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(54) **IMPLANTABLE NEUROSTIMULATOR-IMPLEMENTED METHOD FOR ENHANCING HEART FAILURE PATIENT AWAKENING THROUGH VAGUS NERVE STIMULATION**

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CPC ..... ***A61N 1/36114*** (2013.01); ***A61B 5/0205*** (2013.01); ***A61B 5/4809*** (2013.01);
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See application file for complete search history.

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(57) **ABSTRACT**

An implantable neurostimulator-implemented method for managing tachyarrhythmias upon a patient's awakening from sleep through vagus nerve stimulation is provided. An implantable neurostimulator, including a pulse generator, is 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 the cervical vagus nerve of a patient. Operating modes of the pulse generator are stored. An enhanced dose of the electrical therapeutic stimulation is parametrically defined and tuned to prevent initiation of or disrupt tachyarrhythmia upon the patient's awakening from a sleep state through at least one of continuously-cycling, intermittent and periodic ON-OFF cycles of electrical pulses. Other operating modes, including a maintenance dose and a restorative dose are defined. The patient's physiological state is monitored via at least one sensor to detect
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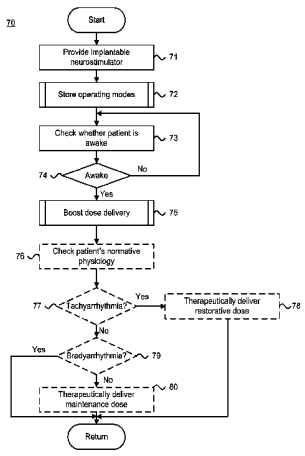

that patient's awakening, which activates the delivery of the enhanced dose.

**20 Claims, 5 Drawing Sheets**

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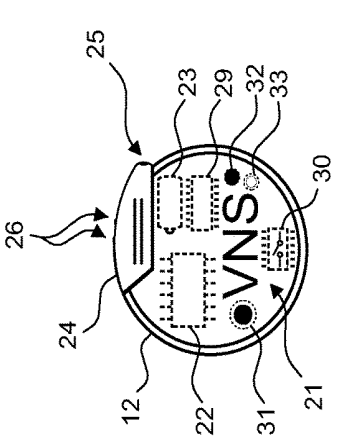


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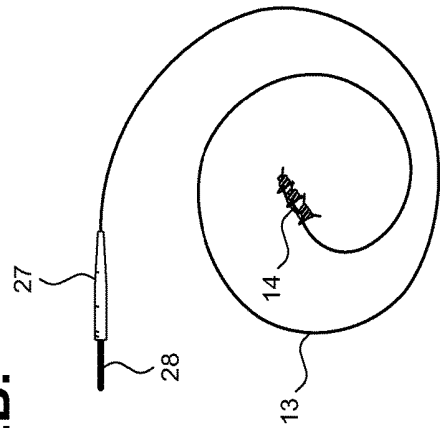


