US009643008B2

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

(10) **Patent No.: US 9,643,008 B2**
(45) **Date of Patent: May 9, 2017**

(54) **IMPLANTABLE NEUROSTIMULATOR-IMPLEMENTED METHOD FOR ENHANCING POST-EXERCISE RECOVERY THROUGH VAGUS NERVE STIMULATION**

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

(21) Appl. No.: **13/673,795**

(22) Filed: **Nov. 9, 2012**

(65) **Prior Publication Data**

US 2014/0135863 A1 May 15, 2014

(51) **Int. Cl.**
A61N 1/36 (2006.01)
A61B 5/11 (2006.01)
(Continued)

(52) **U.S. Cl.**
CPC ***A61N 1/36114*** (2013.01); ***A61N 1/36053*** (2013.01); ***A61N 1/36139*** (2013.01);
(Continued)

(58) **Field of Classification Search**
CPC A61N 1/36114
(Continued)

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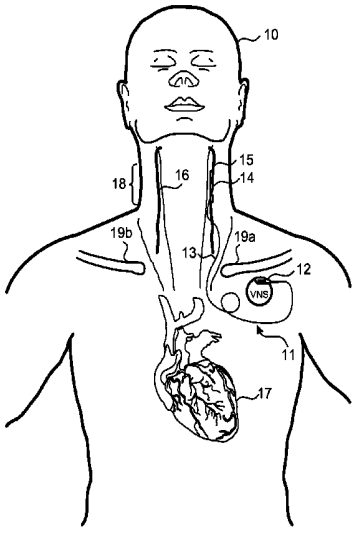
(57) **ABSTRACT**

An implantable neurostimulator-implemented method for enhancing post-exercise recovery through vagus nerve stimulation is provided. An implantable neurostimulator, including a pulse generator configured to deliver electrical therapeutic stimulation in a manner that results in creation and propagation (in both afferent and efferent directions) of action potentials within neuronal fibers including a patient's cervical vagus nerve. An operating mode is stored in the pulse generator. An enhanced dose of the electrical therapeutic stimulation is parametrically defined and tuned to prevent or disrupt tachyarrhythmia through continuously-cycling, intermittent and periodic electrical pulses. The patient's physiological state is monitored during physical exercise via at least one sensor included in the implantable neurostimulator, and upon sensing a condition indicative of cessation of the physical exercise, the enhanced dose is delivered for a period of time the enhanced dose to the vagus nerve.

20 Claims, 4 Drawing Sheets



(51) **Int. Cl.**
A61B 5/00 (2006.01)
A61N 1/362 (2006.01)

(52) **U.S. Cl.**
CPC *A61B 5/1118* (2013.01); *A61B 5/4836* (2013.01); *A61N 1/3621* (2013.01)

(58) **Field of Classification Search**
USPC 607/14
See application file for complete search history.

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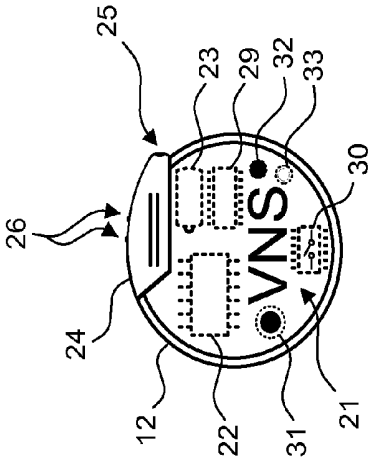

Fig. 2A.

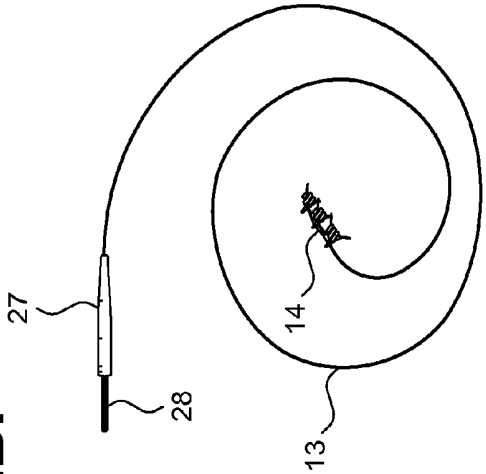

Fig. 2B.

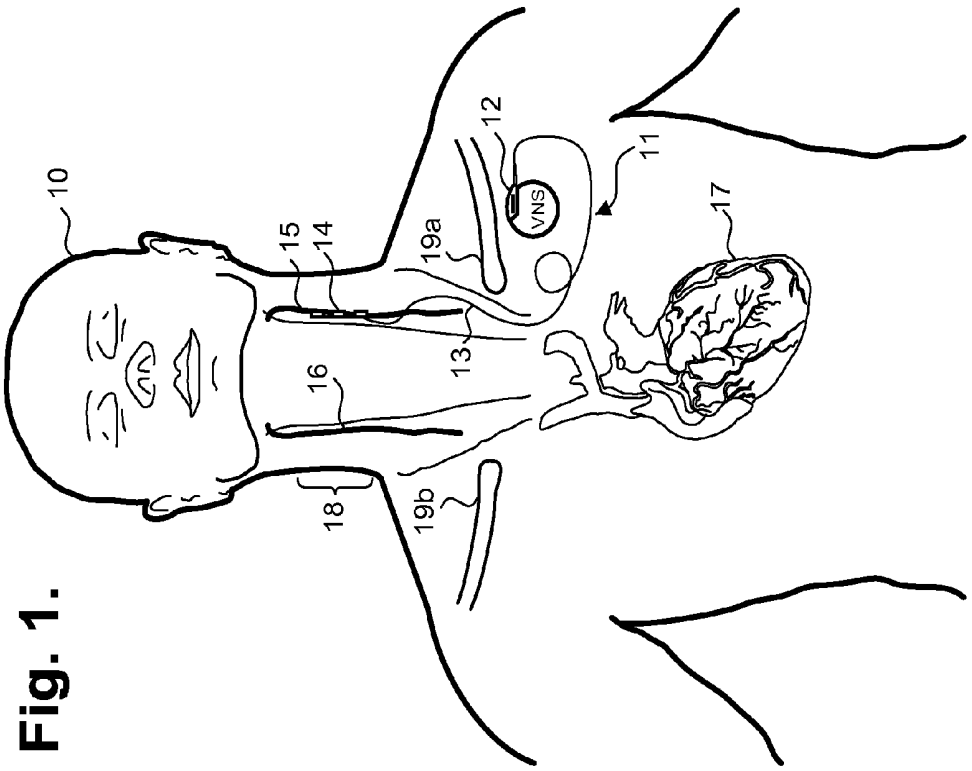

Fig. 1.

Fig. 3.

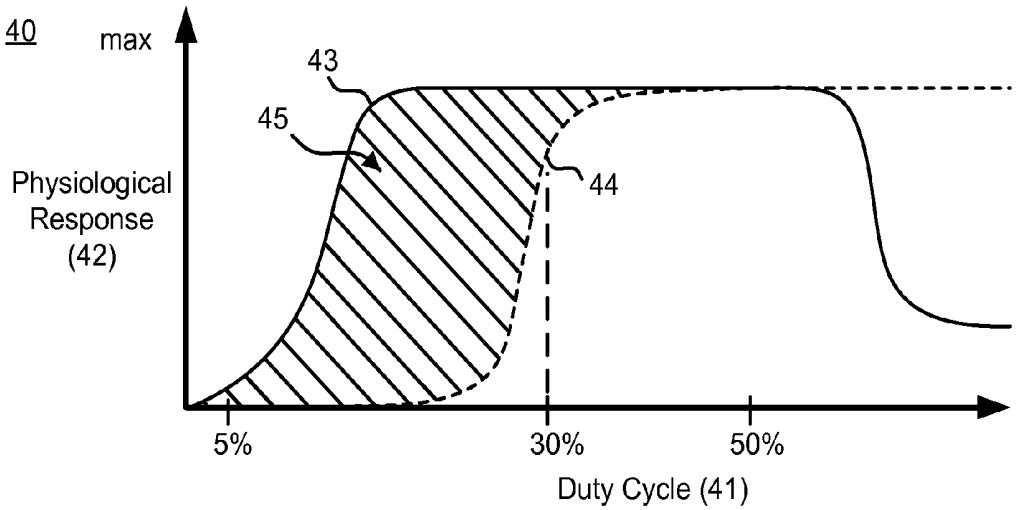

Fig. 4.

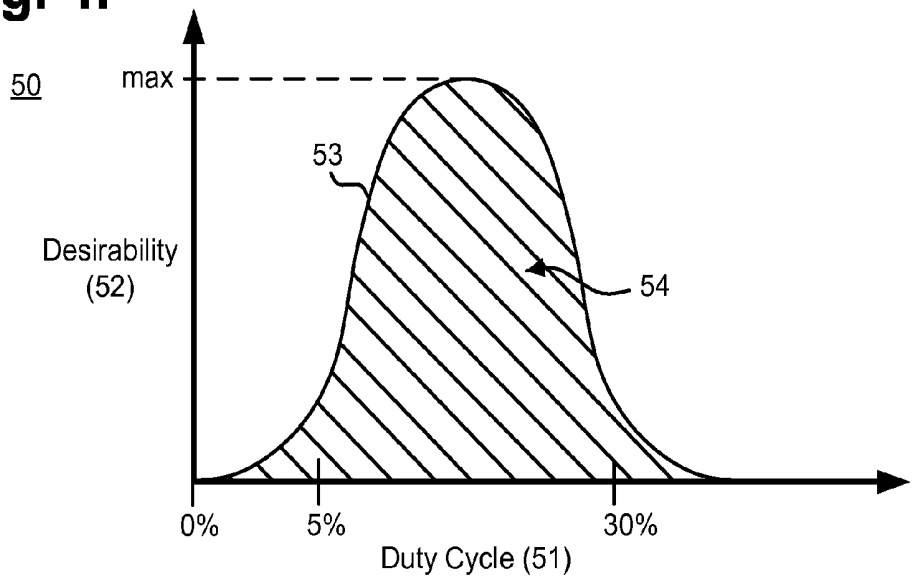

Fig. 5.

