG BEI EINEM PATIENTEN MIT CHRONISCHER HERZDYSFUNKTION

DISPOSITIF IMPLANTABLE POUR ÉVALUER UN ENTRAÎNEMENT CARDIO-VASCULAIRE AUTONOME CHEZ UN PATIENT SOUFFRANT D'UN DYSFONCTIONNEMENT CARDIAQUE CHRONIQUE

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Description

TECHNICAL FIELD

[0001] This application relates in general to chronic cardiac dysfunction therapy and, in particular, to an implantable device for evaluating autonomic cardiovascular drive in a patient suffering from chronic cardiac dysfunction.

BACKGROUND ART

[0002] Congestive heart failure (CHF) is a progressive and physically debilitating chronic medical condition in which the heart is unable to supply sufficient blood flow to meet the body's needs. CHF is a form of chronic cardiac dysfunction that affects nearly five million people each year in the United States alone and continues to be the leading cause of hospitalization for persons over the age of 65. CHF requires seeking timely medical attention.

[0003] Pathologically, CHF is characterized by an elevated neuroexitatory state that is accompanied by impaired arterial and cardiopulmonary baroreflex function and reduced vagal activity. CHF is initiated by cardiac dysfunction, which triggers compensatory activations of the sympathoadrenal (sympathetic) nervous and the renin-angiotensin-aldosterone hormonal systems. Initially, these two mechanisms help the heart to compensate for deteriorating pumping function. Over time, however, overdriven sympathetic activation and increased heart rate promote progressive left ventricular dysfunction and remodeling, and ultimately foretell poor long term patient outcome.

[0004] Anatomically, the heart is innervated by sympathetic and parasympathetic nerves originating through the vagus nerve and arising from the body's cervical and upper thoracic regions. The sympathetic and parasympathetic nervous systems, though separate aspects of the autonomous nervous system, dynamically interact thorough signals partially modulated by cAMP and cGMP secondary messengers. When in balance, each nervous system can presynaptically inhibit the activation of the other nervous system's nerve traffic. During CHF, however, the body suffers an autonomic imbalance of these two nervous systems, which leads to cardiac arrhythmogenesis, progressively worsening cardiac function, and eventual mortality.

[0005] Currently, the standard of care for managing chronic cardiac dysfunction, such as CHF, includes prescribing medication and mandating changes to a patient's diet and lifestyle, to counteract cardiac dysfunction. These medications include diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, and aldosterone antagonists, which cause vasodilation, reduce secretion of vasopressin, reduce production and secretion of aldosterone, lower arteriolar resistance, increase venous capacity, increase cardiac output, index and volume, lower renovascular resistance, and lead to increased natriuresis, among other effects. The effectiveness of these medications is palliative, but not curative. Moreover, patients often suffer side effects and comorbidities, such as pulmonary edema, sleep apnea, and myocardial ischemia. Re-titration of drug therapy following crisis may be required, and neither continued drug efficacy nor patient survival are assured.

[0006] More recently, cardiac resynchronization therapy (CRT) has become available to patients presenting with impairment of systolic function, such as is caused by an intraventricular conduction delay or bundle-branch block that forces the heart's ventricles to contract dyssynchronously. Typically, implantable CRT devices use a set of biventricular leads to stimulate both the ventricular septum and the lateral wall of the left ventricle. CRT restores the synchronous beating of the heart through coordinated pacing of both ventricles. However, CRT is only helpful for treating systolic dysfunction and is not indicated for patients presenting with preserved ejection fraction. Thus, CRT is limited to patients exhibiting a wide QRS complex and mechanical dyssynchrony, whereas patients presenting with systolic dysfunction or impaired ejection fraction and a narrow QRS have limited therapeutic options.

[0007] Medication and CRT are only partial solutions to managing chronic cardiac dysfunction, and neural stimulation has been proposed as an alternative way to treat chronic cardiac dysfunction conditions, such as CHF, by correcting the underlying autonomic imbalance of the sympathetic and parasympathetic nervous systems. The heart contains an intrinsic nervous system that includes spatially-distributed sensory afferent neurons, interconnecting local circuit neurons, and motor adrenergic and cholinergic efferent neurons. Peripheral cell stations of these neurons activate under the tonic influence of spinal cord and medullary reflexes and circulating catecholamines to influence overlapping regions of the heart. Suppression of excessive neural activation by electrically modulating select vagal nerve fibers may help improve the heart's mechanical function as well as to reduce the heart's intrinsic nervous system's propensity to induce atrial arrhythmias during autonomic imbalance.

[0008] Electrical vagus nerve stimulation (VNS) is currently used clinically for the treatment of drug-refractory epilepsy and depression, and is under investigation for applications in Alzheimer's disease, anxiety, heart failure, inflammatory disease, and obesity. In particular, vagus nerve stimulation has been proposed as a long-term therapy for the treatment of CHF, as described in Sabbah et al., "Vagus Nerve Stimulation in Experimental Heart Failure," Heart Fail. Rev., 16:171-178 (2011). The Sabbah paper discusses canine studies using a vagus stimulation device, manufactured by BioControl Medical Ltd., Yehud, Israel, which includes a signal generator, right ventricular sensing lead, and right vagus nerve cuff stimulation lead. The sensing leads enable stimulation of the right vagus nerve to be synchronized to the cardiac

cycle through feedback on-demand heart rate control. A bipolar nerve cuff electrode was surgically implanted on the right vagus nerve at the mid-cervical position. Electrical stimulation to the right cervical vagus nerve was delivered only when heart rate increased beyond a preset level to reduce basal heart rate by ten percent. Self-titration using "magnet mode" was impracticable in light of the test subject, here canine. Stimulation was provided at an impulse rate and intensity intended to keep the heart rate within a desired range by preferential stimulation of efferent nerve fibers leading to the heart while blocking afferent neural impulses to the brain. An asymmetric bipolar multi-contact cuff electrode was employed to provide cathodic induction of action potentials while simultaneously applying asymmetric anodal blocks that were expected to lead to preferential, but not exclusive, activation of vagal efferent fibers. Although effective in restoring baroreflex sensitivity and, in the canine model, significantly increasing left ventricular ejection fraction and decreasing left ventricular end diastolic and end systolic volumes, restoration of autonomic balance was left unaddressed.

[0009] Other uses of electrical nerve stimulation for therapeutic treatment of various physiological conditions are described. For instance, U.S. Patent No. 6,600,954, issued July 29, 2003 to Cohen et al. discloses a method and apparatus for selective control of nerve fibers. At least one electrode device is applied to a nerve bundle capable, upon activation, of generating unidirectional action potentials to be propagated through both small diameter and large diameter sensory fibers in the nerve bundle, and away from the central nervous system. The device is particularly useful for reducing pain sensations, such as propagating through the legs and arms.

[0010] US 2007/255320 A1 discloses a vagus nerve neurostimulator comprising a pulse generator and a heart rate sensor. US 2006/253161 A1 discloses a vagus nerve neurostimulator comprising a pulse generator, helical electrodes and a heart rate sensor. US 2008/183258 A1 also teaches employment of helical electrodes for nerve stimulation. WO 03/099377 A1 discloses an apparatus for treating a subject including an electrode device, adapted to be coupled to a vagus nerve of the subject, and a heart rate sensor, configured to detect a heart rate of the subject, and to generate a heart rate signal responsive thereto. U.S. Patent No. 6,684,105, issued January 27, 2004 to Cohen et al. discloses an apparatus for treatment of disorders by unidirectional nerve stimulation. An apparatus for treating a specific condition includes a set of one or more electrode devices that are applied to selected sites of the central or peripheral nervous system of the patient. For some applications, a signal is applied to a nerve, such as the vagus nerve, to stimulate efferent fibers and treat motility disorders, or to a portion of the vagus nerve innervating the stomach to produce a sensation of satiety or hunger. For other applications, a signal is applied to the vagus nerve to modulate electrical activity in the brain and rouse a comatose patient, or to treat epilepsy and involuntary movement disorders.

[0011] U.S. Patent No. 7,123,961, issued October 17, 2006 to Kroll et al. discloses stimulation of autonomic nerves. An autonomic nerve is stimulated to affect cardiac function using a stimulation device in electrical communication with the heart by way of three leads suitable for delivering multi-chamber stimulation and shock therapy. In addition, the device includes a fourth lead having three electrodes positioned in or near the heart, or near an autonomic nerve remote from the heart. Power is delivered to the electrodes at a set power level. The power is delivered at a reduced level if cardiac function was affected.

[0012] U.S. Patent No. 7,225,017, issued May 29, 2007 to Shelchuk discloses terminating ventricular tachycardia. Cardioversion stimulation is delivered upon detecting a ventricular tachycardia. A stimulation pulse is delivered to a lead having one or more electrodes positioned proximate to a parasympathetic pathway. Optionally, the stimulation pulse is delivered post inspiration or during a refractory period to cause a release of acetylcholine.

[0013] U.S. Patent No. 7,277,761, issued October 2, 2007 to Shelchuk discloses vagal stimulation for improving cardiac function in heart failure or CHF patients. An autonomic nerve is stimulated to affect cardiac function using a stimulation device in electrical communication with the heart by way of three leads suitable for delivering multi-chamber stimulation and shock therapy. In addition, the device includes a fourth lead having three electrodes positioned in or near the heart, or near an autonomic nerve remote from the heart. A need for increased cardiac output is detected and a stimulation pulse is delivered through an electrode, for example, proximate to the left vagosympathetic trunk or branch to thereby stimulate a parasympathetic nerve. If the stimulation has caused sufficient increase in cardiac output, ventricular pacing may then be initiated at an appropriate reduced rate.

[0014] U.S. Patent No. 7,295,881, issued November 13, 2007 to Cohen et al. discloses nerve branch-specific action potential activation, inhibition and monitoring. Two preferably unidirectional electrode configurations flank a nerve junction from which a preselected nerve branch issues, proximally and distally to the junction, with respect to the brain. Selective nerve branch stimulation can be used in conjunction with nerve-branch specific stimulation to achieve selective stimulation of a specific range of fiber diameters, substantially restricted to a preselected nerve branch, including heart rate control, where activating only the vagal B nerve fibers in the heart, and not vagal A nerve fibers that innervate other muscles, can be desirous.

[0015] U.S. Patent No. 7,778,703, issued August 17, 2010 to Gross et al. discloses selective nerve fiber stimulation for treating heart conditions. An electrode device is adapted to be coupled to a vagus nerve of a subject and a control unit drives the electrode device by applying

to the vagus nerve a stimulating current and also an inhibiting current, which are capable of respectively inducing action potentials in a therapeutic direction in a first set and a second set of nerve fibers in the vagus nerve and inhibiting action potentials in the therapeutic direction in the second set of nerve fibers only. The nerve fibers in the second set have larger diameters than the nerve fibers in the first set. The control unit typically drives the electrode device to apply signals to the vagus nerve to induce the propagation of efferent action potentials towards the heart and suppress artificially-induced afferent action potentials toward the brain.

[0016] U.S. Patent No. 7,813,805, issued October 12, 2010 to Farazi and U.S. Patent No. 7,869,869, issued January 11, 2011 to Farazi both disclose subcardiac threshold vagal nerve stimulation. A vagal nerve stimulator is configured to generate electrical pulses below a cardiac threshold of the heart, which are transmitted to a vagal nerve, so as to inhibit or reduce injury resulting from ischemia. The cardiac threshold is a threshold for energy delivered to the heart above which there is a slowing of the heart rate or conduction velocity. In operation, the vagal nerve stimulator generates the electrical pulses below the cardiac threshold, such that heart rate is not affected.