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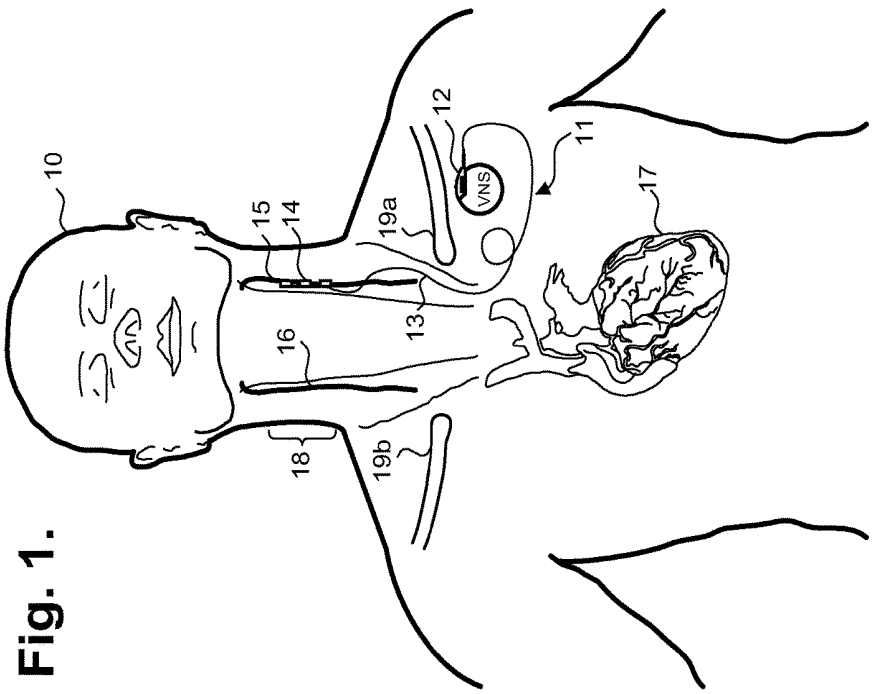
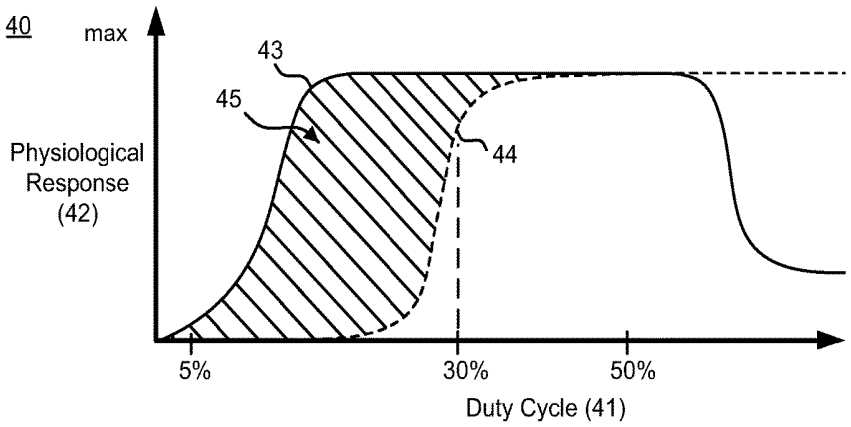



Fig. 1.

Fig. 3.

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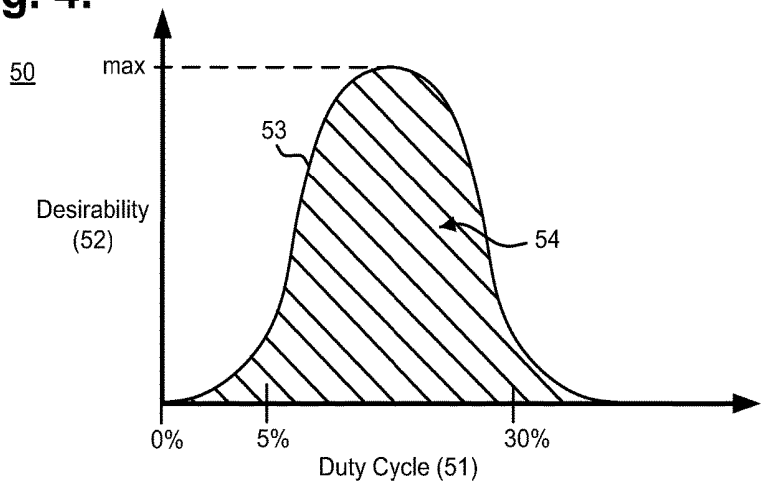