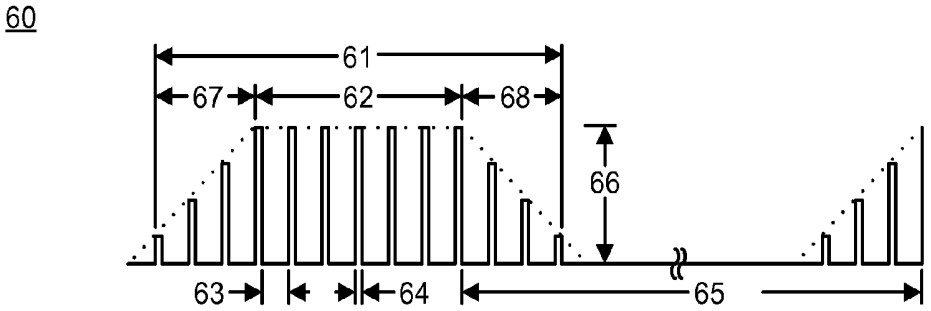

Fig. 6.

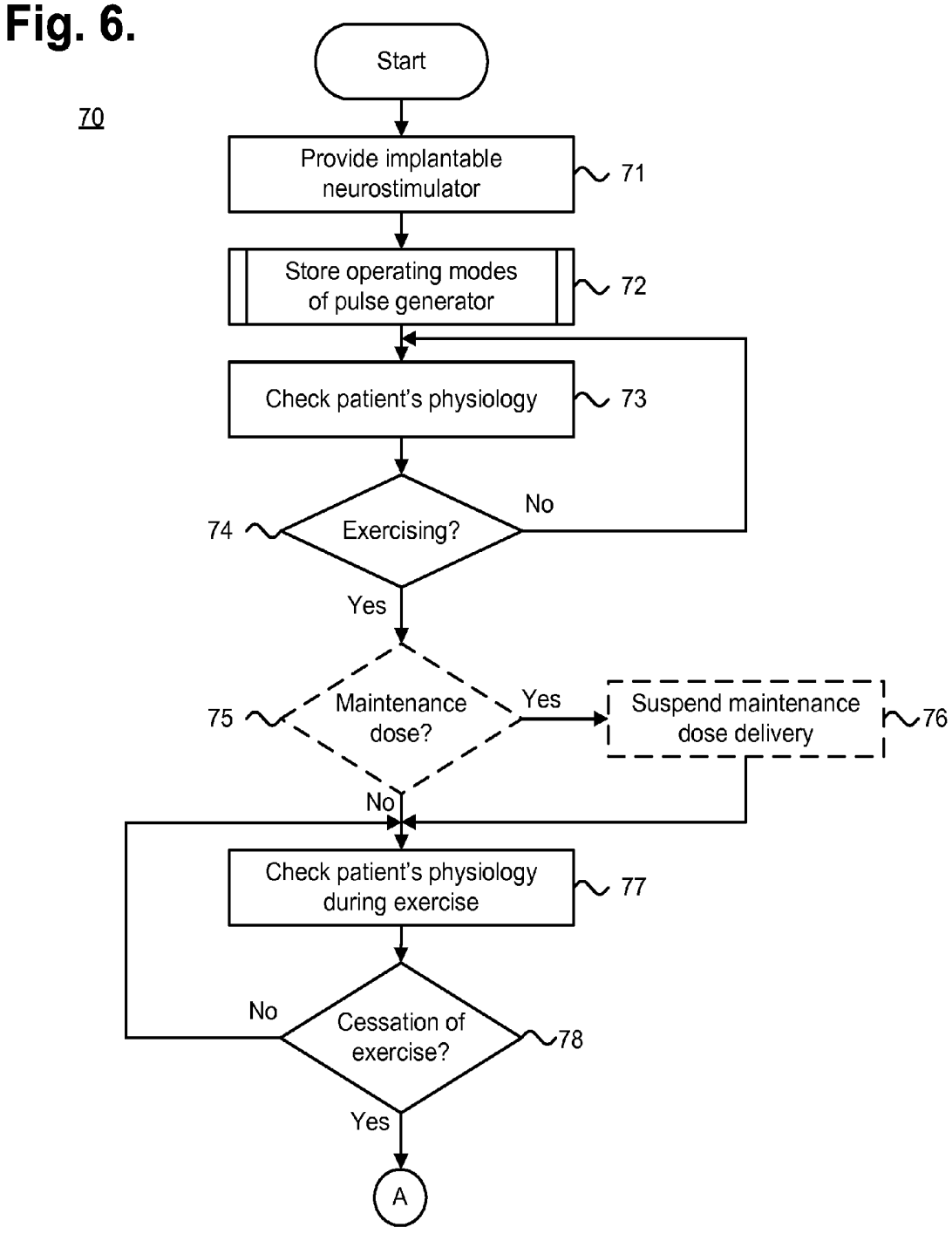
70
Start
Provide implantable neurostimulator
71
Store operating modes of pulse generator
72
Check patient's physiology
73
74
Exercising?
No
Yes
75
Maintenance dose?
Yes
Suspend maintenance dose delivery
76
No
Check patient's physiology during exercise
77
No
Cessation of exercise?
78
Yes
A

Fig. 6 (con'd).

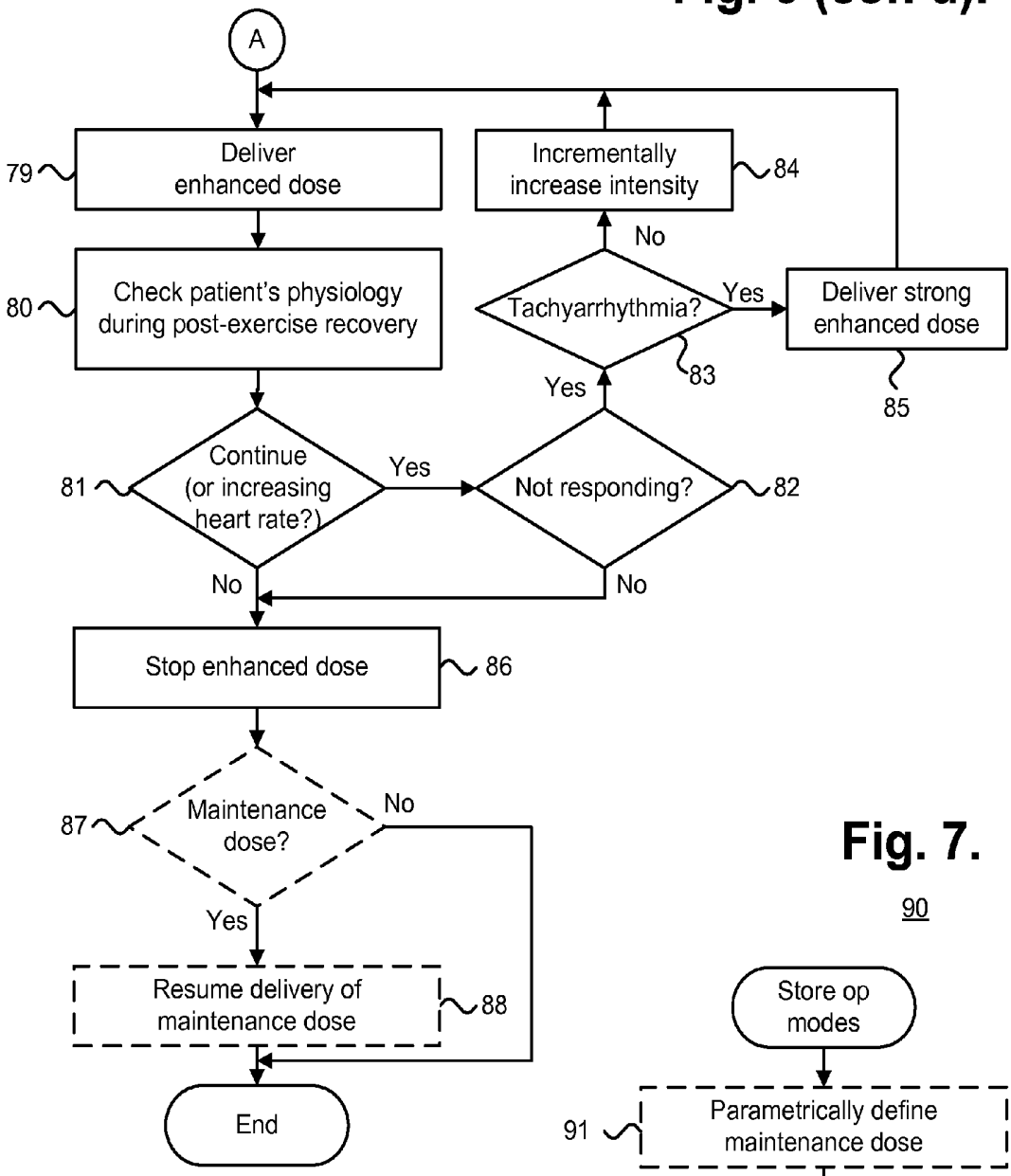

Fig. 7.