[0017] Finally, U.S. Patent No. 7,885,709, issued February 8, 2011 to Ben-David discloses nerve stimulation for treating disorders. A control unit can be configured to drive an electrode device to stimulate the vagus nerve, so as to modify heart rate variability, or to reduce heart rate, by suppressing the adrenergic (sympathetic) system. The vagal stimulation reduces the release of catecholamines in the heart, thereby lowering adrenergic tone at its source. For some applications, the control unit synchronizes the stimulation with the subject's cardiac cycle, while for other applications, the stimulation can be applied, for example, in a series of pulses. To reduce heart rate, stimulation is applied using a target heart rate lower than the subject's normal average heart rate.

[0018] Accordingly, a need remains for an approach to therapeutically treating chronic cardiac dysfunction, including CHF, through a form of electrical stimulation of the cervical vagus nerve to confirm pre-therapeutic cardiovascular drive and subsequently restore autonomic balance.

DISCLOSURE OF THE INVENTION

[0019] Excessive sustained activation of the sympathetic nervous system has a deleterious effect on long term cardiac performance and ultimately on the survival of chronic cardiac dysfunction patients. Bi-directional afferent and efferent neural stimulation through the vagus nerve can beneficially restore autonomic balance and improve long term patient outcome. Stimulus delivery can be provided through a vagal neurostimulator per a schedule specified in stored stimulation parameters or based on sensory-based therapy triggers provided through an integrated heart rate sensor.

[0020] One example provides a vagus nerve neurostimulator for evaluating autonomic cardiovascular drive. An implantable neurostimulator includes a pulse generator configured to drive electrical therapeutic stimulation tuned to restore autonomic balance through electrical pulses continuously and periodically delivered in both afferent and efferent directions of the cervical vagus nerve through a pair of helical electrodes via an electrically coupled nerve stimulation therapy lead. The implantable neurostimulator also includes a leadless heart rate sensor configured to continually monitor heart rate against a stored baseline heart rate.

[0021] A further example provides an implantable device for evaluating autonomic cardiovascular drive. An implantable neurostimulator device includes a pulse generator configured to deliver both afferent and efferent therapeutic electrical stimulation to a cervical vagus nerve in continuous alternating cycles of stimuli application and stimuli inhibition. A cervical vagus nerve stimulation therapy lead is electrically coupled to the pulse generator and is terminated by a pair of helical electrodes through which the therapeutic electrical stimulation is delivered to the cervical vagus nerve. An integrated leadless heart rate sensor configured to continually monitor heart rate against a baseline heart rate stored in a memory in the pulse generator.

[0022] A still further example provides an implantable device for evaluating autonomic cardiovascular drive in a patient suffering from chronic cardiac dysfunction. A cervical vagus nerve stimulation therapy lead includes a pair of helical electrodes configured to conform to an outer diameter of a cervical vagus nerve sheath of a patient and a set of connector pins electrically connected to the helical electrodes by an insulated electrical lead body. A neurostimulator is powered by a primary battery and enclosed in a hermetically sealed housing. The neurostimulator includes an electrical receptacle included on an outer surface of the housing into which the connector pins are securely and electrically coupled. The neurostimulator also includes a pulse generator configured to therapeutically stimulate the cervical vagus nerve through the helical electrodes in alternating cycles of stimuli application and stimuli inhibition that are tuned to both efferently activate the heart's intrinsic nervous system and afferently activate the patient's central reflexes by triggering bi-directional action potentials. The neurostimulator further includes a recordable memory within which is stored a baseline heart rate for the patient prior to stimulation therapy initiation. Finally, the neurostimulator includes an integrated leadless heart rate sensor configured to continually monitor the patient's heart rate in light of the baseline heart rate.

[0023] By restoring autonomic balance, therapeutic VNS operates acutely to decrease heart rate, increase heart rate variability and coronary flow, reduce cardiac workload through vasodilation, and improve left ventricular relaxation. Over the long term, VNS provides the

chronic benefits of decreased negative cytokine production, increased baroreflex sensitivity, increased respiratory gas exchange efficiency, favorable gene expression, renin-angiotensin-aldosterone system down-regulation, and anti-arrhythmic, anti-apoptotic, and ectopy-reducing anti-inflammatory effects.

[0024] Embodiments of the present invention will become readily apparent to those skilled in the art from the following detailed description, wherein are described embodiments by way of illustrating the best mode contemplated for carrying out the invention. As will be realized, the invention is capable of other and different embodiments and its several details are capable of modifications in various obvious respects, all without departing from the spirit and the scope of the present invention. Accordingly, the drawings and detailed description are to be regarded as illustrative in nature and not as restrictive. The invention is defined in claim 1. Further aspects and preferred embodiments are defined in the dependent claims. Aspects, embodiments and examples of the present disclosure which do not fall under the scope of the appended claims do not form part of the invention and are merely provided for illustrative purposes.

DESCRIPTION OF THE DRAWINGS

[0025]

FIGURE 1 is a front anatomical diagram showing, by way of example, placement of an implantable vagus stimulation device in a male patient, in accordance with one embodiment.

FIGURE 2 is a diagram showing the implantable neurostimulator and stimulation therapy lead of FIGURE 1 with the therapy lead unplugged.

FIGURE 3 is a diagram showing an external programmer for use with the implantable neurostimulator of FIGURE 1.

FIGURE 4 is a diagram showing the helical electrodes provided as on the stimulation therapy lead of FIGURE 2 in place on a vagus nerve in situ.

FIGURE 5 is a graph showing, by way of example, the relationship between the targeted therapeutic efficacy and the extent of potential side effects resulting from use of the implantable neurostimulator of FIGURE 1.

FIGURE 6 is a graph showing, by way of example, the optimal duty cycle range based on the intersection depicted in FIGURE 5.

FIGURE 7 is a timing diagram showing, by way of example, a stimulation cycle and an inhibition cycle of VNS as provided by implantable neurostimulator of FIGURE 1.

BEST MODE FOR CARRYING OUT THE INVENTION

[0026] The sympathetic nervous system affects cardiovascular physiology in an "all-or-nothing" form of neurological response, whereas the parasympathetic nervous system selectively modulates specific regions of the heart at various levels of activation. Through these two nervous systems, the autonomic nervous system directly controls the heart by affecting conduction, refractoriness, impulse formation, and the electrophysiological properties of the cardiac tissue, and indirectly by influencing the heart's homodynamics, blood flow, and metabolism, as well as exercising control over other body functions that rely on the heart.

[0027] The sympathetic and parasympathetic nervous systems dynamically interact thorough signals partially modulated by cAMP and cGMP secondary messengers to presynaptically influence the activation of each other's nerve traffic. Changes to one nervous system can indirectly affect nerve activation in the other. For instance, during autonomic imbalance, sympathetic neural activity increases while cardiac vagal activation, and therefore sympathetic innervation, is withdrawn. In view of their collaborative influence over cardiac function, the restoration of autonomic balance between these nervous systems is crucial to managing chronic cardiac dysfunction.

[0028] Conventional therapeutic alteration of cardiac vagal efferent activation through electrical stimulation of sympathetic vagal nerve fibers can produce beneficial bradycardia and modification in atrial and ventricular contractile function. However, such targeting of only the efferent nerves of the sympathetic nervous system is clinically insufficient to restore autonomic balance, as any affect on parasympathetic activation merely occurs due to incidental recruitment of parasympathetic nerve fibers. In contrast, propagating bi-directional action potentials through parasympathetic afferent and efferent nerve fibers in the vagus nerve resulting from neural stimulation engages both medullary and cardiac reflex control components and works to directly restore autonomic balance by engaging both components of both nervous systems. Moreover, many of the conventional approaches to VNS monitor heart rate through an intracardiac lead, typically implanted into the right ventricle and adapted from sensing leads used in pacemakers and defibrillators. Implantation of these leads is surgically complex and increases risk of injury to the patient and post-surgical complications.

[0029] An implantable vagus nerve stimulator with integrated heart rate sensor, such as used to treat drug-refractory epilepsy and depression, can be adapted to use in managing chronic cardiac dysfunction through therapeutic bi-directional vagal stimulation. In addition, an integrated heart rate sensor can allow the patient's heart rate to be determined prior to the initiation of therapy delivery, or the heart rate can be provided to the stimulator from an external source. FIGURE 1 is a front anatomical diagram showing, by way of example, placement of an implantable vagus stimulation device 11 in a male patient 10. The VNS provided through the stimulation device 11 operates under several mechanisms of action. These mechanisms include increasing parasympathetic

outflow and inhibiting sympathetic effects by blocking norepinephrine release. More importantly, VNS triggers the release of acetylcholine (ACh) into the synaptic cleft, which has beneficial anti-arrhythmic, anti-apoptotic, and ectopy-reducing anti-inflammatory effects.

[0030] The implantable vagus stimulation device 11 includes three main components, an implantable neurostimulator 12, a therapy lead 13, and helical electrodes 14. In addition, the operation of the neurostimulator 12 can be remotely checked, downloaded, diagnosed, and programmed by healthcare professionals using an external programmer (as further described below with reference to FIGURE 3). Together, the implantable vagus stimulation device 11 and the external programmer form a VNS therapeutic delivery system.

[0031] The neurostimulator 12 is implanted in the patient's right or left pectoral region generally on the same side of the patient's body as the vagus nerve 15, 16 to be stimulated. A subcutaneous pocket is formed in the subclavicular region into which the neurostimulator 12 is placed. The helical electrodes 14 are generally implanted on the vagus nerve 15, 16 about halfway between the clavicle 19a-b and the mastoid process. The therapy lead 13 and helical electrodes 14 are implanted by first exposing the carotid sheath and chosen vagus nerve 15, 16 through a latero-cervical incision on the ipsilateral side of the patient's neck 18. The helical electrodes 14 are then placed onto the exposed nerve sheath and tethered. A subcutaneous tunnel is formed between the respective implantation sites of the neurostimulator 12 and helical electrodes 14, through which the therapy lead 13 is guided to the neurostimulator 12 and securely connected.

[0032] Anatomically, the vagus nerve includes a pair of nerve fiber bundles 15, 16 that both proceed laterally through the neck, thorax, and abdomen, and distally innervate the heart 17 and other major organs and body tissue. The stimulation device 11 bi-directionally stimulates the vagus nerve 15, 16 through application of continuous, periodic electrical stimuli. Both sympathetic and parasympathetic nerve fibers are stimulated through the helical electrodes 14 of the stimulation device 11. Stimulation of the cervical vagus nerve results in propagation of action potentials in both afferent and efferent directions from the site of stimulation. Afferent action potentials propagate toward the parasympathetic nervous system's origin in the medulla in the nucleus ambiguus, nucleus tractus solitarius, and the dorsal motor nucleus, as well as towards the sympathetic nervous system's origin in the intermediolateral cell column of the spinal cord.