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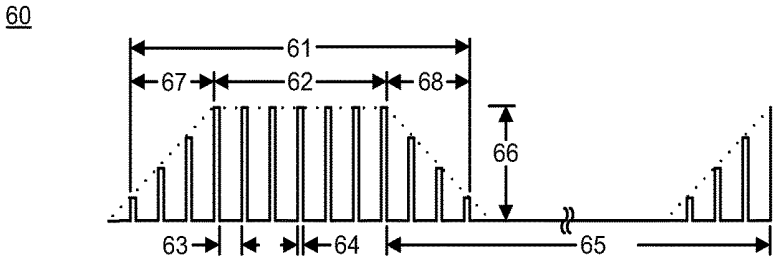

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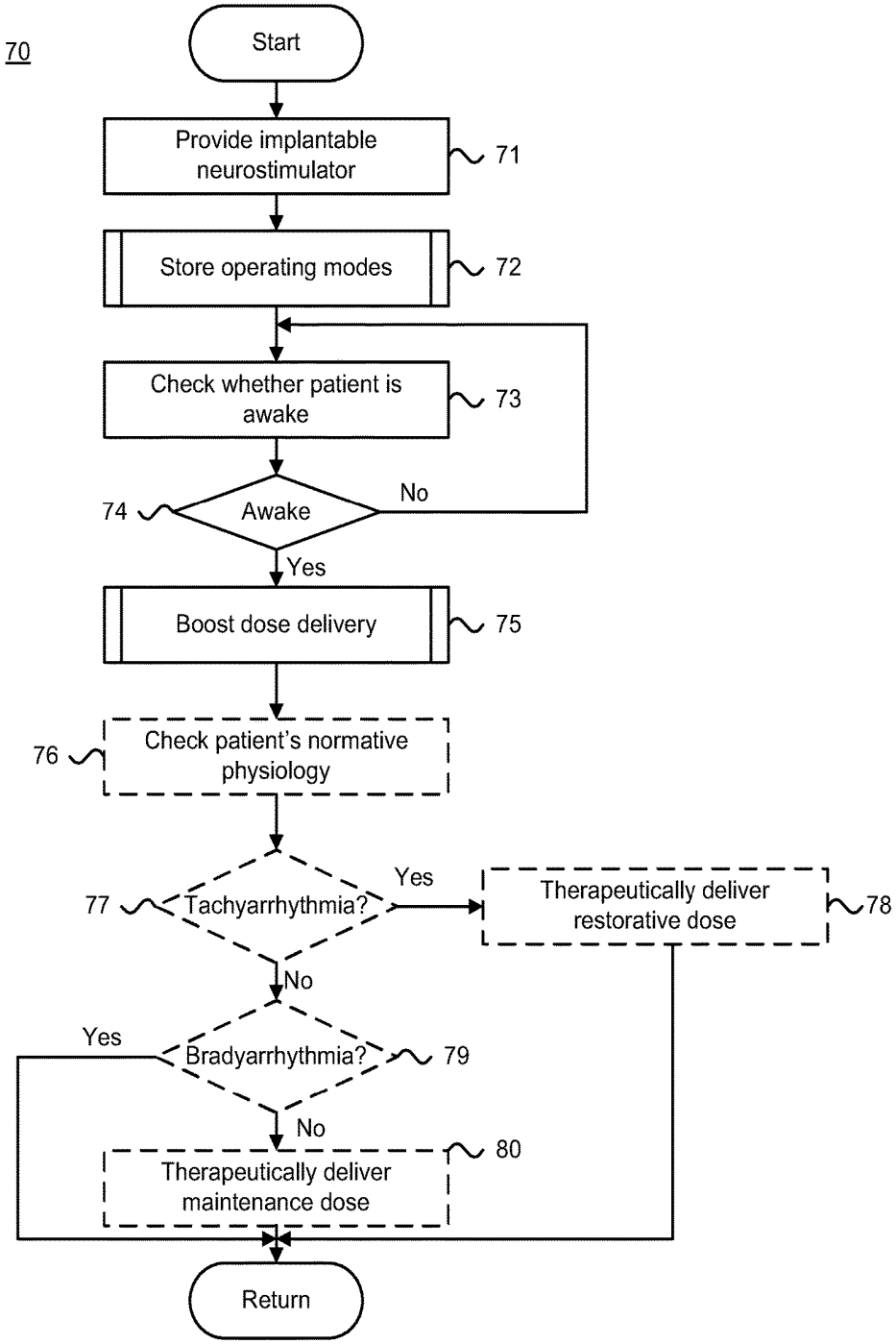