IMPLANTABLE NEUROSTIMULATOR-IMPLEMENTED METHOD FOR ENHANCING POST-EXERCISE RECOVERY THROUGH VAGUS NERVE STIMULATION

FIELD

This application relates in general to chronic cardiac dysfunction therapy and, in particular, to an implantable neurostimulator-implemented method for enhancing post-exercise recovery through vagus nerve stimulation.

BACKGROUND

Congestive heart failure (CHF) and other forms of chronic cardiac dysfunction (CCD) are generally attributed to an autonomic imbalance of the sympathetic and parasympathetic nervous systems that, if left untreated, can lead to cardiac arrhythmogenesis, progressively worsening cardiac function and eventual patient death. CHF is pathologically characterized by an elevated neuroexitatory state and is accompanied by physiological indications of impaired arterial and cardiopulmonary baroreflex function with reduced vagal activity.

CHF triggers compensatory activations of the sympathoadrenal (sympathetic) nervous system and the renin-angiotensin-aldosterone hormonal system, which initially help to compensate for deteriorating heart pumping function, yet, over time, can promote progressive left ventricular dysfunction and deleterious cardiac remodeling. Patients suffering from CHF are at increased risk of tachyarrhythmias, such as atrial fibrillation (AF), ventricular tachyarrhythmias (ventricular tachycardia (VT) and ventricular fibrillation (VF)), and atrial flutter, particularly when the underlying morbidity is a form of coronary artery disease, cardiomyopathy, mitral valve prolapse, or other valvular heart disease. Sympathoadrenal activation also significantly increases the risk and severity of tachyarrhythmias due to neuronal action of the sympathetic nerve fibers in, on, or around the heart and through the release of epinephrine (adrenaline), which can exacerbate an already-elevated heart rate.

Heart rate naturally rises in response to exercise and other forms of physical exertion as the body's need for oxygenated blood increases. Physiologically, exercise triggers heightened sympathoadrenal activation accompanied by the release of epinephrine (adrenaline) and norepinephrine (noradrenaline), which induce sinus tachycardia and ensuing heart rate increase. In a healthy person, this physiologic response to physical exertion is countered during post-exercise recovery period by parasympathetic outflow. A patient suffering from CCD, however, is at increased risk of tachyarrhythmias during the post-exercise recovery period, due to the exercise-induced exacerbation of already-increased sympathoadrenal drive.

Other forms of tachycardia, specifically supraventricular (SVT), are relatively benign unless episodic or prolonged. In a patient with compromised cardiac function, though, any form of tachyarrhythmia carries the potential of degrading into a life-threatening condition during the post-exercise recovery period. Despite these increased risks, the current standard of care for treating CCD patients still relies on palliative patient management, in which patients are cautioned to control the amount and degree of exercise undertaken to avoid triggering exercise-induced tachyarrhythmias and their potential sequela.

The standard of care for managing CCD in general continues to evolve. For instance, new therapeutic approaches that employ electrical stimulation of neural structures that directly address the underlying cardiac autonomic nervous system imbalance and dysregulation have been proposed. In one form, controlled stimulation of the cervical vagus nerve beneficially modulates cardiovascular regulatory function. Currently, vagus nerve stimulation (VNS) is only approved for the clinical treatment of drug-refractory epilepsy and depression, although VNS has been proposed as a therapeutic treatment of CHF in general and has been demonstrated in canine studies as efficacious in simulated treatment of AF and heart failure, such as described in Zhang et al., "Therapeutic Effects of Selective Atrioventricular Node Vagal Stimulation in Atrial Fibrillation and Heart Failure," J. Cardiovasc. Electrophysiol., Vol. pp. 1-6 (Jul. 9, 2012), the disclosure of which is incorporated by reference.

Conventional general therapeutic alteration of cardiac vagal efferent activation through electrical stimulation targets only the efferent nerves of the parasympathetic nervous system, such as described in Sabbah et al., "Vagus Nerve Stimulation in Experimental Heart Failure," Heart Fail. Rev., 16:171-178 (2011), the disclosure of which is incorporated by reference. The Sabbah paper discusses canine studies using a vagus nerve stimulation system, manufactured by BioControl Medical Ltd., Yehud, Israel, which includes an electrical pulse generator, right ventricular endocardial sensing lead, and right vagus nerve cuff stimulation lead. The sensing lead enables stimulation of the right vagus nerve in a highly specific manner, which involves closed-loop synchronization of the vagus nerve stimulation pulse to the cardiac cycle. An asymmetric tri-polar nerve cuff electrode is implanted on the right vagus nerve at the mid-cervical position. The electrode provides cathodic induction of action potentials while simultaneously applying asymmetric anodal blocks that lead to preferential activation of vagal efferent fibers. Electrical stimulation of the right cervical vagus nerve is delivered only when heart rate increases beyond a preset threshold. Stimulation is provided at an impulse rate and intensity intended to reduce basal heart rate by ten percent by preferential stimulation of efferent vagus nerve fibers leading to the heart while blocking afferent neural impulses to the brain. Although effective in partially restoring baroreflex sensitivity and, in the canine model, increasing left ventricular ejection fraction and decreasing left ventricular end diastolic and end systolic volumes, the degree of therapeutic effect on parasympathetic activation occurs through incidental recruitment of afferent parasympathetic nerve fibers in the vagus, as well as through recruitment of efferent fibers. Efferent stimulation alone is less effective at restoring autonomic balance than bi-directional stimulation.

Other uses of electrical nerve stimulation for generalized therapeutic treatment of various cardiac and physiological conditions are described. For instance, U.S. Pat. No. 6,600,954, issued Jul. 29, 2003 to Cohen et al. discloses a method and apparatus for selective control of nerve fiber activations. An electrode device is applied to a nerve bundle capable of generating, upon activation, unidirectional action potentials that propagate 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 in the legs and arms.

U.S. Pat. No. 6,684,105, issued Jan. 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.

U.S. Pat. No. 7,123,961, issued Oct. 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. For arrhythmia detection, the device utilizes atrial and ventricular sensing circuits to sense cardiac signals to determine whether a rhythm is physiologic or pathologic. The timing intervals between sensed events are classified by comparing them to a predefined rate zone limit and other characteristics to determine the type of remedial therapy needed, which includes bradycardia pacing, anti-tachycardia pacing, cardioversion shocks (synchronized with an R-wave), or defibrillation shocks (delivered asynchronously).

U.S. Pat. No. 7,225,017, issued May 29, 2007 to Shelchuk discloses terminating VT in connection with any stimulation device that is configured or configurable to stimulate nerves, or stimulate and shock a patient's heart. Parasympathetic stimulation is used to augment anti-tachycardia pacing, cardioversion, or defibrillation therapy. To sense atrial or ventricular cardiac signals and provide chamber pacing therapy, particularly on the left side of the patient's heart, the stimulation device is coupled to a lead designed for placement in the coronary sinus or its tributary veins. Cardioversion stimulation is delivered to a parasympathetic pathway upon detecting a ventricular tachycardia. A stimulation pulse is delivered via the lead to one or more electrodes positioned proximate to the parasympathetic pathway according to stimulation pulse parameters based on the probability of reinitiation of an arrhythmia.

U.S. Pat. No. 7,277,761, issued Oct. 2, 2007 to Shelchuk discloses vagal stimulation for improving cardiac function in heart failure 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 endocardial stimulation and shock therapy. Where the stimulation device is intended to operate as an implantable cardioverter-defibrillator (ICD), the device detects the occurrence of an arrhythmia, and applies a therapy to the heart aimed at terminating the detected arrhythmia. Defibrillation shocks are generally of moderate to high energy level, delivered asynchronously, and pertaining exclusively to the treatment of fibrillation.

U.S. Pat. No. 7,295,881, issued Nov. 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 with nerve-branch specific stimulation to achieve selective stimulation of a specific range of fiber diameters, 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.

U.S. Pat. No. 7,778,703, issued Aug. 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 stimulating and inhibiting currents to the vagus nerve, 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. Typically, the system is configured to treat heart failure or heart arrhythmia, such as atrial fibrillation or tachycardia by slowing or stabilizing the heart rate, or reducing cardiac contractility.

U.S. Pat. No. 7,813,805, issued Oct. 12, 2010 to Farazi and U.S. Pat. No. 7,869,869, issued Jan. 11, 2011 to Farazi both disclose subcardiac threshold vagus nerve stimulation. A vagus nerve stimulator is configured to generate electrical pulses below a cardiac threshold, which are transmitted to a vagus nerve, so as to inhibit or reduce injury resulting from ischemia. For arrhythmia detection, a heart stimulator utilizes atrial and ventricular sensing circuits to sense cardiac signals to determine whether a rhythm is physiologic or pathologic. In low-energy cardioversion, an ICD device typically delivers a cardioversion stimulus synchronously with a QRS complex; thus, avoiding the vulnerable period of the T-wave and avoiding an increased risk of initiation of VF. In general, if anti-tachycardia pacing or cardioversion fails to terminate a tachycardia, then, for example, after a programmed time interval or if the tachycardia accelerates, the ICD device initiates defibrillation therapy.