[0033] Efferent action potentials propagate toward the heart to innervate the components of the heart's intrinsic nervous system. Intracardially, the cardiac nervous system is conceived as two major outflow branches exerting reciprocal control over cardiac indices under sole influence of central neuronal command. The outflow branches respectively regulate adrenergic (sympathetic) and cholinergic (parasympathetic) efferent preganglionic neuronal activity. Innervation of the heart 17 is regionalized and exhibits a high degree of asymmetry. Within the heart 17, the greatest concentration of vagal nerves is found first in the sinus node and then in the atrioventricular node. Cardiac efferents of the left vagus nerve 15 regulate cardiac contractility through their influence on conduction in the atrioventricular (AV) node. Cardiac efferents of the right vagus nerve 16 affect sinus node automaticity and regulate heart rate. Thus, right-sided cervical vagal stimulation tends to produce sinus bradycardia, whereas left-sided cervical vagal stimulation tends to produce AV nodal blockage.

[0034] Either the left or right vagus nerve 15, 16 can be stimulated by the stimulation device 11, although stimulation of the left vagus nerve 15 is preferred because stimulation of the left vagus nerve 15 is less likely to be arrhythmogenic. The left vagus nerve 15 has fewer projections to the sinoatrial node and is therefore less likely to severely reduce heart rate. Left VNS increases AV nodal conduction time and refractory period. In current form, VNS elicits bi-directional activation of both afferent and efferent nerve fibers. The balance between achieving therapeutic benefits (afferent) and side-effects (efferent) is largely determined by the threshold differences between activation of the different vagus nerve fibers.

[0035] The VNS therapy is autonomously delivered to the patient's vagus nerve 15, 16 through three implanted components, a neurostimulator 12, therapy lead 13, and helical electrodes 14. FIGURE 2 is a diagram showing the implantable neurostimulator 12 and stimulation therapy lead 13 of FIGURE 1 with the therapy lead unplugged 20. In one example, the neurostimulator 12 can be adapted from a VNS Therapy AspireSR Model 106 generator, manufactured and sold by Cyberonics, Inc., Houston, TX, although other manufactures and types of single-pin receptacle implantable VNS neurostimulators with integrated leadless heart rate sensors could also be used. The stimulation therapy lead 13 and helical electrodes 14 are generally fabricated as a combined assembly and can be adapted from a Model 302 lead, PerenniaDURA Model 303 lead, or PerenniaFLEX Model 304 lead, all of which are also manufactured and sold by Cyberonics, Inc., in two sizes based on helical electrode inner diameter, although other manufactures and types of single-pin receptacle-compatible therapy leads and electrodes could also be used.

[0036] The neurostimulator 12 provides continuous alternating ON-OFF cycles of vagal stimulation that when applied to the vagus nerve through the electrodes 14, produce action potentials in the underlying nerves that propagate bi-directionally; afferently propagating action potentials activate the medial medullary sites responsible for central reflex control and efferently propagating action potentials activate the heart's intrinsic nervous system. Cardiac motor neurons, when activated, influence heart rate, AV nodal conduction, and atrial and ventricular inotropy, thereby providing chronic cardiac dysfunction therapeutic effects. In addition, the alternating cycles can be tuned to activate phasic parasympathetic response in

the vagus nerve 15, 16 being stimulated by bi-directionally modulating vagal tone.

[0037] The neurostimulator 12 includes an electrical pulse generator that drives electrical therapeutic stimulation, which is tuned to restore autonomic balance, through electrical pulses that are continuously and periodically delivered in both afferent and efferent directions of the vagus nerve 15, 16. The neurostimulator 12 is enclosed in a hermetically sealed housing 21 constructed of a biocompatible, implantation-safe material, such as titanium. The housing 21 contains electronic circuitry 22 powered by a primary battery 23, such as a lithium carbon monoflouride battery. The electronic circuitry 22 is implemented using complementary metal oxide semiconductor integrated circuits that include a microprocessor that executes a control program according to the stored stimulation parameters as programmed into the neurostimulator 12; a voltage regulator that regulates system power; logic and control circuitry, including a recordable memory 29 within which the stimulation parameters are stored, that controls overall pulse generator function, receives and implements programming commands from the external programmer, or other external source, and collects and stores telemetry information, processes sensory input, and controls scheduled and sensory-based therapy outputs; a transceiver that remotely communicates with the external programmer using radio frequency signals; an antenna, which receives programming instructions and transmits the telemetry information to the external programmer; and a reed switch 30 that provides a manually-actuatable mechanism to place the neurostimulator into an on-demand stimulation mode or to inhibit stimulation, also known as "magnet mode." Other electronic circuitry and components, such as an integrated heart rate sensor, are possible.

[0038] The neurostimulator 12 delivers VNS under control of the electronic circuitry 22, particularly the logic and control circuitry, which control stimulus delivery per a schedule specified in the stored stimulation parameters, based on sensory-based therapy triggers (as further described infra) or on-demand in response to magnet mode, a programming wand instruction, or other external source. The stored stimulation parameters are programmable (as further described below with reference to FIGURE 7). In addition, sets of pre-selected stimulation parameters can be provided to physicians through the external programmer and fine-tuned to a patient's physiological requirements prior to being programmed into the neurostimulator 12, such as described in commonly-assigned U.S. Patent application, entitled "Computer-Implemented System and Method for Selecting Therapy Profiles of Electrical Stimulation of Cervical Vagus Nerves for Treatment of Chronic Cardiac Dysfunction," Serial No. 13/314,138, filed on December 7, 2011, published as US 2013/0158618 A1. The magnet mode can be used by the patient 10 to exercise on-demand manual control over the therapy delivery and titration of the neurostimulator, such as described in commonly-assigned U.S. Patent application, entitled "Implantable Device for Facilitating Control of Electrical Stimulation of Cervical Vagus Nerves for Treatment of Chronic Cardiac Dysfunction," Serial No. 13/314,130, filed on December 7, 2011, published as US2013/0158622 A1. The stimulation parameters also include the levels of stimulation for the bi-directional action potentials.

[0039] Externally, the neurostimulator 12 includes a header 24 to securely receive and connect to the therapy lead 13. In one example, the header 24 encloses a receptacle 25 into which a single pin for the therapy lead 13 can be received, although two or more receptacles could also be provided, along with the requisite additional electronic circuitry 22. The header 24 internally includes a lead connector block (not shown) and a set of set screws 26.

[0040] The therapy lead 13 delivers an electrical signal from the neurostimulator 12 to the vagus nerve 15, 16 via the helical electrodes 14. On a proximal end, the therapy lead 13 has a lead connector 27 that transitions an insulated electrical lead body to a metal connector pin 28. During implantation, the connector pin 28 is guided through the receptacle 25 into the header 24 and securely fastened in place using the set screws 26 to electrically couple the therapy lead 13 to the neurostimulator 12. On a distal end, the therapy lead 13 terminates with the helical electrode 14, which bifurcates into a pair of anodic and cathodic electrodes 62 (as further described below with reference to FIGURE 4). In one example, the lead connector 27 is manufactured using silicone and the connector pin 28 is made of stainless steel, although other suitable materials could be used, as well. The insulated lead body 13 utilizes a silicone-insulated alloy conductor material.

[0041] The housing 21 also contains a heart rate sensor 31 that is electrically interfaced with the logic and control circuitry, which receives the patient's sensed heart rate as sensory inputs. The heart rate sensor 31 monitors heart rate using an ECG-type electrode. Through the electrode, the patient's heart beat can be sensed by detecting ventricular depolarization. In a further example, a plurality of electrodes can be used to sense voltage differentials between electrode pairs, which can be signal processed and combined into other cardiac physiological measures, for instance, P, QRS and T complexes. These cardiac artifacts can be used to derive other physiological measures and diagnose abnormal rhythm disorders and indicia, including sleep apnea, hypopnea index, dysautonomias (postural orthostatic tachycardia syndrome (POTS), vasovagal syncope, inappropriate sinus tachycardia (IST), and the like), and arrhythmia detection (atrial fibrillation, ventricular tachycardia, ventricular fibrillation, heart block, and so forth). Other direct and indirect uses of the heart rate sensor 31 are possible. In one example, the heart rate sensor 31 can be adjusted for sensitivity and is capable of detecting heart beats in the range of 20 to 240 bpm. Other levels and ranges of heart beat sensitivity are possible.

[0042] Prior to the initiation of titration and eventual therapeutic stimulation, the neurostimulator 12 remains idle, yet the time period between implantation and therapy initiation provides an opportunity to passively monitor the patient's heart rate or other physiology, depending upon the capabilities of the neurostimulator 12. Ordinarily, the heart rate sensor 31 provides the sensed heart rate to the control and logic circuitry as sensory inputs, which can be stored as data in the recordable memory 29. When sensed prior to therapy initiation, the sensory inputs of the heart rate sensor 31 can be used as a baseline heart rate, which reflects the pre-therapeutic condition of the patient's cardiovascular drive. The sensed heart rate can be chosen as either a direct measurement of heart rate, or statistically by taking an average, minimum, maximum, or mean heart rate over time. Other ways of determining a baseline heart rate through use of the heart rate sensor 31 or other sensory-input sources or devices integrated into the neurostimulator 12 are possible.

[0043] Once therapy has begun, the sensory inputs of the heart rate sensor 31 serve as sensory-based therapy triggers to autonomously titrate VNS delivery in light of the baseline heart rate. The logic and control circuitry can then determine whether the stimulation needs to be adjusted or inhibited. Alternatively, the baseline heart rate can be programmed into the neurostimulator 12 using, for instance, an external programmer. Importantly, the baseline heart rate need not necessarily be based on the patient's heart rate per se; non-heart rate ECG measurements, for example, could be used to derive the baseline heart rate and then programmed into the neurostimulator 12. Other ways of determining a baseline heart rate from a source outside of the neurostimulator 12 are possible.

[0044] Therapy can be adjusted whenever the sensed heart rate falls out of bounds relative to the baseline heart rate, such as outside of a predetermined heart rate range. A lower bound, stored in the recordable memory 29, can be set to indicate bradycardia or an asystolic heart condition. The lower bound can be expressed as a ratio, percentile, or function, of the baseline heart rate, or as discrete independent (absolute) values with respect to the baseline heart rate. If the heart rate sensed by the heart rate sensor 31 falls below the lower bound on the baseline heart rate, the neurostimulator 12 can be instructed, through the stimulation parameters, to suspend the triggering of the bi-directional action potentials altogether. Therapy can also be programmed to resume automatically after a fixed time period. Alternatively, the neurostimulator 12 can be instructed to down titrate therapy by gradually adjusting the stimulation parameters downwards until the bradycardia or asystole are no longer present. Therapy can also be programmed to gradually up titrate by adjusting the stimulation parameters upwards after first inhibiting stimulation for a fixed time period. Both the down titration and the up titration can occur stepwise, where the changes in the stimulation parameters occur in small increments spread out over time, rather than all at once. VNS therapy can be titrated by adjusting the stored stimulation parameters, including output current, pulse width, and signal frequency, to different VNS therapeutic setting that are less intense (down titrate) or more intense (up titrate). An upper bound, stored in the recordable memory 29, can also be set to indicate insufficient therapy delivery. The upper bound can be expressed as a ratio, percentile, or function, of the baseline heart rate, or as discrete independent (absolute) values with respect to the baseline heart rate. If the heart rate sensed by the heart rate sensor 31 rises above an upper bound on the baseline heart rate, the neurostimulator 12 can be instructed, again through the stimulation parameters, to up titrate the triggering of the bi-directional action potentials and thereby lower heart rate.