70
Start
Provide implantable neurostimulator
71
Store operating modes
72
Check whether patient is awake
73
74
Awake
No
Yes
Boost dose delivery
75
Check patient's normative physiology
76
77
Tachyarrhythmia?
Yes
Therapeutically deliver restorative dose
78
No
Yes
Bradyarrhythmia?
79
No
Therapeutically deliver maintenance dose
80
Return

Fig. 7.

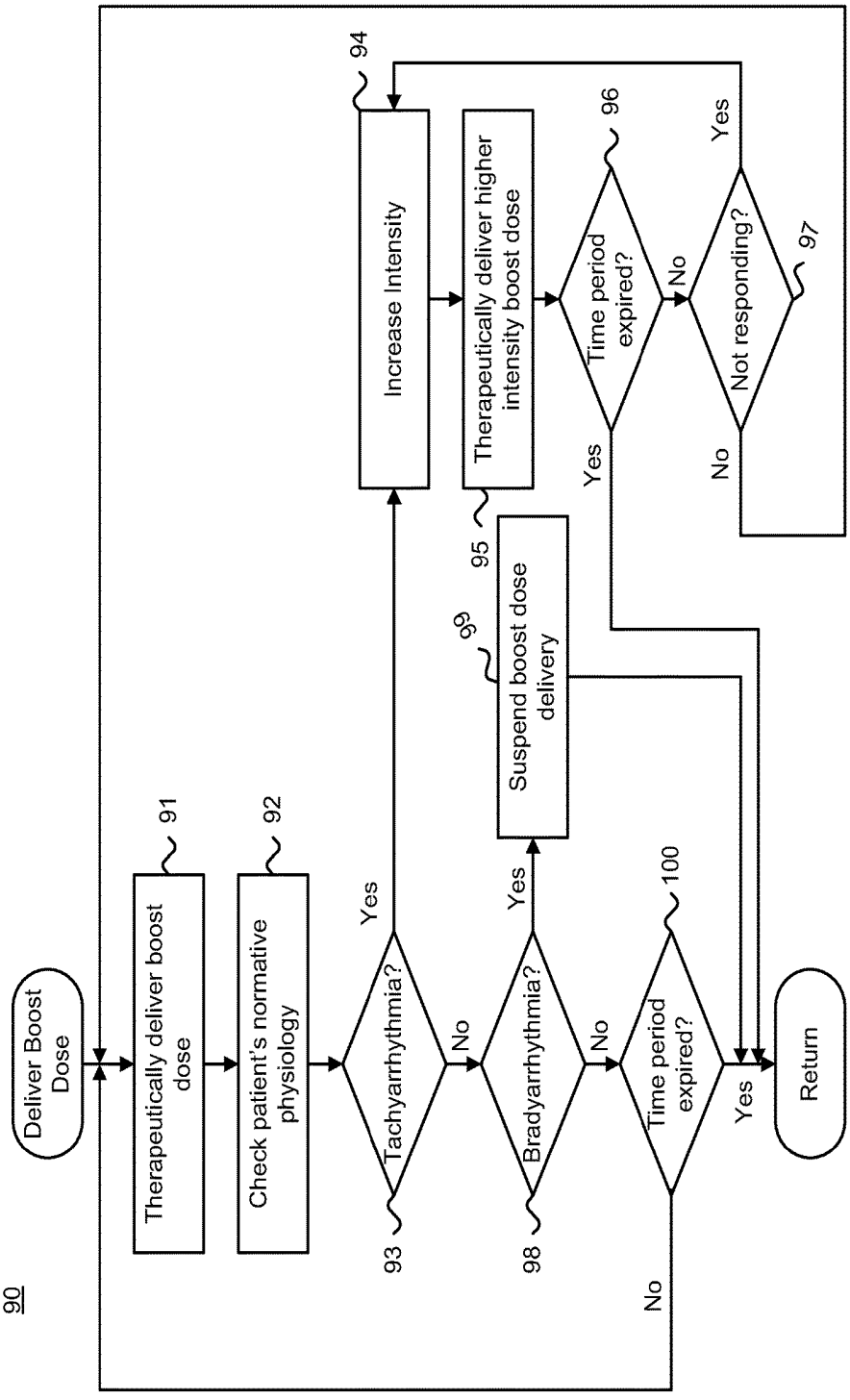