Finally, U.S. Pat. No. 7,885,709, issued Feb. 8, 2011 to Ben-David discloses nerve stimulation for treating disorders. A control unit drives 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. Typically, the system is configured to treat heart failure or heart arrhythmia, such as AF or tachycardia. In one embodiment, a control unit is configured to drive an electrode device to stimulate the vagus nerve, so as to modify heart rate variability to treat a condition of the subject. Therapeutic effects of reduction in heart rate variability include the narrowing of the heart rate range, thereby eliminating very slow heart rates and very fast heart rates. For this therapeutic application, the control unit is typically configured to reduce low-frequency heart rate variability, and to adjust the level of stimulation applied based on the circadian and activity cycles of the subject. Therapeutic effects also include maximizing the mechanical efficiency of the heart by maintaining relatively constant ventricular filling times and pressures. For example, this therapeutic effect may be beneficial for subjects suffering from atrial fibrillation, in which fluctuations in heart filling times and pressure reduce cardiac efficiency.

Accordingly, a need remains for an approach to enhance recovery following exercise in a heart failure patient including attenuating heart rate increase and decreasing risk of tachyarrhythmias.

SUMMARY

Prolonged activation of the sympathetic nervous system during the post-exercise recovery period increases the risk of tachyarrhythmias, particularly in a patient with CCD. In general, bi-directional afferent and efferent neural stimulation through the vagus nerve can beneficially restore auto-

nomic balance and improve long term clinical outcome. During non-exertion periods, VNS can be delivered therapeutically through an implantable vagus neurostimulator and electrode lead to a patient in a maintenance dose, which helps to restore the patient's cardiac autonomic balance. During exercise, VNS can be suspended. Thereafter, during the post-exercise recovery period, VNS can be delivered in an enhanced dose, which is set to a higher level of intensity than the maintenance dose to facilitate exercise recovery and lower tachyarrhythmic risk.

One embodiment provides an implantable neurostimulator-implemented method for enhancing post-exercise recovery through vagus nerve stimulation. An implantable neurostimulator, including a pulse generator configured to deliver electrical therapeutic stimulation in a manner that results in creation and propagation (in both afferent and efferent directions) of action potentials within neuronal fibers including a patient's cervical vagus nerve. An operating mode is stored in the pulse generator. An enhanced dose of the electrical therapeutic stimulation is parametrically defined and tuned to prevent or disrupt tachyarrhythmia through continuously-cycling, intermittent and periodic electrical pulses. The patient's physiological state is monitored during physical exercise via at least one sensor included in the implantable neurostimulator, and upon sensing a condition indicative of cessation of the physical exercise, the enhanced dose is delivered for a period of time to the vagus nerve.

A further embodiment provides an implantable neurostimulator-implemented method for adaptively enhancing post-exercise recovery through vagus nerve stimulation. An implantable neurostimulator, including a pulse generator configured to deliver electrical therapeutic stimulation in a manner that results in creation and propagation (in both afferent and efferent directions) of action potentials within neuronal fibers including a patient's cervical vagus nerve. An operating mode is stored in the pulse generator. An enhanced dose of the electrical therapeutic stimulation is parametrically defined and tuned to prevent or disrupt tachyarrhythmia through continuously-cycling, intermittent and periodic electrical pulses. The patient's physiological state is monitored during physical exercise via at least one sensor included in the implantable neurostimulator, and upon sensing a condition indicative of cessation of the physical exercise, the enhanced dose is delivered based on heart response trajectory to the vagus nerve. The patient's physiological state is monitored throughout the delivering of the enhanced dose. A heart response trajectory is established based on the patient's physiological state and the enhanced dose continues to be delivered while the heart response trajectory is elevated.

By improving autonomic balance and cardiovascular regulatory function, therapeutic VNS operates acutely to decrease heart rate, reflexively increase heart rate variability and coronary flow, reduce cardiac workload through vasodilation, and improve left ventricular relaxation without aggravating comorbid tachyarrhythmia or other cardiac arrhythmic conditions. Over the long term, low dosage 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.

Still other 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.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **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.

FIGS. **2**A and **2**B are diagrams respectively showing the implantable neurostimulator and the simulation therapy lead of FIG. **1**.

FIG. **3** 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 FIG. **1**.

FIG. **4** is a graph showing, by way of example, the optimal duty cycle range based on the intersection depicted in FIG. **3**.

FIG. **5** is a timing diagram showing, by way of example, a stimulation cycle and an inhibition cycle of VNS as provided by implantable neurostimulator of FIG. **1**.

FIG. **6** is a flow diagram showing an implantable neurostimulator-implemented method for enhancing post-exercise recovery through vagus nerve stimulation, in accordance with one embodiment.

FIG. **7** is a diagram showing an external programmer for use with the implantable neurostimulator of FIG. **1**.

DETAILED DESCRIPTION

Changes in autonomic control of the cardiovascular systems of patients suffering from CHF and other cardiovascular diseases push the autonomic nervous system out of balance and favor increased sympathetic and decreased parasympathetic central outflow, a condition that is exacerbated by exercise and other forms of physical exertion and follow-on recovery. The imbalance is accompanied by pronounced elevation of basal heart rate arising from chronic sympathetic hyperactivation along the neurocardiac axis and drawn out post-exercise recovery accompanied by prolonged heart rate elevation.

Peripheral neurostimulation therapies that target the imbalance of the autonomic nervous system have been shown to improve clinical outcomes in patients treated for three to twelve months. Specifically, bi-directional autonomic regulation therapy results in simultaneous creation and propagation of efferent and afferent action potentials within afferent and efferent nerve fibers comprising the vagus nerve. The therapy directly restores autonomic balance by engaging both medullary and cardiovascular reflex control components of the autonomic nervous system. Upon stimulation of the cervical vagus nerve, action potentials propagate away from the stimulation site in two directions, efferently toward the heart and afferently toward the brain. Efferent action potentials influence the intrinsic cardiac nervous system and the heart, while afferent action potentials influence central elements of the nervous system, which can dampen heightened sympathetic overdrive during the post-exercise recovery period.

An implantable vagus nerve stimulator with integrated heart rate sensor, such as used to treat drug-refractory epilepsy and depression, can be adapted for use in managing exercise-induced tachyarrhythmias in patients with CCD through therapeutic bi-directional vagal stimulation. The heart rate sensor provides continual heart rate monitoring that can be used in detecting cessation of physical exercise or other physical exertion to decrease risk of tachyarrhythmia, particularly VT, and confirming therapeutic efficacy. FIG. **1** is a front anatomical diagram showing, by way of example, placement of an implantable vagus nerve stimulation (VNS) device **11** in a male patient **10**, in accordance with one embodiment. 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.

The implantable vagus stimulation device **11** includes at least three implanted components, an implantable neurostimulator **12**, a therapy lead **13**, and helical electrodes **14**. The implantable vagus stimulation device **11** can be remotely accessed following implant through an external programmer by which the neurostimulator **12** can be remotely checked and programmed by healthcare professionals; an external magnet, 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," Ser. No. 13/314,130, filed on Dec. 7, 2011, now U.S. Pat. No. 8,600,505, issued Dec. 3, 2013, the disclosure of which is incorporated by reference, for basic patient control; and an electromagnetic controller, such as described in commonly-assigned U.S. Patent application, entitled "Vagus Nerve Neurostimulator With Multiple Patient-Selectable Modes For Treating Chronic Cardiac Dysfunction," Ser. No. 13/352,244, filed on Jan. 17, 2012, now U.S. Pat. No. 8,571,654, issued Oct. 29, 2013, the disclosure of which is incorporated by reference, that enables the patient **10** to exercise increased control over therapy delivery and suspension. Together, the implantable vagus stimulation device **11** and one or more of the external components form a VNS therapeutic delivery system.

The neurostimulator **12** is implanted in the patient's right or left pectoral region generally on the same side (ipsilateral) as the vagus nerve **15**, **16** to be stimulated, although other neurostimulator-vagus nerve configurations, including contra-lateral and bi-lateral are possible. The helical electrodes **14** are generally implanted on the vagus nerve **15**, **16** about halfway between the clavicle **19***a-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.

In one embodiment, during non-exertion periods, that is, periods when the patient **10** is neither actively exercising nor undergoing other physical exertion, and is also not recovering from exercise, the stimulation device **11** delivers VNS. The stimulation device **11** bi-directionally stimulates the vagus nerve **15**, **16** through multimodal application of continuously-cycling, intermittent and periodic electrical stimuli, which are parametrically defined through stored stimulation parameters and timing cycles. Immediately following exercise during the post-exercise recovery period, an enhanced dose of VNS is delivered to ameliorate the increased tachyarrhythmic risk occasioned by elevated sympathetic activation and release of epinephrine (adrenaline) and norepinephrine (noradrenaline). In a further embodiment, non-exertion induced tachyarrhythmias can be managed through application of a restorative dose of VNS upon the sensing of a condition indicative of tachyarrhythmias, such as described in commonly-assigned U.S. Patent application, entitled "Implantable Neurostimulator-Implemented Method for Managing Tachyarrhythmias through Vagus Nerve Stimulation," Ser. No. 13/673,766, filed on Nov. 9, 2012, published as US 2014/0135862 A1, pending, the disclosure of which is incorporated by reference. In a still further embodiment, bradycardia in VNS-titrated patients can be managed through suspension of on-going low-level VNS, such as described in commonly-assigned U.S. Patent application, entitled "Implantable Neurostimulator-Implemented Method for Managing Bradycardia through Vagus Nerve Stimulation," Ser. No. 13/554,656, filed on Jul. 20, 2012, now U.S. Pat. No. 8,688,212, issued Apr. 1, 2014, the disclosure of which is incorporated by reference.