[0045] The neurostimulator 12 is preferably interrogated prior to implantation and throughout the therapeutic period for checking proper operation, downloading recorded data, diagnosing problems, and programming operational parameters. FIGURE 3 is a diagram showing an external programmer 40 for use with the implantable neurostimulator 12 of FIGURE 1. The external programmer 40 includes a healthcare provider-operable programming computer 41 and a programming wand 42. Generally, use of the external programmer 40 is restricted to healthcare providers, while more limited manual control is provided to the patient through "magnet mode."

[0046] In one example, the programming computer 41 executes application software specially designed to interrogate the neurostimulator 12. The programming computer 41 interfaces to the programming wand 42 through a standardized wired data connection, including a serial data interface, for instance, an EIA RS-232 or USB serial port. Alternatively, the programming computer 41 and the programming wand 42 could interface wirelessly. The programming wand 42 can be adapted from a Model 201 Programming Wand, manufactured and sold by Cyberonics, Inc. Similarly, the application software can be adapted from the Model 250 Programming Software suite, licensed by Cyberonics, Inc. Other configurations and combinations of computer 41, programming wand 42, and application software 45 are possible.

[0047] The programming computer 41 can be implemented using a general purpose programmable computer and can be a personal computer, laptop computer, netbook computer, handheld computer, or other form of computational device. In one example, the programming computer is a personal digital assistant handheld computer operating under the Pocket-PC or Windows Mobile operating systems, licensed by Microsoft Corporation, Redmond, WA, such as the Dell Axim X5 and X50 personal data assistants, sold by Dell, Inc., Round Top, TX, the HP Jornada personal data assistant, sold by Hewlett-Packard Company, Palo Alto, TX. The programming computer 41 functions through those components conventionally found in such devices, including, for instance, a central processing unit, volatile and persistent memory,

touch-sensitive display, control buttons, peripheral input and output ports, and network interface. The computer 41 operates under the control of the application software 45, which is executed as program code as a series of process or method modules or steps by the programmed computer hardware. Other assemblages or configurations of computer hardware, firmware, and software are possible.

[0048] Operationally, the programming computer 41, when connected to a neurostimulator 12 through wireless telemetry using the programming wand 42, can be used by a healthcare provider to remotely interrogate the neurostimulator 12 and modify stored stimulation parameters. The programming wand 42 provides data conversion between the digital data accepted by and output from the programming computer and the radio frequency signal format that is required for communication with the neurostimulator 12.

[0049] The healthcare provider operates the programming computer 41 through a user interface that includes a set of input controls 43 and a visual display 44, which could be touch-sensitive, upon which to monitor progress, view downloaded telemetry and recorded physiology, and review and modify programmable stimulation parameters. The telemetry can include reports on device history that provide patient identifier, implant date, model number, serial number, magnet activations, total ON time, total operating time, manufacturing date, and device settings and stimulation statistics and on device diagnostics that include patient identifier, model identifier, serial number, firmware build number, implant date, communication status, output current status, measured current delivered, lead impedance, and battery status. Other kinds of telemetry or telemetry reports are possible.

[0050] During interrogation, the programming wand 42 is held by its handle 46 and the bottom surface 47 of the programming wand 42 is placed on the patient's chest over the location of the implanted neurostimulator 12. A set of indicator lights 49 can assist with proper positioning of the wand and a set of input controls 48 enable the programming wand 42 to be operated directly, rather than requiring the healthcare provider to awkwardly coordinate physical wand manipulation with control inputs via the programming computer 41. The sending of programming instructions and receipt of telemetry information occur wirelessly through radio frequency signal interfacing. Other programming computer and programming wand operations are possible.

[0051] Preferably, the helical electrodes 14 are placed over the cervical vagus nerve 15, 16 at the location below where the superior and inferior cardiac branches separate from the cervical vagus nerve. FIGURE 4 is a diagram showing the helical electrodes 14 provided as on the stimulation therapy lead 13 of FIGURE 2 in place on a vagus nerve 15, 16 in situ 50. Although described with reference to a specific manner and orientation of implantation, the specific surgical approach and implantation site selection particulars may vary, depending upon physician discretion and patient physical structure.

[0052] The helical electrodes 14 are positioned over the patient's vagus nerve 61 oriented with the end of the helical electrodes 14 facing the patient's head. At the distal end, the insulated electrical lead body 13 is bifurcated into a pair of lead bodies 57, 58 that are connected to a pair of electrodes proper 51, 52. The polarity of the electrodes 51, 52 could be configured into a monopolar cathode, a proximal anode and a distal cathode, or a proximal cathode and a distal anode. In addition, an anchor tether 53 is fastened over the lead bodies 57, 58 that maintains the helical electrodes' position on the vagus nerve 61 following implant. In one example, the conductors of the electrodes 51, 52 are manufactured using a platinum and iridium alloy, while the helical materials of the electrodes 51, 52 and the anchor tether 53 are a silicone elastomer.

[0053] During surgery, the electrodes 51, 52 and the anchor tether 53 are coiled around the vagus nerve 61 proximal to the patient's head, each with the assistance of a pair of sutures 54, 55, 56, made of polyester or other suitable material, which help the surgeon to spread apart the respective helices. The lead bodies 57, 58 of the electrodes 51, 52 are oriented distal to the patient's head and aligned parallel to each other and to the vagus nerve 61. A strain relief bend 60 can be formed on the distal end with the insulated electrical lead body 13 aligned parallel to the helical electrodes 14 and attached to the adjacent fascia by a plurality of tie-downs 59a-b.

[0054] In one example, the stimulation protocol calls for a six-week titration period. During the first three-weeks, the surgical incisions are allowed to heal and no VNS therapy occurs. During the second three-weeks, the neurostimulator 12 is first turned on and operationally tested. The impulse rate and intensity of the VNS is then gradually increased every three or four days until full therapeutic levels of stimulation are achieved, or maximal patient tolerance is reached, whichever comes first. Patient tolerance can be gauged by physical discomfort or pain, as well as based on presence of known VNS side-effects, such as ataxia, coughing, hoarseness, or dyspnea.

[0055] Therapeutically, the VNS is delivered through continual alternating cycles of electrical pulses and rest (inhibition), which is specified to the neurostimulator 12 through the stored stimulation parameters. The neurostimulator 12 can operate either with or without an integrated heart rate sensor, such as respectively described in commonly-assigned U.S. Patent application, entitled "Implantable Device for Providing Electrical Stimulation of Cervical Vagus Nerves for Treatment of Chronic Cardiac Dysfunction with Leadless Heart Rate Monitoring," Serial No. 13/314,126, filed on December 7, 2011, published as US8,577,458 B1 and U.S. Patent application, entitled "Implantable Device for Providing Electrical Stimulation of Cervical Vagus Nerves for Treatment of Chronic Cardiac Dysfunction," Serial No. 13/314,119, filed on December 7, 2011, pending, the disclosures of which are

incorporated by reference. Additionally, where an integrated leadless heart rate sensor is available, the neurostimulator 12 can provide self-controlled titration, such as described in commonly-assigned U.S. Patent application, entitled "Implantable Device for Providing Electrical Stimulation of Cervical Vagus Nerves for Treatment of Chronic Cardiac Dysfunction with Bounded Titration," Serial No. 13/314,135, filed on December 7, 2011, published as US2013/0158617 A1.

[0056] A "duty cycle" is the percentage of time that the neurostimulator 12 is stimulating, that is, the percentage of ON times. The VNS can be delivered with a periodic duty cycle in the range of around 5% to 30%. The selection of duty cycle is a tradeoff between competing medical considerations. FIGURE 5 is a graph 70 showing, by way of example, the relationship between the targeted therapeutic efficacy 73 and the extent of potential side effects 74 resulting from use of the implantable neurostimulator 12 of FIGURE 1. The x-axis represents the duty cycle 71. The duty cycle is determined by dividing the stimulation time by the sum of the ON and OFF times of the neurostimulator 12. However, the stimulation time may also need to include ramp-up time and ramp-down time, where the stimulation frequency exceeds a minimum threshold (as further described below with reference to FIGURE 7). The y-axis represents physiological response 72 to VNS therapy. The physiological response 72 can be expressed quantitatively for a given duty cycle 71 as a function of the targeted therapeutic efficacy 73 and the extent of potential side effects 74, as described infra. The maximum level of physiological response 72 ("max") signifies the highest point of targeted therapeutic efficacy 73 or potential side effects 74.

[0057] Targeted therapeutic efficacy 73 and the extent of potential side effects 74 can be expressed as functions of duty cycle 71 and physiological response 72. The targeted therapeutic efficacy 73 represents the intended effectiveness of VNS in provoking a beneficial physiological response for a given duty cycle and can be quantified by assigning values to the various acute and chronic factors that contribute to the physiological response 72 of the patient 10 due to the delivery of therapeutic VNS. Acute factors that contribute to the targeted therapeutic efficacy 73 include increase in heart rate variability and coronary flow, reduction in cardiac workload through vasodilation, and improvement in left ventricular relaxation. Chronic factors that contribute to the targeted therapeutic efficacy 73 include decreased parasympathetic activation and increased sympathetic activation, as well as decreased negative cytokine production, increased baroreflex sensitivity, increased respiratory gas exchange efficiency, favorable gene expression, renin-angiotensin-aldosterone system down-regulation, anti-arrhythmic, anti-apoptotic, and ectopy-reducing anti-inflammatory effects. These contributing factors can be combined in any manner to express the relative level of targeted therapeutic efficacy 73, including weighting particular effects more heavily than others or applying statistical or numeric functions based directly on or derived from observed physiological changes. Empirically, targeted therapeutic efficacy 73 steeply increases beginning at around a 5% duty cycle, and levels off in a plateau near the maximum level of physiological response at around a 30% duty cycle. Thereafter, targeted therapeutic efficacy 73 begins decreasing at around a 50% duty cycle and continues in a plateau near a 25% physiological response through the maximum 100% duty cycle.

[0058] The extent of potential side effects 74 represents the occurrence of a possible physiological effect, either adverse or therapeutic, that is secondary to the benefit intended, which presents in the patient 10 in response to VNS and can be quantified by assigning values to the physiological effects presented due to the delivery of therapeutic VNS. The degree to which a patient 10 may be prone to exhibit side effects depends in large part upon the patient's condition, including degree of cardiac dysfunction, both acute and chronic, any comobidities, prior heart problems, family history, general health, and similar considerations. As well, the type and severity of a side effect is patient-dependent. For VNS in general, the more common surgical- and stimulation-related adverse side effects include infection, asystole, bradycardia, syncope, abnormal thinking, aspiration pneumonia, device site reaction, acute renal failure, nerve paralysis, hypesthesia, facial paresis, vocal cord paralysis, facial paralysis, hemidiaphragm paralysis, recurrent laryngeal injury, urinary retention, and low grade fever. The more common non-adverse side effects include hoarseness (voice alteration), increased coughing, pharyngitis, paresthesia, dyspnea, dyspepsia, nausea, and laryngismus. Less common side effects, including adverse events, include ataxia, hypesthesia, increase coughing, insomnia, muscle movement or twitching associated with stimulation, nausea, pain, paresthesia, pharyngitis, vomiting, aspiration, blood clotting, choking sensation, nerve damage, vasculature damage, device migration or extrusion, dizziness, dysphagia, duodenal or gastric ulcer, ear pain, face flushing, facial paralysis or paresis, implant rejection, fibrous tissue formation, fluid pocket formation, hiccupping, incision site pain, irritability, laryngeal irritation, hemidiaphragm paralysis, vocal cord paralysis, muscle pain, neck pain, painful or irregular stimulation, seroma, skin or tissue reaction, stomach discomfort, tinnitus, tooth pain, unusual scarring at incision site, vagus nerve paralysis, weight change, worsening of asthma or bronchitis. These quantified physiological effects can be combined in any manner to express the relative level of extent of potential side effects 74, including weighting particular effects more heavily than others or applying statistical or numeric functions based directly on or derived from observed physiological changes. Empirically, the extent of potential side effects 74 is initially low until around a 25% duty cycle, at which point the potential begins to steeply increase. The extent of potential side effects 74 levels off in a plateau near the maximum level of physiological response at around a 50% duty cycle through the maxi-

mum 100% duty cycle.