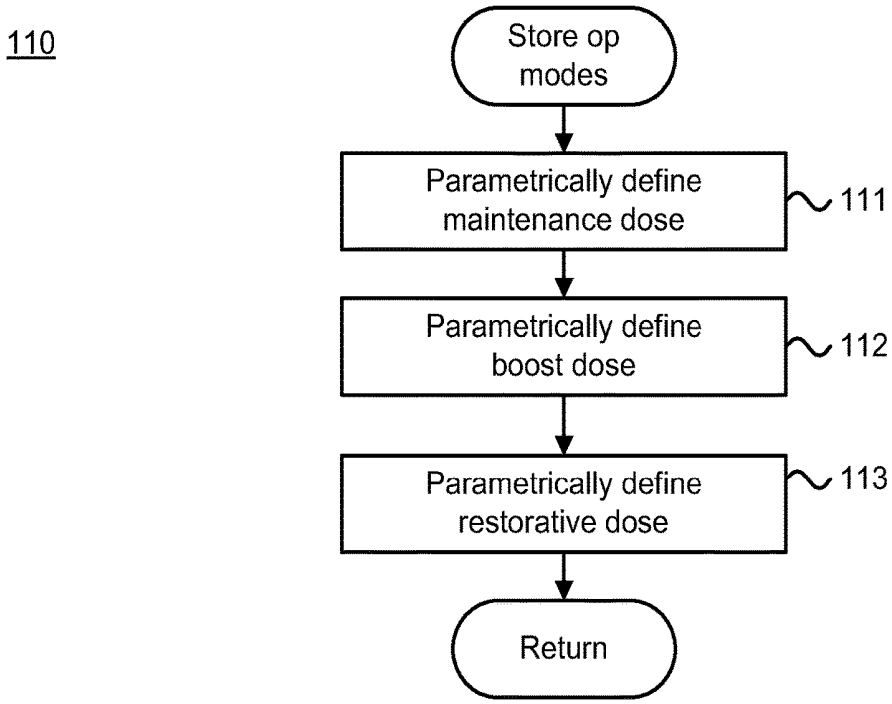

90
Deliver Boost Dose
Therapeutically deliver boost dose
91
Check patient's normative physiology
92
Tachyarrhythmia?
93
Yes
No
Increase Intensity
94
Therapeutically deliver higher intensity boost dose
95
Time period expired?
96
No
Yes
Not responding?
97
Yes
No
Bradyarrhythmia?
98
Yes
No
Suspend boost dose delivery
99
Time period expired?
100
Yes
No
Return

Fig. 8.