Both sympathetic and parasympathetic neuronal fibers are stimulated. Cervical vagus nerve stimulation results in propagation of action potentials from the site of stimulation in a manner that results in creation and propagation (in both afferent and efferent directions) of action potentials within neuronal fibers comprising the cervical vagus nerve to restore cardiac autonomic balance. 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. Efferent action potentials propagate toward the heart **17** to activate the components of the heart's intrinsic nervous system. Either the left or right vagus nerve **15**, **16** can be stimulated by the stimulation device **11**. The right vagus nerve **16** has a moderately lower stimulation threshold than the left vagus nerve **15** for heart rate affects at the same parametric levels.

The VNS therapy is delivered autonomously to the patient's vagus nerve **15**, **16** through three implanted components that include a neurostimulator **12**, therapy lead **13**, and helical electrodes **14**. FIGS. **2**A and **2**B are diagrams respectively showing the implantable neurostimulator **12** and the simulation therapy lead **13** of FIG. **1**. In one embodiment, the neurostimulator **12** can be adapted from a VNS Therapy AspireSR Model 106 pulse generator, manufactured and sold by Cyberonics, Inc., Houston, Tex., 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, 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.

Referring first to FIG. **2**A, the neurostimulator **12** provides multimodal vagal stimulation. During post-exercise recovery period, the neurostimulator **12** is parametrically programmed to deliver an enhanced dose of continuously-

cycling, intermittent and periodic ON-OFF cycles of VNS, that is delivered to produce action potentials in the underlying nerves that propagate bi-directionally during non-exertion periods, as further described infra beginning with reference to FIG. **6**. The enhanced dose is tuned to prevent initiation of or disrupt tachyarrhythmia. In a further embodiment, the neurostimulator **12** is parametrically programmed to deliver a maintenance dose of continuously-cycling, intermittent and periodic ON-OFF cycles of VNS, that is delivered to produce action potentials in the underlying nerves that propagate bi-directionally. The maintenance dose is delivered at lower intensity, which could be lower output current, lower duty cycle, lower frequency, shorter pulse width, or a combination of the foregoing parameters, than the enhanced dose delivered during post-exercise recovery period.

The neurostimulator **12** includes an electrical pulse generator that is tuned to restore autonomic balance by triggering action potentials that propagate both afferently and efferently within 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 monofluoride battery. The electronic circuitry **22** is implemented using complementary metal oxide semiconductor integrated circuits that include a microprocessor controller that executes a control program according to stored stimulation parameters and timing cycles; 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, 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 remote access to the operation of the neurostimulator **12** using an external programmer, a simple patient magnet, or an electromagnetic controller. The recordable memory **29** can include both volatile (dynamic) and persistent (static) forms of memory, such as firmware within which the stimulation parameters and timing cycles can be stored. Other electronic circuitry and components are possible.

Externally, the neurostimulator **12** includes a header **24** to securely receive and connect to the therapy lead **13**. In one embodiment, 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**.

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 heartbeat can be sensed by detecting ventricular depolarization. In a further embodiment, a plurality of electrodes can be used to sense voltage differentials between electrode pairs, which can undergo signal processing for cardiac physiological measures, for instance, detection of the P-wave, QRS complex, and T-wave. The heart rate sensor **31** provides the sensed heart rate to the control and logic circuitry as sensory inputs that can be used to sense cessation of physical exercise and determine the presence of possible tachyarrhythmias, particularly VT, during post-exercise recovery period.

In a further embodiment, the housing **21** contains an accelerometer **32** that is electrically interfaced with the logic and control circuitry, which receives the patient's physical movement as sensory inputs. The accelerometer **32** contains the circuitry and mechanical components necessary to measure acceleration of the patient's body along at least two axes, and may include multiple uniaxial accelerometers, a dual axial accelerometer, or a triaxial accelerometer. By measuring the acceleration along multiple axes, the accelerometer **32** provides sensory inputs that can be used to determine the patient's posture and rate of movement, which can augment or supplant the heart rate sensor **31** in sensing cessation of physical exercise.

In a still further embodiment, the housing **21** contains a minute ventilation sensor **33** that is electrically interfaced with the logic and control circuitry, which receives the patient's respiratory dynamics as sensory inputs. The minute ventilation sensor **32**, such as described in U.S. Pat. No. 7,092,757, issued Aug. 15, 2006, to Larson et al., whose disclosure is incorporated by reference, measures the patient's respiratory rate and tidal volume, and calculates the patient's minute ventilation volume. The relationship between oxygen uptake and tidal volume during aerobic metabolism closely ties minute ventilation to heart rate during physical exercise, which can augment or supplant the heart rate sensor **31** and accelerometer **32** in sensing cessation of physical exercise.

The neurostimulator **12** is preferably interrogated prior to implantation and throughout the therapeutic period with a healthcare provider-operable external programmer and programming wand (not shown) for checking proper operation, downloading recorded data, diagnosing problems, and programming operational parameters, such as described in commonly-assigned U.S. patent application Ser. Nos. 13/314,130 and 13/352,244, cited supra. Generally, use of the external programmer is restricted to healthcare providers, while more limited manual control is provided to the patient through "magnet mode." In one embodiment, the external programmer executes application software specifically designed to interrogate the neurostimulator **12**. The programming computer interfaces to the programming wand through a standardized wired or wireless data connection. The programming wand can be adapted from a Model 201 Programming Wand, manufactured and sold by Cyberonics, Inc. and the application software can be adapted from the Model 250 Programming Software suite, licensed by Cyberonics, Inc. Other configurations and combinations of external programmer, programming wand and application software are possible.

The neurostimulator **12** delivers VNS under control of the electronic circuitry **22**. The stored stimulation parameters are programmable. 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 include output current, signal frequency, pulse width, signal ON time, signal OFF time, magnet activation (for VNS specifically triggered by "magnet mode"), and reset parameters. Other programmable parameters are possible. In addition, sets or "profiles" of pre-selected stimulation parameters can be provided to physicians with 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," Ser. No. 13/314,138, filed on Dec. 7, 2011, now U.S. Pat. No. 8,630,709, issued Jan. 14, 2014, the disclosure of which is incorporated by reference.

Referring next to FIG. **2**B, 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 infra with reference to FIG. **4**). In one embodiment, 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.

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. In alternative embodiments, the helical electrodes may be placed at a location above where one or both of the superior and inferior cardiac branches separate from the cervical vagus nerve. In one embodiment, the helical electrodes **14** are positioned around the patient's vagus nerve oriented with the end of the helical electrodes **14** facing the patient's head. In an alternate embodiment, the helical electrodes **14** are positioned around the patient's vagus nerve **15**, **16** oriented with the end of the helical electrodes **14** facing the patient's heart **17**. At the distal end, the insulated electrical lead body **13** is bifurcated into a pair of lead bodies that are connected to a pair of electrodes proper. The polarity of the electrodes can be configured into a monopolar cathode, a proximal anode and a distal cathode, or a proximal cathode and a distal anode.

Therapeutically, the VNS is delivered as a multimodal set of therapeutic and event-based doses, which are system output behaviors that are pre-specified within the neurostimulator **12** through the stored stimulation parameters and timing cycles implemented in firmware and executed by the microprocessor controller. The therapeutic doses include a cardiac cycle-independent enhanced dose delivered during post-exercise recovery period that includes continuously-cycling, intermittent and periodic cycles of electrical stimulation during periods in which the pulse amplitude is greater than 0 mA ("therapy ON") and during periods in which the pulse amplitude is 0 mA ("therapy OFF"). The therapeutic doses also include, in a further embodiment, a maintenance dose that is delivered at a lower level of intensity than the enhanced dose, which could be lower output current, lower duty cycle, lower frequency, shorter pulse width, or a combination of the foregoing parameters, during non-exertion periods.

The neurostimulator **12** can operate either with or without an integrated heart rate sensor (provided that patient physiology can be monitored through some other type of sensing mechanism), 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," Ser. No. 13/314,126, filed on Dec. 7, 2011, now U.S. Pat. No. 8,577,458, issued Nov. 5, 2013, and U.S. Patent application, entitled "Implantable Device for Providing Electrical Stimulation of Cervical Vagus Nerves for Treatment of Chronic Cardiac Dysfunction," Ser. No. 13/314,119, filed on Dec. 7, 2011, pending, the disclosures of which are hereby incorporated by reference herein in their entirety. Additionally, where an integrated leadless heart rate monitor is available, the neurostimulator **12** can provide autonomic cardiovascular drive evaluation and self-controlled titration, such as respectively described in commonly-assigned U.S. Patent application, entitled "Implantable Device for Evaluating Autonomic Cardiovascular Drive in a Patient Suffering from Chronic Cardiac Dysfunction," Ser. No. 13/314,133, filed on Dec. 7, 2011, now U.S. Pat. No. 8,918,190, issued Dec. 23, 2014, and U.S. Patent application, entitled "Implantable Device for Providing Electrical Stimulation of Cervical Vagus Nerves for Treatment of Chronic Cardiac Dysfunction with Bounded Titration," Ser. No. 13/314,135, filed on Dec. 7, 2011, now U.S. Pat. No. 8,918,191, issued Dec. 23, 2014, the disclosures of which are incorporated by reference. Finally, the neurostimulator **12** can be used to counter natural circadian sympathetic surge upon awakening and manage the risk of cardiac arrhythmias during or attendant to sleep, particularly sleep apneic episodes, such as respectively described in commonly-assigned U.S. Patent application, entitled "Implantable Neurostimulator-Implemented Method For Enhancing Heart Failure Patient Awakening Through Vagus Nerve Stimulation," Ser. No. 13/673,811, filed Nov. 9, 2012, now U.S. Pat. No. 8,923,964, issued Dec. 30, 2014, and U.S. Patent application, entitled "Implantable Neurostimulator-Implemented Method For Managing Tachyarrhythmic Risk During Sleep Through Vagus Nerve Stimulation," Ser. No. 13/673,811, filed Nov. 9, 2012, now U.S. Pat. No. 8,923,964, issued Dec. 30, 2014, the disclosures of which are incorporated by reference.