[0059] The intersection 75 of the targeted therapeutic efficacy 73 and the extent of potential side effects 74 represents the optimal duty cycle range for VNS. FIGURE 6 is a graph 80 showing, by way of example, the optimal duty cycle range 83 based on the intersection 75 depicted in FIGURE 5. The x-axis represents the duty cycle 81 as a percentage of stimulation time over inhibition time. The y-axis represents the desirability 82 of operating the neurostimulator 12 at a given duty cycle 81. The optimal duty range 83 is a function 84 of the intersection 74 of the targeted therapeutic efficacy 73 and the extent of potential side effects 74. The desirability 82 can be expressed quantitatively for a given duty cycle 81 as a function of the values of the targeted therapeutic efficacy 73 and the extent of potential side effects 74 at their point of intersection in the graph 70 of FIGURE 5. The maximum level of desirability 82 ("max") signifies a trade-off that occurs at the point of highest targeted therapeutic efficacy 73 in light of lowest potential side effects 74 and that point will typically be found within the range of a 5% to 30% duty cycle 81. Other expressions of duty cycles and related factors are possible.

[0060] The neurostimulator 12 delivers VNS according to stored stimulation parameters, which are programmed using an external programmer 40 (shown in FIGURE 3). Each stimulation parameter can be independently programmed to define the characteristics of the cycles of therapeutic stimulation and inhibition to ensure optimal stimulation for a patient 10. The programmable stimulation parameters affecting stimulation include output current, signal frequency, pulse width, signal ON time, signal OFF time, magnet activation (for VNS specifically triggered by "magnet mode"), "AutoStim" activation (delivered upon detection of a biological signal indicative of physiological conditions, such as bradycardia or asystole), and reset parameters. Other programmable parameters are possible.

[0061] VNS is delivered in alternating cycles of stimuli application and stimuli inhibition that are tuned to both efferently activate the heart's intrinsic nervous system and heart tissue and afferently activate the patient's central reflexes. FIGURE 7 is a timing diagram showing, by way of example, a stimulation cycle and an inhibition cycle of VNS 90 as provided by implantable neurostimulator 12 of FIGURE 1. The stimulation parameters enable the electrical stimulation pulse output by the neurostimulator 12 to be varied by both amplitude (output current 96) and duration (pulse width 94). The number of output pulses delivered per second determines the signal frequency 93. In one embodiment, a pulse width in the range of 100 to 250 μsec delivers between 0.02 and 50 mA of output current at a signal frequency of about 20 Hz, although other therapeutic values could be used as appropriate.

[0062] In the simplest case, the stimulation time is the time period during which the neurostimulator 12 is ON and delivering pulses of stimulation. The OFF time 95 is always the time period occurring in-between stimulation times 91 during which the neurostimulator 12 is OFF and inhibited from delivering stimulation. In one example, the neurostimulator 12 implements a ramp-up time 97 and a ramp-down time 98 that respectively precede and follow the ON time 92 during which the neurostimulator 12 is ON and delivering pulses of stimulation at the full output current 96. The ramp-up time 97 and ramp-down time 98 are used when the stimulation frequency is at least 10 Hz, although other minimum thresholds could be used, and both times last two seconds, although other time periods could also be used. The ramp-up time 97 and ramp-down time 98 allow the strength of the output current 96 of each output pulse to be gradually increased and decreased, thereby avoiding unnecessary trauma to the vagus nerve due to sudden delivery or inhibition of stimulation at full strength.

[0063] While the invention has been particularly shown and described as referenced to the embodiments thereof, those skilled in the art will understand that the foregoing and other changes in form and detail may be made therein without departing from the scope of the appended claims.

Claims

1. An implantable device (11) for evaluating autonomic cardiovascular drive, comprising:

   an implantable neurostimulator (12) comprising a pulse generator configured to deliver electrical therapeutic stimulation tuned to restore autonomic balance through continuously-cycling, intermittent and periodic electrical pulses delivered in a manner that results in creation and propagation (in both afferent and efferent directions) of action potentials within neuronal fibers comprising a cervical vagus nerve (15, 16, 61) of a patient (10) in continuous alternating cycles of stimuli application and stimuli inhibition (90) and configured to deliver the electrical therapeutic stimulation according to stored stimulation parameters comprising a pulse width falling within the range of 100 to 250 μsec, an output current (96) falling within the range of 0.02 to 50 mA, and a signal frequency (93) at least being 10 Hz to about 20 Hz; a cervical vagus nerve stimulation therapy lead (13) electrically coupled to the pulse generator and terminated by at least one electrode through which the therapeutic electrical stimulation is delivered to the patient's cervical vagus nerve (15, 16, 61).

2. An implantable device (11) according to Claim 1, further comprising
   an integrated leadless heart rate sensor (31) configured to continually monitor the patient's heart rate against a baseline heart rate that, particularly, is

stored in a recordable memory (29) in the pulse generator.

3. An implantable device (11) according to Claim 2 or 3, wherein the pulse generator is further configured to suspend the therapeutic electrical stimulation for a fixed period of time in response to the monitored the patient's heart rate falling below a lower bound of acceptable heart rates stored in a recordable memory (29) in the pulse generator that, particularly, is indicative of at least one of bradycardia and asystole, after which the therapeutic electrical stimulation resumes.

4. An implantable device (11) according to Claim 2, 3 or 4, wherein the pulse generator is further configured to gradually down titrate the therapeutic electrical stimulation in response to the monitored heart rate falling below a lower bound of acceptable heart rates stored in a recordable memory (29) in the pulse generator that is, particularly, indicative of at least one of bradycardia and asystole.

5. An implantable device (11) according to Claim 4, wherein the pulse generator is further configured to suspend the therapeutic electrical stimulation for a fixed period of time and gradually up titrate the therapeutic electrical stimulation after the down titration.

6. An implantable device (11) according to one of the Claims 2 to 5, wherein the pulse generator is further configured to gradually up titrate the therapeutic electrical stimulation in response to the monitored heart rate rising above an upper bound of acceptable heart rates stored in the recordable memory (29) that is indicative of insufficient therapy delivery.

7. An implantable device (11) according to one of the preceding Claims, further comprising:

a connector pin (28) and an insulated electrical lead body (13) that further comprise the therapy lead (13) and which are electrically connected to helical electrodes (14); and
an electrical receptacle (25) comprised on an outer surface of the neurostimulator (12) into which the connector pin (28) is securely and electrically connected to the pulse generator.

8. An implantable device (11) according to one of the Claims 2 to 7, wherein the integrated leadless heart rate sensor (31) is further configured to sense the baseline heart rate during a time period prior to stimulation therapy initiation.

9. An implantable device (11) according to one of the Claims 2 to 8, wherein the pulse generator is further configured to determine the baseline heart rate as at least one of a direct measurement of the patient's heart rate, an average heart rate over time, a minimum heart rate over time, a maximum heart rate over time, and a mean heart rate over time, as sensed by the integrated leadless heart rate sensor (31).

10. An implantable device (11) according to one of the Claims 2 to 9, wherein the baseline heart rate is programmed into a recordable memory (29) in the pulse generator prior to stimulation therapy initiation.

11. An implantable device (11) according to one of the Claims 2 to 10, wherein the baseline heart rate is determined by ECG measurements other than the patient's heart rate prior to stimulation therapy initiation and thereafter programmed into a recordable memory (29) in the pulse generator.

12. An implantable device (11) according to one of the Claims 2 to 11, wherein a lower bound of acceptable heart rates, which is indicative of at least one of bradycardia and asystole, defined below the baseline heart rate, is stored in a recordable memory (29) in the pulse generator and the pulse generator is further configured to suspend the creation and propagation of the action potentials for a fixed period of time in response to the sensed heart rate falling below the lower bound of the acceptable heart rates, after which the creation and propagation of the action potentials resumes; and wherein, in particular, the lower bound of the acceptable heart rates is expressed as at least one of a ratio, a percentile, a function, and discrete independent values with respect to the baseline heart rate.

13. An implantable device (11) according to one of the Claims 2 to 12, wherein a lower bound of acceptable heart rates, which is indicative of at least one of bradycardia and asystole, defined below the baseline heart rate, is stored in a recordable memory (29) in the pulse generator and the pulse generator is further configured to gradually down titrate the creation and propagation of the action potentials in response to the sensed heart rate falling below the lower bound of the acceptable heart rates.

14. An implantable device (11) according to Claim 13, wherein the pulse generator is further configured to suspend the creation and propagation of the action potentials for a fixed period of time and gradually up titrate the creation and propagation of the action potentials after the down titration.

15. An implantable device (11) according to one of the Claims 2 to 14, wherein an upper bound of acceptable heart rates, which is indicative of insufficient therapy delivery, defined above the baseline heart

rate, is stored in a recordable memory (29) in the pulse generator and the pulse generator is further configured to gradually up titrate the creation and propagation of the action potentials in response to the sensed heart rate rising above the upper bound of the acceptable heart rates, wherein, in particular, the upper bound of the acceptable heart rates is expressed as at least one of a ratio, a percentile, a function, and discrete independent values with respect to the baseline heart rate.

Patentansprüche

1. Eine implantierbare Vorrichtung (11) zum Bewerten des autonomen Herz-KreislaufSystems, umfassend:

einen implantierbaren Neurostimulator (12), der einen Pulsgenerator umfasst, der dazu ausgebildet ist, eine elektrische therapeutische Stimulation zu verabreichen, die so eingestellt ist, dass sie die autonome Balance durch kontinuierlich-zyklische, intermittierende und periodische elektrische Pulse wiederherstellt, die in einer Weise geliefert werden, die in der Erzeugung und Propagation (sowohl in afferente als auch efferente Richtung) von Aktionspotentialen innerhalb neuronaler Fasern eines Patienten (10), die den Vagusnerv (15, 16, 61) umfassen, in kontinuierlichen alternierenden Zyklen von Stimulation und Nicht-Stimulation (90) resultiert, und der dazu ausgebildet ist, die elektrische therapeutische Stimulation gemäß gespeicherten Stimulationsparametern zu verabreichen, die eine Pulsbreite innerhalb von 100 bis 250 μsec, einen Ausgangsstroms (96) innerhalb des Bereichs von 0,02 bis 50 mA und eine Signalfrequenz (93) von zumindest 10 Hz bis etwa 20 Hz umfassen;
ein Therapiekabel (13) zur cervikalen Vagusnervstimulation, das mit dem Pulsgenerator elektrisch verbunden ist und in zumindest eine Elektrode endet, durch die die therapeutische elektrische Stimulation an den cervikalen Vagusnerv (15, 16, 61) des Patienten geliefert wird.