Therapeutically, VNS is delivered for post-exercise recovery attenuation independent of cardiac cycle and in an enhanced dose having an intensity that is insufficient to elicit side-effects, such as cardiac arrhythmias. The selection of duty cycle is a tradeoff among competing medical considerations. FIG. **3** is a graph **40** showing, by way of example, the relationship between the targeted therapeutic efficacy **43** and the extent of potential side effects **44** resulting from use of the implantable neurostimulator **12** of FIG. **1**. The x-axis represents the duty cycle **41**. The duty cycle is determined by dividing the stimulation ON time by the sum of the ON and OFF times of the neurostimulator **12** during a single ON-OFF cycle. 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 infra with reference to FIG. **5**). The y-axis represents physiological response **42** to VNS therapy. The physiological response **42** can be expressed quantitatively for a given duty cycle **41** as a function of the targeted therapeutic efficacy **43** and the extent of potential side effects **44**, as described infra. The maximum level of physiological response **42** ("max") signifies the highest point of targeted therapeutic efficacy **43** or potential side effects **44**.

Targeted therapeutic efficacy **43** and the extent of potential side effects **44** can be expressed as functions of duty cycle **41** and physiological response **42**. The targeted therapeutic efficacy **43** 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 **42** of the patient **10** due to the delivery of therapeutic VNS. Acute factors that contribute to the targeted therapeutic efficacy **43** include beneficial changes in heart rate variability and increased coronary flow, reduction in cardiac workload through vasodilation, and improvement in left ventricular relaxation. Chronic factors that contribute to the targeted therapeutic efficacy **43** include improved cardiovascular regulatory function, 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 **43**, 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 **43** 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 **43** begins decreasing at around a 50% duty cycle and continues in a plateau near a 25% physiological response through the maximum 100% duty cycle.

The intersection **45** of the targeted therapeutic efficacy **43** and the extent of potential side effects **44** represents one optimal duty cycle range for VNS. FIG. **4** is a graph **50** showing, by way of example, the optimal duty cycle range **53** based on the intersection **45** depicted in FIG. **3**. The x-axis represents the duty cycle **51** as a percentage of stimulation time over inhibition time. The y-axis represents therapeutic points **52** reached in operating the neurostimulator **12** at a given duty cycle **51**. The optimal duty range **53** is a function **54** of the intersection **44** of the targeted therapeutic efficacy **43** and the extent of potential side effects **44**. The therapeutic operating points **52** can be expressed quantitatively for a given duty cycle **51** as a function of the values of the targeted therapeutic efficacy **43** and the extent of potential side effects **44** at their point of intersection in the graph **40** of FIG. **3**. The optimal therapeutic operating point **55** ("max") signifies a tradeoff that occurs at the point of highest targeted therapeutic efficacy **43** in light of lowest potential side effects **44** and that point will typically be found within the range of a 5% to 30% duty cycle **51**. Other expressions of duty cycles and related factors are possible.

Therapeutically and in the absence of patient physiology of possible medical concern, such as cardiac arrhythmias, VNS is delivered during non-exertion periods in a low level maintenance dose that uses alternating cycles of stimuli application (ON) and stimuli inhibition (OFF) that are tuned to activate both afferent and efferent pathways. Stimulation results in parasympathetic activation and sympathetic inhibition, both through centrally-mediated pathways and through efferent activation of preganglionic neurons and local circuit neurons.

FIG. **5** is a timing diagram showing, by way of example, a stimulation cycle and an inhibition cycle of VNS **60** as provided by implantable neurostimulator **12** of FIG. **1**. The stimulation parameters enable the electrical stimulation pulse output by the neurostimulator **12** to be varied by both amplitude (output current **66**) and duration (pulse width **64**). The number of output pulses delivered per second determines the signal frequency **63**. 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.

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 **65** is always the time period occurring in-between stimulation times **61** during which the neurostimulator **12** is OFF and inhibited from delivering stimulation. In one embodiment, the neurostimulator **12** implements a ramp-up time **67** and a ramp-down time **68** that respectively precede and follow the ON time **62** during which the neurostimulator **12** is ON and delivering pulses of stimulation at the full output current **66**. The ramp-up time **67** and ramp-down time **68** are used when the stimulation frequency is at least 10 Hz, although other minimum thresholds could be used, and both ramp-up and ramp-down times **67**, **68** last two seconds, although other time periods could also be used. The ramp-up time **67** and ramp-down time **68** allow the strength of the output current **66** of each output pulse to be gradually increased and decreased, thereby avoiding deleterious reflex behavior due to sudden delivery or inhibition of stimulation at a programmed intensity.

The triggering of CHF compensatory mechanisms underlying a CCD increases the risk of tachyarrhythmias. After physical exercise or other physical activity, the risk of tachyarrhythmia is even higher. Although delivered in an enhanced dose during post-recovery period and, in a further embodiment, in a maintenance dose during non-exertion periods, with an intensity that is insufficient to elicit side-effects, such as cardiac arrhythmias, therapeutic VNS can nevertheless potentially prevent formation of pathological tachyarrhythmias or at least ameliorate their occurrence during post-exercise recovery period in some patients. Although VNS has been shown to decrease defibrillation threshold, VNS is unlikely to terminate VF in the absence of defibrillation. VNS prolongs ventricular action potential duration, so may be effective in terminating VT. In addition, the effect of VNS on the AV node may be beneficial in patients with AF by slowing conduction to the ventricles and controlling ventricular rate.

Upon sensing cessation of physical exercise or other physical exertion, VNS that is tuned to prevent initiation of or disrupt tachyarrhythmia is provided in an enhanced dose during post-exercise recovery period for a fixed period of time or as determined by heart response trajectory. FIG. **6** is a flow diagram showing an implantable neurostimulator-implemented method for managing exercise-induced tachyarrhythmias through vagus nerve stimulation **70**, in accordance with one embodiment. The method is implemented on the stimulation device **11**, the operation of which is parametrically defined through stored stimulation parameters and timing cycles.

Preliminarily, an implantable neurostimulator **12** with an integrated heart rate sensor **31**, which includes a pulse generator **11**, a nerve stimulation therapy lead **13**, and a pair of helical electrodes **14**, is provided (step **71**). In an alternative embodiment, electrodes may be implanted with no implanted neurostimulator or leads. Power may be provided to the electrodes from an external power source and neurostimulator through wireless RF or inductive coupling. Such an embodiment may result in less surgical time and trauma to the patient. Furthermore, the integrated heart rate sensor **31** could be omitted in lieu of or supplemented by other types of sensing mechanisms for measuring the patient's activity level and physiology, including an accelerometer **32** or minute ventilation sensor **33**, as further described infra.

The pulse generator stores a set of one or more operating modes (step **72**) that parametrically defines an enhanced dose and, in a further embodiment, a maintenance dose of the stimulation, as further described infra with reference to FIG. **7**. Patient's physiology is periodically checked (step **73**). In one embodiment, heart rate is used to check the patient **10**'s physiology using the heart rate sensor **31**. A normative heart rate is generally considered to fall between 60 to 100 beats per minute (bpm). When exercising, the heart rate may go up to 150 bpm or more, depending upon patient condition and degree of exertion. The normative heart rate of the patient **10** is monitored and recorded periodically during non-exertion periods to determine whether the patient **10** is now exercising or performing other types of physical exertion.

In general, engaging in physical exercise is characterized by the gradual onset of an elevated heart rate, as well as by evaluation of rhythm stability or related rate and rhythm morphological indicators, such as conventionally used in cardiac rhythm management devices. If the heart rate of the patient **10** is gradually elevated above the mean normative heart rate level, for instance, a heart rate that gradually increases to over 100 bpm over a five-minute period and is then maintained for a non-transitory period of time, the patient **10** is considered to be exercising. In contrast, abrupt onset of increased heart rate could be indicative of a non-sinus tachyarrhythmia.

In a further embodiment, an accelerometer **32** can be used to determine whether the patient's movement is indicative of exercise. The rate of change in patient's posture and movement are sensed by the accelerometer **32** during both non-exertion and exercise periods. A normative activity level is established by determining the mean of the frequency of movement during non-exertion periods. Both frequency and amplitude signals are continually sensed; increased frequency of movement is indicative of physical exertion. If the acceleration of the patient's physical movement exceeds the mean frequency of movement at the normative activity level, the patient is considered to be engaging in physical exercise. In a still further embodiment, the heart rate sensor **31**, the accelerometer **32**, or both can be used in combination.