2. Eine implantierbare Vorrichtung (11) gemäß Anspruch 1, die weiterhin umfasst:

einen integrierten kabellosen Herzratensensor (31), der dazu ausgebildet ist, die Herzrate des Patienten kontinuierlich im Abgleich mit einer Basislinienherzrate, die insbesondere in einem beschreibbaren Speicher (29) des Pulsgenerators gespeichert ist, zu überwachen.

3. Eine implantierbare Vorrichtung (11) gemäß Anspruch 2 oder 3, in der der Pulsgenerator weiterhin dazu ausgebildet ist, die therapeutische elektrische Stimulation für eine festgelegte Zeitdauer in Reaktion darauf auszusetzen, dass die überwachte Herzrate des Patienten unter eine untere Grenze für akzeptable Herzraten, die in einem beschreibbaren Speicher (29) des Pulsgenerators gespeichert ist und die insbesondere zumindest eines von einer Bradykardie und einer Asystole anzeigt, fällt, wonach die therapeutische elektrische Stimulation wieder aufgenommen wird.

4. Eine implantierbare Vorrichtung (11) gemäß Anspruch 2, 3 oder 4, in der der Pulsgenerator weiterhin dazu ausgebildet ist, die therapeutische elektrische Stimulation in Reaktion darauf niedriger zu dosieren, dass die überwachte Herzrate unter eine untere Grenze für akzeptable Herzraten, die in einem beschreibbaren Speicher (29) des Pulsgenerators gespeichert ist und die insbesondere zumindest eines von einer Bradykardie und einer Asystole anzeigt, fällt.

5. Eine implantierbare Vorrichtung (11) gemäß Anspruch 4, in der der Pulsgenerator weiterhin dazu ausgebildet ist, die therapeutische elektrische Stimulation für eine festgelegte Zeitdauer auszusetzen und nach der niedrigeren Dosierung schrittweise die Dosierung der therapeutische elektrische Stimulation höher zu dosieren.

6. Eine implantierbare Vorrichtung (11) gemäß einem der Ansprüche 2 bis 5, in der der Pulsgenerator weiterhin dazu ausgebildet ist, die therapeutische elektrische Stimulation in Reaktion darauf schrittweise höher zu dosieren, dass die überwachte Herzrate über eine obere Grenze für akzeptable Herzraten, die in dem beschreibbaren Speicher (29) gespeichert ist und die eine nicht hinreichende Therapieverabreichung anzeigt, steigt.

7. Eine implantierbare Vorrichtung (11) gemäß einem der vorhergehenden Ansprüche, die weiterhin umfasst:

einen Verbindungsstift (28) und einen isolierten elektrischen Kabelkörper (13), der weiterhin das Therapiekabel (13) umfasst, die mit helischen Elektroden (14) elektrisch verbunden sind; und eine elektrische Buchse (25), die von einer äußeren Oberfläche des Neurostimulators (12) umfasst ist, in der der Verbindungsstift (28) sicher und elektrisch mit dem Pulsgenerator verbunden ist.

8. Eine implantierbare Vorrichtung (11) gemäß einem der Ansprüche 2 bis 7, in der der integrierte kabellose Herzratensensor (31) weiterhin dazu ausgebildet ist,

die Basislinienherzrate während einer Zeitdauer vor dem Beginn der Stimulationstherapie zu erfassen.

9. Eine implantierbare Vorrichtung (11) gemäß einem der Ansprüche 2 bis 8, in der der Pulsgenerator weiterhin dazu ausgebildet ist, die Basislinienherzrate als zumindest eines des Folgenden zu bestimmen: eine direkte Messung der Herzrate des Patienten, einen zeitlichen Mittelwert einer Herzrate, eine über eine Zeit minimale Herzrate, eine über eine Zeit maximale Herzrate und eine über eine Zeit durchschnittliche Herzrate, wie sie durch den integrierten kabellosen Herzratensensor (31) erfasst werden.

10. Eine implantierbare Vorrichtung (11) gemäß einem der Ansprüche 2 bis 9, in der die Basislinienherzrate vor dem Beginn der Stimulationstherapie in einen beschreibbaren Speicher (29) des Pulsgenerators programmiert wird.

11. Eine implantierbare Vorrichtung (11) gemäß einem der Ansprüche 2 bis 10, in der die Basislinienherzrate vor dem Beginn der Stimulationstherapie durch EKG-Messungen anderer Herzraten als derjenigen des Patienten bestimmt wird und danach in einen beschreibbaren Speicher (29) des Pulsgenerators programmiert wird.

12. Eine implantierbare Vorrichtung (11) gemäß einem der Ansprüche 2 bis 11, in der eine untere Grenze für akzeptable Herzraten, die zumindest eines von einer Bradykardie und einer Asystole anzeigt und die unterhalb der Basisherzrate definiert ist, in einem beschreibbaren Speicher (29) des Pulsgenerators gespeichert wird, und wobei der Pulsgenerator weiterhin dazu ausgebildet ist, die Erzeugung und Propagation von Aktionspotentialen für eine festgelegte Zeitdauer in Reaktion darauf auszusetzen, dass die erfasste Herzrate unter die untere Grenze für akzeptable Herzraten fällt, wonach die Erzeugung und Propagation von Aktionspotentialen wieder aufgenommen wird; und wobei insbesondere die untere Grenze für akzeptable Herzraten als zumindest eines des Folgenden ausgedrückt wird: ein Verhältnis, ein Perzentil eine Funktion und diskrete unabhängige Werte hinsichtlich der Basisherzrate.

13. Eine implantierbare Vorrichtung (11) gemäß einem der Ansprüche 2 bis 12, in der eine untere Grenze für akzeptable Herzraten, die zumindest eines von einer Bradykardie und einer Asystofe anzeigt und die unterhalb der Basisherzrate definiert ist, in einem beschreibbaren Speicher (29) des Pulsgenerators gespeichert wird, und wobei der Pulsgenerator weiterhin dazu ausgebildet ist, die Erzeugung und Propagation der Aktionspotentiale in Reaktion darauf, dass die erfasste Herzrate unter die untere Grenze für akzeptable Herzraten fällt, schrittweise niedriger zu dosieren.

14. Eine implantierbare Vorrichtung (11) gemäß Anspruch 13, in der der Pulsgenerator weiterhin dazu ausgebildet ist, die Erzeugung und Propagation von Aktionspotentialen für eine festgelegte Zeitdauer auszusetzen und nach der niedrigeren Dosierung die Erzeugung und Propagation von Aktionspotentialen schrittweise höher zu dosieren.

15. Eine implantierbare Vorrichtung (11) gemäß einem der Ansprüche 2 bis 14, in der eine obere Grenze für akzeptable Herzraten, die eine nicht hinreichende Therapieverabreichung anzeigt und die oberhalb der Basisherzrate definiert ist, in einem beschreibbaren Speicher (29) des Pulsgenerators gespeichert wird, und wobei der Pulsgenerator weiterhin dazu ausgebildet ist, die Erzeugung und Propagation der Aktionspotentiale in Reaktion darauf, dass die detektierte Herzrate über die obere Grenze für akzeptable Herzraten steigt, schrittweise höher zu dosieren, und wobei insbesondere die obere Grenze für akzeptable Herzraten als zumindest eines des Folgenden ausgedrückt wird: ein Verhältnis, ein Perzentil eine Funktion und diskrete unabhängige Werte hinsichtlich der Basisherzrate.

Revendications

1. Dispositif implantable (11) pour évaluer un entraînement cardiovasculaire autonome, comprenant:

un neurostimulateur implantable (12) comprenant un générateur d'impulsions configuré de manière à délivrer une stimulation thérapeutique électrique réglée pour rétablir l'équilibre autonome par le biais d'impulsions électriques en cycle continu, intermittentes et périodiques délivrées d'une manière qui aboutit à la création et la propagation (dans les deux directions afférentes et efférentes) des potentiels d'action dans les fibres neuronales comprenant un nerf vague cervical (15, 16, 61) d'un patient (10) dans des cycles continus alternés d'application de stimuli et d'inhibition de stimuli (90) et configurés pour délivrer le signal électrique stimulation thérapeutique selon des paramètres de stimulation mémorisés comprenant une largeur d'impulsion dans la fourchette de 100 à 250 μs, un courant de sortie (96) compris dans la fourchette de 0,02 à 50 mA, et une fréquence de signal (93) au moins comprise entre 10 Hz et environ 20 Hz;
un fil de thérapie par stimulation du nerf vague cervical (13) couplé électriquement au générateur d'impulsions et terminé par au moins une électrode permettant de délivrer au nerf vague cervical (15, 16, 61) du patient une stimulation

électrique thérapeutique.

2. Dispositif implantable (11) selon la revendication 1, comprenant en outre:

un capteur de fréquence cardiaque sans fil intégré (31) configuré pour surveiller de façon continue la fréquence cardiaque du patient par rapport à une fréquence cardiaque de référence qui, en particulier, est stockée dans une mémoire enregistrable (29) dans le générateur d'impulsions.

3. Dispositif implantable (11) selon les revendications 2 ou 3, dans lequel le générateur d'impulsions est en outre configuré pour suspendre la stimulation électrique thérapeutique pendant une période de temps fixe en réponse à la fréquence cardiaque surveillée qui tomberait au-dessous d'une limite inférieure des fréquences cardiaques acceptables stockées dans une mémoire enregistrable (29) dans le générateur d'impulsions, ce qui indique en particulier la présence d'au moins une bradycardie ou une asystolie, après quoi la stimulation électrique thérapeutique reprend.

4. Dispositif implantable (11) selon les revendications 2, 3 ou 4, dans lequel le générateur d'impulsions est en outre configuré pour diminuer progressivement la stimulation électrique thérapeutique en réponse à la fréquence cardiaque surveillée qui tomberait au-dessous d'une limite inférieure des fréquences cardiaques acceptables stockées dans une mémoire enregistrable (29) dans le générateur d'impulsions, ce qui indique en particulier la présence d'au moins une bradycardie ou une asystolie.

5. Dispositif implantable (11) selon la revendication 4, dans lequel le générateur d'impulsions est en outre configuré pour suspendre la stimulation électrique thérapeutique pendant un laps de temps donné et augmenter de manière progressive de la stimulation électrique thérapeutique après la réduction de la posologie.

6. Dispositif implantable (11) selon l'une des revendications 2 à 5, dans lequel le générateur d'impulsions est en outre configuré pour augmenter graduellement la stimulation électrique thérapeutique en réponse à l'augmentation de fréquence cardiaque surveillée au-dessus d'une limite supérieure des fréquences cardiaques acceptables stockées dans une mémoire enregistrable (29) ce qui, en particulier, indique une administration thérapeutique insuffisante.

7. Dispositif implantable (11) selon l'une des revendications précédentes, comprenant en outre:

une broche de connexion (28) et un corps de fil conducteur électrique isolé (13) qui comprennent en outre le fil conducteur thérapeutique (13) et qui sont connectés électriquement aux électrodes hélicoïdales (14); et
un réceptacle électrique (25) comprise sur une surface extérieure du neurostimulateur (12) dans laquelle la broche de connexion (28) est reliée solidement et électriquement au générateur d'impulsions.