In a still further embodiment, a minute ventilation sensor **33** can be used to determine a state of physical exercise. Minute ventilation is closely tied to heart rate during exercise, as ventilatory volume (tidal volume) and breathing frequency (respiratory rate) increase synchronously, as does heart rate, at a higher exercise level. Tidal volume at rest is measured by the minute ventilation sensor **33**. In general, tidal volume at rest is around 0.5 L/min and can increase up to 3 L/min at a higher intensity level of exertion. Similarly, respiratory rate at rest is measured by the minute ventilation **33**. In general, respiratory rate at rest is around 12 to 16 breathes/min and can increase 40 to 50 breathes/min during maximum levels of exercise. A normative activity level is established by determining means of the tidal volume and respiratory rate during non-exertion periods. If tidal volume and respiratory rate of the patient **10** respectively exceed the mean resting values of tidal volume and respiratory rate, the patient **10** is considered to be engaging in physical exercise. In a still further embodiment, the heart rate sensor **31** and the accelerometer **32** can be used in combination with the minute ventilation sensor **33**. Still other measures and indications of engagement, as well as cessation, of physical exercise are possible.

In a still further embodiment, the neurostimulator **12** can use a multiple forms of sensory data in determining whether the patient **10** a state of physical exercise. As well, the neurostimulator **12** can assign more weight to one type of sensory data over other types of sensory data. For example, more weight can be assigned to accelerometer **32** data, which would discount a rise in heart rate that occurs while the patient **10** remains still, such as while seated and watching an exciting movie. Other ways of preferentially weighting the data are possible.

If the physiology indicates that the patient is exercising (step **74**), an exercise protocol (steps **76-78**) is initiated. If the patient **10** is receiving a maintenance dose (step **75**), such as described in commonly-assigned U.S. patent application Ser. No. 13/673,766, entitled "Implantable Neurostimulator-Implemented Method For Managing Tachyarrhythmias Through Vagus Nerve Stimulation," and Ser. No. 13/554,656, cited supra, the maintenance dose delivery is suspended (step **76**). The maintenance dose is tuned to rehabilitatively restore cardiac autonomic balance through continuously-cycling, intermittent and periodic electrical pulses. However, in the context of continuous physical exercise, the continued delivery of the maintenance dose can potentially be counter-productive by influencing a decrease in heart rate during a time when the obverse affect on heart rate is desired.

During exercises, the patient's physiology is periodically checked to determine whether the patient **10** continues to exercise or has stopped (step **77**). In one embodiment, cessation of physical exercise can be determined when a sustained heart rate of around 100 bpm or higher drops progressively, for instance, by at least 10 bpm. In general, a constant decrease in heart rate for more than three minutes indicates a cessation of physical exercise. In a further embodiment, when the increased frequency level of movement of the patient **10** measured by the accelerometer **32** drops and returns to the mean frequency of movement at the normative activity level, the data can indicate the cessation of physical exercise. In a still further embodiment, if tidal volume and respiratory rate of the patient **10** monitored by the minute ventilation sensor **33** gradually decrease, the data indicates that the patient **10** ceases from exercising.

Upon sensing cessation of physical exercise (step **78**), a post-exercise recovery protocol (steps **79-85**) is initiated. VNS, as parametrically defined by an enhanced dose in an operating mode, is delivered to at least one of the vagus nerve during post-exercise recovery period (step **79**). The pulse generator **11** delivers electrical therapeutic stimulation to the cervical vagus nerve of the patient **10** in a manner that results in creation and propagation (in both afferent and efferent directions) of action potentials within neuronal fibers of either the left or right vagus nerve **15**, **16** independent of cardiac cycle.

The patient's physiology is periodically monitored during the post-exercise recovery period (step **80**), as described supra. Enhanced dose therapy delivery is continued for a fixed amount of time or, in a further embodiment, as determined by the patient's heart response trajectory based upon heart rate or sinus rhythm. If the fixed amount of time has not elapsed (step **81**), the neurostimulator **12** continues the delivery of the enhanced dose (step **79**).

In a further embodiment, rather than the fixed amount of time, the delivery of the enhanced dose is adapted to respond to the patient's observed heart response trajectory (step **81**). During post-exercise recovery, the patient's heart rate is expected to continually decrease at a steady rate of about 17 bpm. In a patient suffering CCD, already elevated parasympathetic activation is exacerbated by the normally benign sinus tachyarrhythmia induced through exercise, which puts

the patient **10** at risk of degenerate tachyarrhythmias, potentially VT and VF. The heart response trajectory during enhanced dose delivery is monitored (step **81**) to evaluate heart rate responsiveness (step **82**). Non-responsiveness to the delivery of the enhanced dose can occur due to continuing heart rate elevation, which can present as no appreciable change in heart rate, insufficient heart rate decrease, or non-transitory increase in heart rate. If the heart rate increase is significant, say, in excess of 180 bpm or more, the patient **10** may be suffering onset of a tachyarrhythmia (step **83**) and a strongly enhanced dose of higher intensity VNS that is tuned to prevent initiation of or disrupt tachyarrhythmia is delivered (step **85**). In general, the onset or presence of pathological tachyarrhythmia can be determined by heart rate or rhythm, as well as rhythm stability, onset characteristics, and similar rate and rhythm morphological indicators, as conventionally detected in cardiac rhythm management devices, such as described in K. Ellenbogen et al., "Clinical Cardiac Pacing and Defibrillation," Ch. 3, pp. 68-126 (2d ed. 2000), the disclosure of which is incorporated by reference. Otherwise, in the absence of tachyarrhythmia but continued non-responsiveness (step **83**), the intensity of the enhanced dose may be incrementally increased (step **84**) until improved response is seen or a maximum VNS dose is reached.

The delivery of the enhanced dose is maintained (steps **79-85**). If, after multiple checks of the patient's physiology, the patient's physiology indicates improvement, such as satisfactory decrease in heart rate or having reached normal sinus rhythm, the enhanced dose is stopped (step **86**). In a further embodiment, when the patient is receiving a maintenance dose prior to the physical exercise (step **87**), the maintenance dose delivery is resumed (step **88**).

In a still further embodiment, delivery of the enhanced dose, as well as the strongly enhanced dose, can be manually triggered, increased, decreased, or suspended by providing the neurostimulator **12** with a magnetically-actuated reed switch, such as described in commonly-assigned U.S. patent application Ser. Nos. 13/314,130 and 13/352,244, cited supra. In addition, the delivery of the enhanced dose and the maintenance dose can also be manually swapped. For instance, the switch can be used when the maintenance dose is tolerable to the patient **10**, while the enhanced dose and the restorative dose are intolerable. Other uses of the switch are possible.

The recordable memory **29** in the electronic circuitry **22** of the neurostimulator **12** (shown in FIG. **2**A) stores the stimulation parameters that control the overall functionality of the pulse generator **11** in providing VNS therapy. FIG. **7** is a flow diagram showing a routine **90** for storing operating modes for use with the method **70** of FIG. **6**. Two operating modes are stored, which include a maintenance dose of VNS tuned to restore cardiac autonomic balance (step **91**) through continuously-cycling, intermittent and periodic electrical pulses, and an enhanced dose tuned to prevent initiation of or disrupt tachyarrhythmia (step **92**) through periodic electrical pulses delivered at higher intensity than the maintenance dose.

In one embodiment, the autonomic regulation therapy is provided in a low level maintenance dose independent of cardiac cycle to activate both parasympathetic afferent and efferent neuronal fibers in the vagus nerve simultaneously and a high level enhanced dose. In the maintenance dose, a pulse width in the range of 250 to 500 μsec delivering between 0.02 and 1.0 mA of output current at a signal frequency in the range of 10 to 20 Hz, and a duty cycle of 5 to 30%, although other therapeutic values could be used as appropriate.

Different enhanced doses can be provided to respond to different tachyarrhythmic events. The enhanced dose settings are physician-programmable. For a default enhanced dose, the stimulation parameters would be in the same range as the maintenance dose, but would be moderately higher, with a pulse width again in the range of 250 to 500 μsec delivering between 1.5 and 2.0 mA of output current at a signal frequency in the range of 10 to 20 Hz. The duty cycle may change significantly from nominally 10% to temporarily 50% or 100%, although other therapeutic values could be used as appropriate. For non-life-threatening or non-paroxysmal tachyarrhythmias, the intensity of the enhanced dose is progressively increased over time by increasing output current, duty cycle, or frequency, lengthening pulse width, or through a combination of the foregoing parameters. Discretely-defined enhanced doses, each using different parameters sets, may be delivered in the course of treating a single continuing tachyarrhythmic event, such as for life-threatening or paroxysmal arrhythmias that rapidly generate and require a significantly strongly enhanced dose with no ramp up time.

In a further embodiment, the suspension and resumption of the enhanced dose and, in a further embodiment, the maintenance dose, can be titrated to gradually withdraw or introduce their respective forms of VNS.

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 spirit and scope.

What is claimed is:

1. An implantable neurostimulator-implemented method for enhancing post-exercise recovery through vagus nerve stimulation, comprising the steps of:

providing an implantable neurostimulator comprising a pulse generator configured to deliver electrical therapeutic stimulation in a manner that results in creation and propagation in both afferent and efferent directions of action potentials within neuronal fibers comprising a patient's cervical vagus nerve;

storing an operating mode of the pulse generator in a recordable memory, comprising:

parametrically defining an enhanced dose of the electrical therapeutic stimulation tuned to prevent or disrupt tachyarrhythmia through intermittent and periodic electrical pulses; and

parametrically defining a maintenance dose of the electrical therapeutic stimulation delivered at a lower intensity than the enhanced dose; and

monitoring the patient's physiological state during physical exercise via at least one sensor comprised in the implantable neurostimulator, and upon sensing a condition indicative of cessation of the physical exercise, delivering for a period of time the enhanced dose to the vagus nerve.

2. A method according to claim **1**, further comprising the steps of:

providing a heart rate sensor as the at least one sensor comprised in the implantable neurostimulator;

establishing a normative heart rate of the patient with the heart rate sensor as a mean heart rate sensed during non-exertion periods exclusive of the physical exercise;

periodically sensing the patient's heart rate with the heart rate sensor;

confirming that the patient is undergoing the physical exercise when the patient's heart rate gradually rises and is sustained at an elevated heart rate above the normative heart rate; and

subsequently confirming the cessation of the physical exercise when the patient's heart rate falls below the elevated heart rate by a threshold amount.

3. A method according to claim **1**, further comprising the steps of:

providing an accelerometer as the at least one sensor comprised in the implantable neurostimulator;

establishing a normative activity level of the patient with the accelerometer as a mean frequency of movement sensed during non-exertion periods exclusive of the physical exercise;

periodically sensing the patient's activity level with the accelerometer;

confirming that the patient is undergoing the physical exercise when the patient's activity level gradually rises and is sustained at an elevated activity level above the normative activity level accompanied by an increased frequency of movement; and

subsequently confirming the cessation of the physical exercise when the patient's activity level falls below the elevated activity level accompanied by a decreased frequency of movement by a threshold amount.

4. A method according to claim **1**, further comprising the steps of:

providing a minute ventilation sensor as the at least one sensor comprised in the implantable neurostimulator;

establishing a normative tidal volume and normative respiratory rate of the patient with the minute ventilation sensor sensed during non-exertion periods exclusive of the physical exercise;

periodically sensing the patient's tidal volume and respiratory rate with the minute ventilation sensor;

confirming that the patient is undergoing the physical exercise when the patient's tidal volume and respiratory rate gradually rise and are sustained at elevated levels respectively above the normative tidal volume and the normative respiratory rate; and

subsequently confirming the cessation of the physical exercise when the patient's tidal volume and respiratory rate fall below the respective elevated levels by a threshold amount.

5. A method according to claim **1**, further comprising the step of:

monitoring the patient's physiological state throughout the delivering of the enhanced dose, and upon sensing a condition indicative of an onset of tachyarrhythmia, intensifying the electrical therapeutic stimulation as specified in the operating mode.

6. A method according to claim **5**, further comprising the step of:

progressively intensifying the electrical therapeutic stimulation as specified in the operating mode as the tachyarrhythmia continues.

7. A method according to claim **5**, further comprising the step of:

maximizing the electrical therapeutic stimulation as specified in the operating mode when the tachyarrhythmia fails to respond to the intensified electrical therapeutic stimulation.

8. A method according to claim **1**, further comprising the step of:

delivering the maintenance dose to the vagus nerve via the pulse generator through a pair of helical electrodes following the delivering of the enhanced dose,

wherein storing the operating mode of the pulse generator in the recordable memory further comprises parametrically defining the maintenance dose of the electrical therapeutic stimulation tuned to restore cardiac autonomic balance through intermittent and periodic electrical pulses.

9. A method according to claim **8**, further comprising the steps of:

providing a magnetically-actuated reed switch configured to control the pulse generator; and

controlling the pulse generator in response to a magnetic signal remotely applied to the reed switch, comprising at least one of:

switching between delivery of the enhanced dose and the maintenance dose;

triggering or increasing delivery of either the enhanced dose or the maintenance dose; and

decreasing or suspending delivery of either the enhanced dose or the maintenance dose.

10. A method according to claim **1**, wherein the maintenance dose comprises one or more of the following: a lower output current than the enhanced dose, a lower duty cycle than the enhanced dose, a lower frequency than the enhanced dose, or a shorter pulse width than the enhanced dose.

11. An implantable neurostimulator-implemented method for adaptively enhancing post-exercise recovery through vagus nerve stimulation, comprising the steps of:

providing an implantable neurostimulator comprising a pulse generator configured to deliver electrical therapeutic stimulation in a manner that results in creation and propagation in both afferent and efferent directions of action potentials within neuronal fibers comprising a patient's cervical vagus nerve;

storing an operating mode of the pulse generator in a recordable memory, comprising:

parametrically defining an enhanced dose of the electrical therapeutic stimulation tuned to prevent or disrupt tachyarrhythmia through intermittent and periodic electrical pulses; and

parametrically defining a maintenance dose of the electrical therapeutic stimulation delivered at a lower intensity than the enhanced dose;

monitoring the patient's physiological state during physical exercise via at least one sensor comprised in the implantable neurostimulator; and

upon sensing a condition indicative of cessation of the physical exercise, delivering the enhanced dose to the vagus nerve, comprising:

monitoring the patient's physiological state throughout the delivering of the enhanced dose with the at least one sensor and establishing a heart response trajectory based on the patient's physiological state; and

continuing the delivering of the enhanced dose while the heart response trajectory remains elevated.

12. A method according to claim **11**, further comprising the steps of:

providing a heart rate sensor as the at least one sensor comprised in the implantable neurostimulator;

establishing a normative heart rate of the patient with the heart rate sensor as a mean heart rate sensed during non-exertion periods exclusive of the physical exercise;

periodically sensing the patient's heart rate with the heart rate sensor;

confirming that the patient is undergoing the physical exercise when the patient's heart rate gradually rises and is sustained at an elevated heart rate above the normative heart rate; and

subsequently confirming the cessation of the physical exercise when the patient's heart rate falls below the elevated heart rate by a threshold amount.

13. A method according to claim **11**, further comprising the steps of:

providing an accelerometer as the at least one sensor comprised in the implantable neurostimulator;

establishing a normative activity level of the patient with the accelerometer as a mean frequency of movement sensed during non-exertion periods exclusive of the physical exercise;

periodically sensing the patient's activity level with the accelerometer;

confirming that the patient is undergoing the physical exercise when the patient's activity level gradually rises and is sustained at an elevated activity level above the normative activity level accompanied by an increased frequency of movement; and

subsequently confirming the cessation of the physical exercise when the patient's activity level falls below the elevated activity level accompanied by a decreased frequency of movement by a threshold amount.

14. A method according to claim **11**, further comprising the steps of:

providing a minute ventilation sensor as the at least one sensor comprised in the implantable neurostimulator;

establishing a normative tidal volume and normative respiratory rate of the patient with the minute ventilation sensor sensed during non-exertion periods exclusive of the physical exercise;

periodically sensing the patient's tidal volume and respiratory rate with the minute ventilation sensor;

confirming that the patient is undergoing the physical exercise when the patient's tidal volume and respiratory rate gradually rise and are sustained at elevated levels respectively above the normative tidal volume and the normative respiratory rate; and

subsequently confirming the cessation of the physical exercise when the patient's tidal volume and respiratory rate fall below the respective elevated levels by a threshold amount.

15. A method according to claim **11**, further comprising the step of:

monitoring the patient's physiological state throughout the delivering of the enhanced dose, and upon sensing a condition indicative of an onset of tachyarrhythmia, intensifying the electrical therapeutic stimulation as specified in the operating mode.

16. A method according to claim **15**, further comprising the step of:

progressively intensifying the electrical therapeutic stimulation as specified in the operating mode as the tachyarrhythmia continues.

17. A method according to claim **15**, further comprising the step of:

maximizing the electrical therapeutic stimulation as specified in the operating mode when the tachyarrhythmia fails to respond to the intensified electrical therapeutic stimulation.

18. A method according to claim **11**, further comprising the step of:

delivering the maintenance dose to the vagus nerve via the pulse generator through a pair of helical electrodes following the delivering of the enhanced dose,

wherein storing the operating mode of the pulse generator further comprises parametrically defining the maintenance dose of the electrical therapeutic stimulation tuned to restore cardiac autonomic balance through intermittent and periodic electrical pulses.

19. A method according to claim **18**, further comprising the steps of:

providing a magnetically-actuated reed switch configured to control the pulse generator; and

controlling the pulse generator in response to a magnetic signal remotely applied to the reed switch, comprising at least one of:

switching between delivery of the enhanced dose and the maintenance dose;

triggering or increasing delivery of either the enhanced dose or the maintenance dose; and

decreasing or suspending delivery of either the enhanced dose or the maintenance dose.

20. A method according to claim **11**, wherein the maintenance dose comprises one or more of the following: a lower output current than the enhanced dose, a lower duty cycle than the enhanced dose, a lower frequency than the enhanced dose, or a shorter pulse width than the enhanced dose.

* * * * *

专利名称(译)	植入式神经刺激器实施的方法，通过迷走神经刺激增强运动后恢复		
公开(公告)号	US9643008	公开(公告)日	2017-05-09
申请号	US13/673795	申请日	2012-11-09
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	A61N1/36 A61B5/11 A61N1/362 A61B5/00		
CPC分类号	A61N1/36114 A61N1/36053 A61N1/36139 A61B5/1118 A61B5/4836 A61N1/3621		
代理机构(译)	FOLEY & Lardner的律师事务所		
其他公开文献	US20140135863A1		
外部链接	Espacenet USPTO		

摘要(译)

提供了一种植入式神经刺激器实现的方法，用于通过迷走神经刺激来增强运动后恢复。一种可植入的神经刺激器，包括脉冲发生器，其配置成以导致神经元纤维（包括患者的颈部迷走神经）内的动作电位的产生和传播（在传入和传出方向上）的方式递送电治疗刺激。操作模式存储在脉冲发生器中。通过连续循环，间歇和周期性电脉冲参数化地定义和调整增强剂量的电治疗刺激以防止或破坏快速性心律失常。在体育锻炼期间通过包括在可植入神经刺激器中的至少一个传感器监测患者的生理状态，并且在感测到指示停止体育锻炼的状况时，增强剂量被递送一段时间，增强剂量到迷走神经。 。