8. Dispositif implantable (11) selon l'une des revendications 2 à 7, dans lequel le capteur de fréquence cardiaque sans fil intégré (31) est en outre configuré pour détecter la fréquence cardiaque de référence pendant une période de temps donnée avant l'initiation de la thérapie de stimulation.

9. Dispositif implantable (11) selon l'une des revendications 2 à 8, dans lequel le générateur d'impulsions est en outre configuré pour déterminer la fréquence cardiaque de base comme au moins une mesure directe de la fréquence cardiaque du patient, une fréquence cardiaque moyenne dans le temps, une fréquence cardiaque minimale dans le temps, une fréquence cardiaque maximale dans le temps, et une moyenne de la fréquence cardiaque dans le temps, mesure effectuée par le capteur de fréquence cardiaque sans fil intégré (31).

10. Dispositif implantable (11) selon l'une des revendications 2 à 9, dans lequel la fréquence cardiaque de référence est programmée dans une mémoire enregistrable (29) dans le générateur d'impulsions avant initiation de la thérapie de stimulation.

11. Dispositif implantable (11) selon l'une des revendications 2 à 10, dans lequel la fréquence cardiaque de référence est programmée dans une mémoire enregistrable (29) dans le générateur d'impulsions avant initiation de la thérapie de stimulation.

12. Dispositif implantable (11) selon l'une des revendications 2 à 11, dans lequel une limite inférieure des fréquences cardiaques acceptables, indicative d'au moins une bradycardie ou d'une asystolie, définie au-dessous de la fréquence cardiaque de référence, est stockée dans une mémoire enregistrable (29) du générateur d'impulsions et le générateur d'impulsions est en outre configuré pour suspendre la création et la propagation des potentiels d'action pendant une période déterminée en réponse à la chute de la fréquence cardiaque détectée sous la limite inférieure des fréquences cardiaques acceptables, après quoi la création et la propagation des potentiels d'action reprennent et dans lequel, en particulier, la limite inférieure des fréquences cardiaques acceptable est exprimée comme au moins un ratio, un centile, une

fonction et des valeurs indépendantes par rapport à la fréquence cardiaque de base.

13. Dispositif implantable (11) selon l'une des revendications 2 à 12, dans lequel une limite inférieure des fréquences cardiaques acceptables, indicative d'au moins une bradycardie ou d'une asystolie, définie au-dessous de la fréquence cardiaque de référence, est stockée dans une mémoire enregistrable (29) du générateur d'impulsions et le générateur d'impulsions est en outre configuré pour diminuer de manière progressive la création et la propagation des potentiels d'action en réponse à la chute de la fréquence cardiaque détectée sous la limite inférieure des fréquences cardiaques acceptables.

14. Dispositif implantable (11) selon la revendication 13, dans lequel le générateur d'impulsions est en outre configuré pour suspendre la création et la propagation des potentiels d'action pour une période fixe de temps et progressivement augmenter la création et la propagation des potentiels d'action après la réduction de la posologie.

15. Dispositif implantable (11) selon l'une des revendications 2 à 14, dans lequel une limite supérieure des fréquences cardiaques acceptables, indicative d'une administration thérapeutique insuffisante, définie au-dessus de la fréquence cardiaque de référence, est stockée dans une mémoire enregistrable (29) dans le générateur d'impulsions et le générateur d'impulsions est en outre configuré pour augmenter de manière progressive la création et la propagation des potentiels d'action en réponse à l'augmentation de la fréquence cardiaque détectée au-dessus de la limite supérieure des fréquences cardiaques acceptables, dans lequel, en particulier, la limite supérieure des fréquences cardiaques acceptables est exprimée comme au moins un ratio, un centile, une fonction et des valeurs indépendantes discrètes par rapport à la fréquence cardiaque de référence.

Fig. 1.

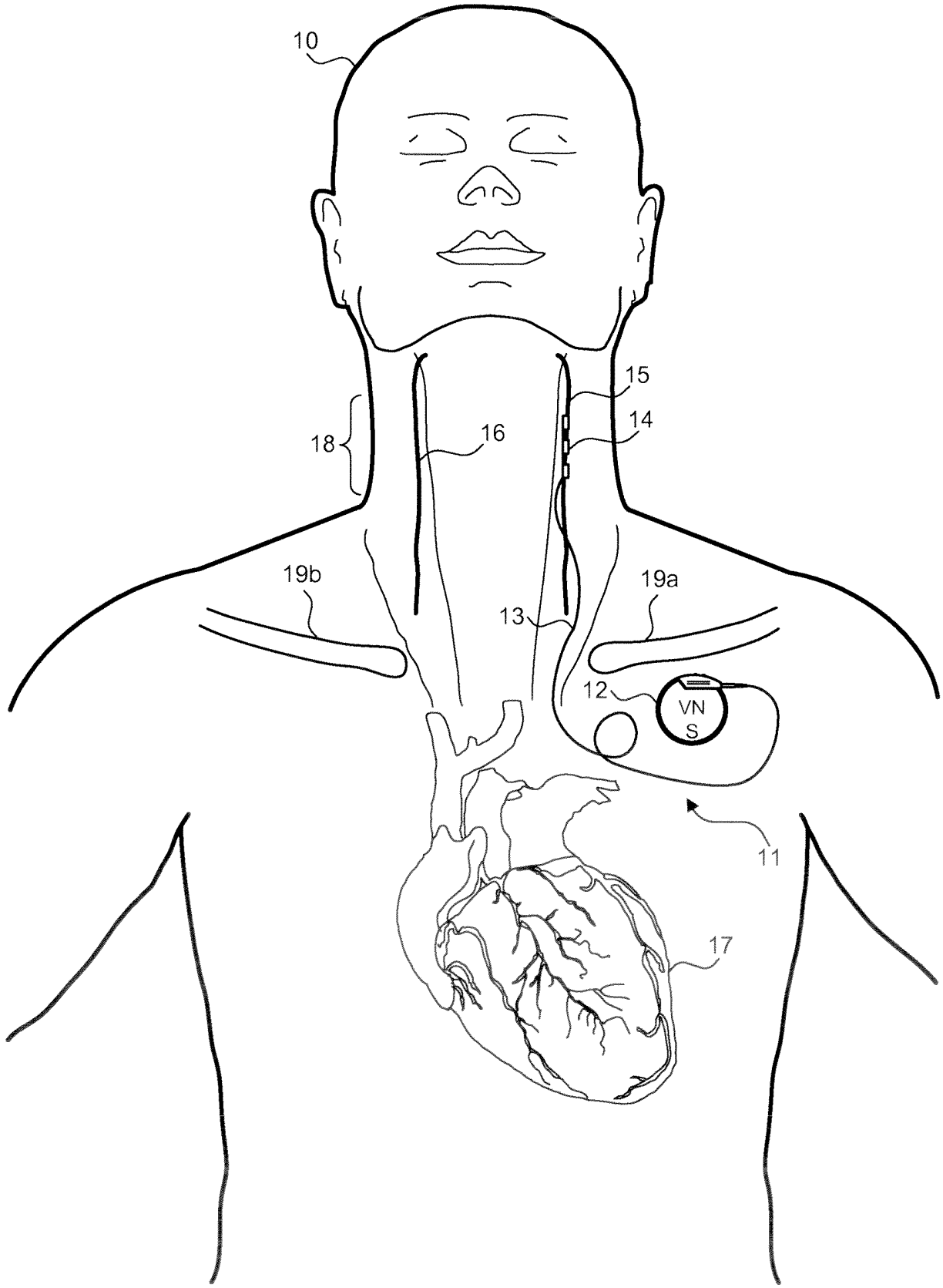
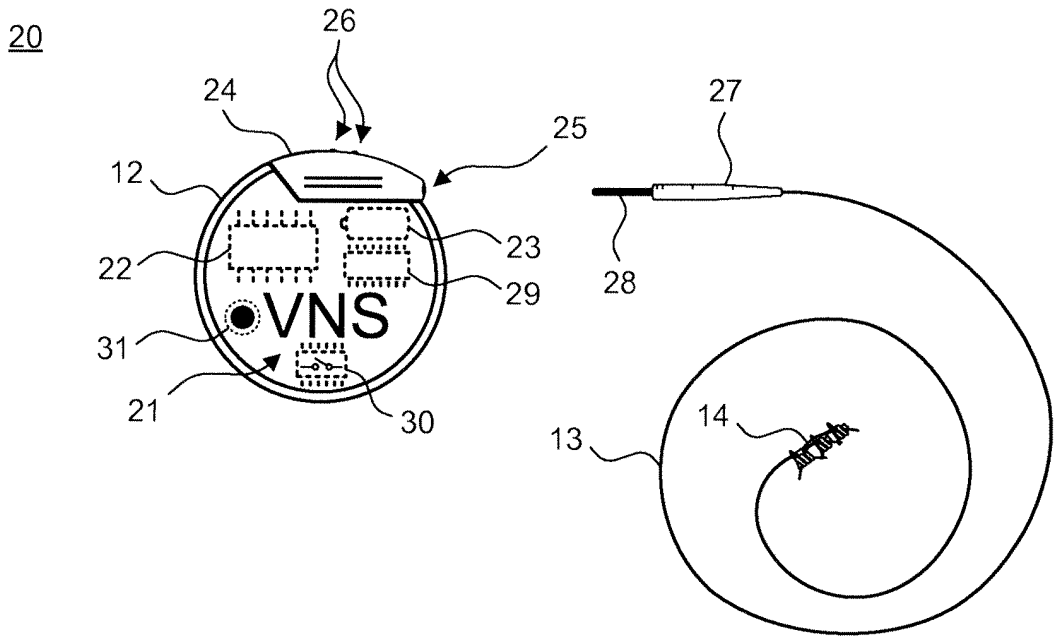


Fig. 2.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VNS
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Fig. 3.

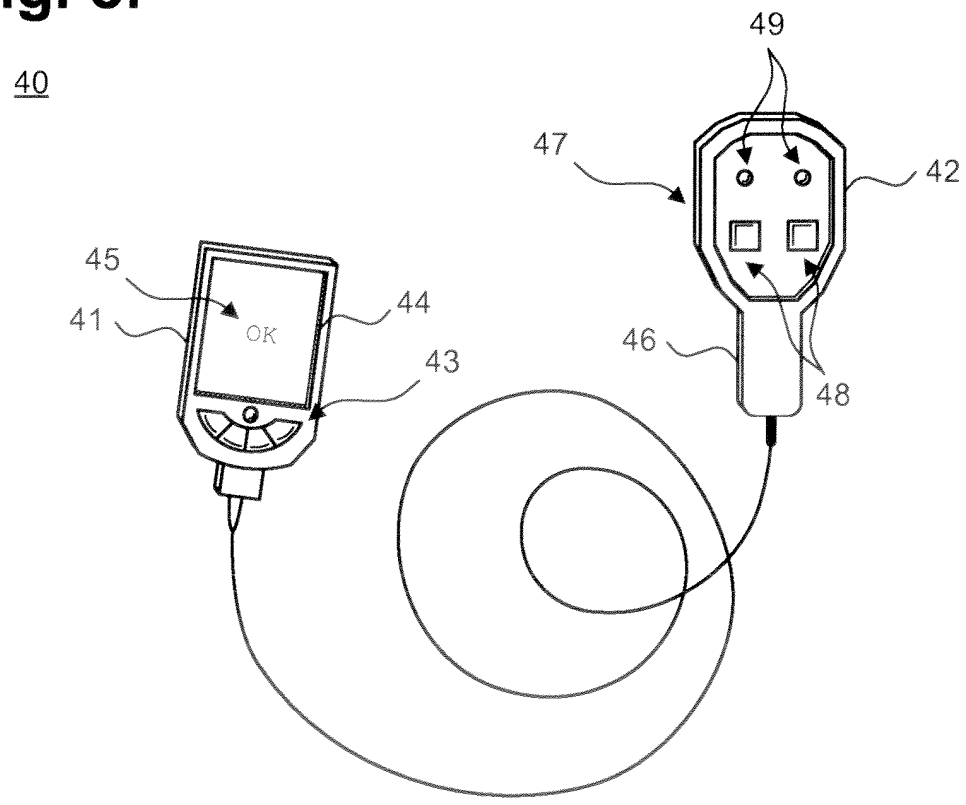
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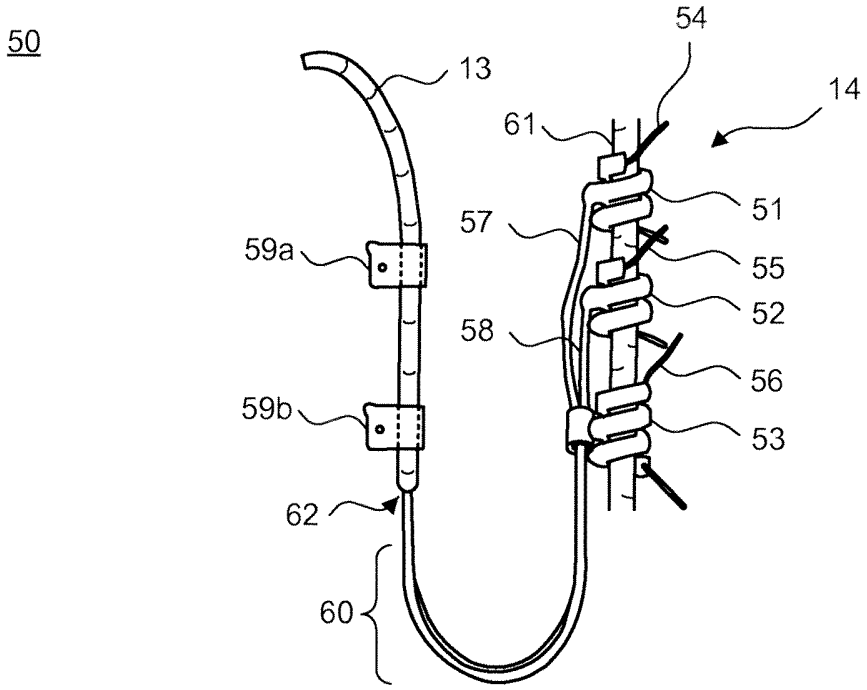
Fig. 4.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59b
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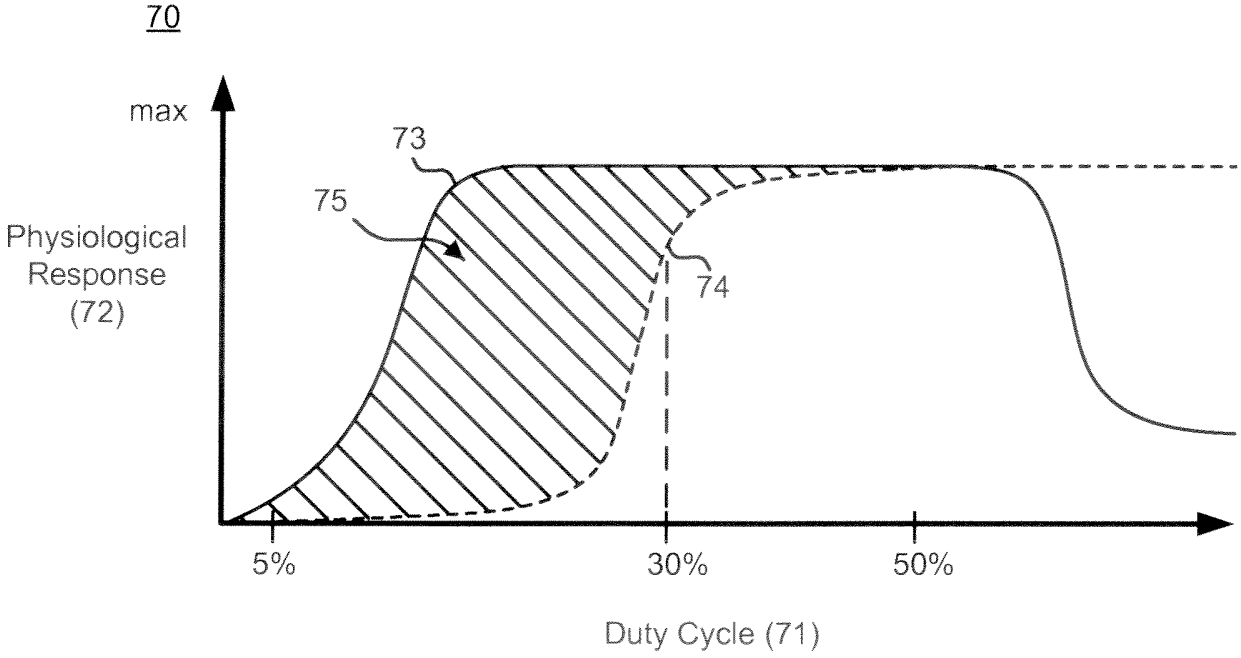
62
60

Fig. 5.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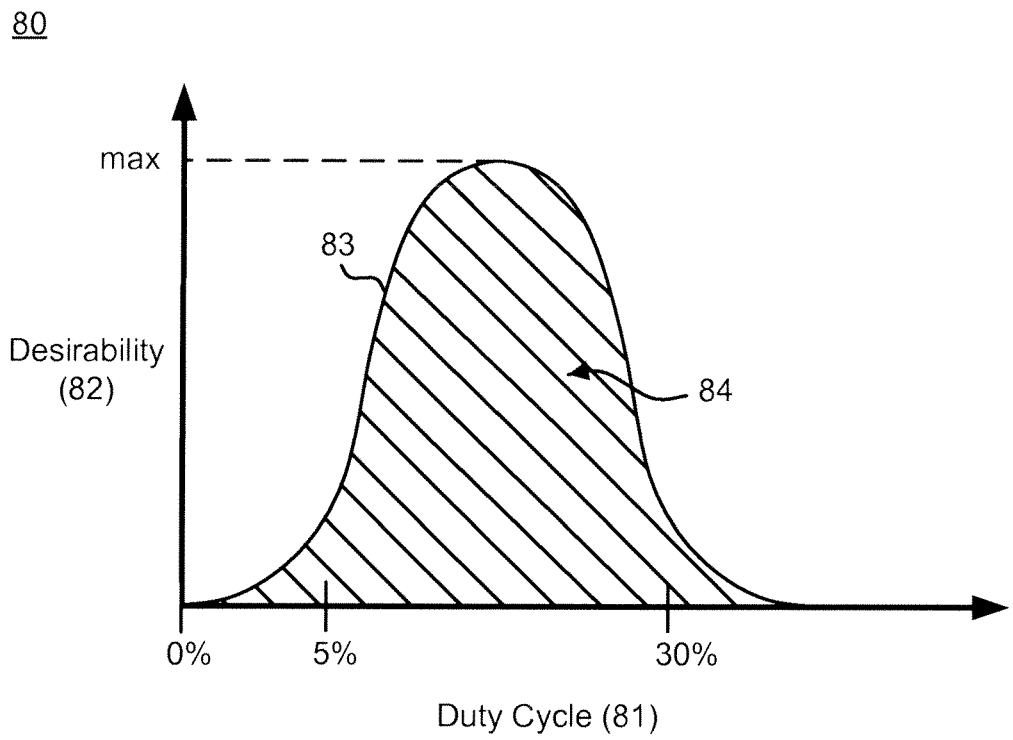
max
73
75
Physiological Response (72)
74
5%
30%
50%
Duty Cycle (71)

Fig. 6.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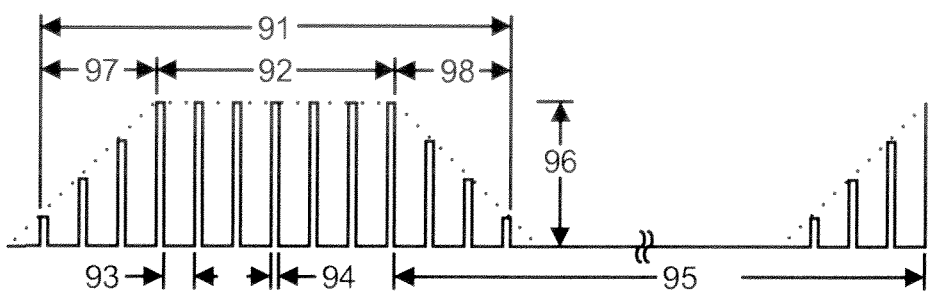
max
83
Desirability
(82)
84
0%
5%
30%
Duty Cycle (81)

Fig. 7.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专利名称(译)	用于评估患有慢性心脏功能障碍的患者的自主心血管驱动的可植入装置		
公开(公告)号	EP3088041B1	公开(公告)日	2018-03-14
申请号	EP2016168072	申请日	2012-12-06
申请(专利权)人(译)	Cyberonics公司，INC.		
当前申请(专利权)人(译)	Cyberonics公司，INC.		
[标]发明人	LIBBUS IMAD AMURTHUR BADRI KENKNIGHT BRUCE H		
发明人	LIBBUS, IMAD AMURTHUR, BADRI KENKNIGHT, BRUCE, H		
IPC分类号	A61B5/024 A61N1/36 A61N1/05 A61B5/00 A61B5/02		
CPC分类号	A61B5/02438 A61B5/4836 A61B5/686 A61N1/05 A61N1/0551 A61N1/36053 A61N1/36114 A61N1/36139 A61N1/36167 A61B5/02		
优先权	13/314133 2011-12-07 US		
其他公开文献	EP3088041A1		
外部链接	Espacenet		

摘要(译)

一种用于评估自主心血管驱动的可植入装置（11），包括：可植入神经刺激器（12），其包括脉冲发生器，该脉冲发生器被配置成通过以如下方式递送的连续循环，间歇和周期性电脉冲来调节以调节以恢复自主平衡的电治疗刺激。在刺激施加和刺激抑制的连续交替循环中，在包括患者（10）的颈部迷走神经（15,16,61）的神经元纤维内的动作电位的产生和传播（在传入和传出方向上）导致（90）根据存储的刺激参数，包括脉冲宽度落在100至250微秒范围内，输出电流（96）落在0.02至50毫安范围内，以及信号频率（93）至少10赫兹;颈部迷走神经刺激治疗引线（13）电耦合到脉冲发生器并由至少一个电极终止，通过该电极将治疗性电刺激传递到患者的颈部迷走神经（15,16,61）。

Fig. 1.