110
Store op modes
Parametrically define maintenance dose
111
Parametrically define boost dose
112
Parametrically define restorative dose
113
Return

# IMPLANTABLE NEUROSTIMULATOR-IMPLEMENTED METHOD FOR ENHANCING HEART FAILURE PATIENT AWAKENING THROUGH VAGUS NERVE STIMULATION

## CROSS-REFERENCE TO RELATED PATENT APPLICATIONS

This application is a continuation of U.S. application Ser. No. 15/410,316, filed Jan. 19, 2017, which is a continuation of U.S. application Ser. No. 15/212,744, filed Jul. 18, 2016, which is a continuation of U.S. application Ser. No. 14/547,342, filed Nov. 19, 2014, which is a continuation of U.S. application Ser. No. 13/673,811, filed Nov. 9, 2012, all of which are hereby incorporated by reference herein in their entireties.

## FIELD

This application relates in general to chronic cardiac dysfunction therapy and, in particular, to an implantable neurostimulator-implemented method for enhancing heart failure patient awakening 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.

The increased risk of tachyarrhythmias, particularly VT, in CHF patients is seen during the three-hour period following awakening from sleep, which is accompanied by a 2.5 times higher incidence of mortality. Tachyarrhythmias during awakening have been linked to a sympathetic activity surge that naturally occurs whenever a person is waking up as a part of the natural human circadian rhythm cycle. Sleep is characterized by the predominance of the parasympathetic system and a withdrawal of sympathetic activity, followed by a peak of sympathetic activity upon a person assuming an upright position and increasing activity level upon awakening. The surge of sympathetic activity increases heart rate, which in turn makes a CHF patient more vulnerable to the development of tachyarrhythmias that can degenerate into a life-threatening VF episode.



Other forms of non-sleep related 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. Despite these increased risks, the current standard of care for treating CCD patients still relies on palliative patient management, which recognizes the risk of tachyarrhythmias occurring upon patient awakening as an unavoidable side effect of natural circadian rhythm without specific care guidelines to lessen the risk.

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 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 ventricular tachycardia 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 at least in part 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 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 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 automatically applies an appropriate 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 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.

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 atrial fibrillation 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 ameliorate tachyarrhythmic risk in a heart failure patient during awakening.

## SUMMARY

Excessive sustained activation of the sympathetic nervous system has a deleterious effect on long-term cardiac performance and increases the risk of tachyarrhythmias during awakening. In general, bi-directional afferent and efferent neural stimulation through the vagus nerve can beneficially restore autonomic balance and improve long term clinical outcome. Upon sensing a patient's awakening, VNS can be delivered therapeutically through an implantable vagus neurostimulator and electrode lead to a patient in an enhanced dose for a fixed period of time, absent arrhythmogenesis. Upon the expiration of the fixed period, other VNS doses can be engaged, such as a maintenance dose, if no tachyarrhythmia is present, and a restorative dose, which is delivered when the patient experiences a tachyarrhythmic event.

One embodiment provides an implantable neurostimulator-implemented method for managing tachyarrhythmias through vagus nerve stimulation. An implantable neurostimulator, including a pulse generator, is 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 the cervical vagus nerve of a patient. Operating modes are stored in the pulse generator. An enhanced dose of the electrical therapeutic current is parametrically defined and tuned to prevent initiation of or disrupt tachyarrhythmia upon the patient's awakening from a sleep state through at least one of continuously-cycling, intermittent and periodic electrical pulses. A maintenance dose of the electrical therapeutic stimulation is parametrically defined and tuned to restore cardiac autonomic balance through continuously-cycling, intermittent and periodic electrical pulses to be delivered at a lower intensity, which could be a lower output current, lower duty cycle, lower frequency, or shorter pulse width, than the enhanced dose. A restorative dose of the electrical therapeutic stimulation is parametrically defined and tuned to prevent initiation of or disrupt tachyarrhythmia through periodic electrical pulses delivered at higher intensity, which could be higher output current, higher duty cycle, higher frequency, or longer pulse width, than the maintenance dose. The patient's physiological state is monitored using at least one sensor, such as an accelerometer to sense the patient's posture and movements, a minute ventilation sensor to monitor the patient's respiration, and a heart rate sensor to monitor the patient's heart rate. The patient's normative physiology is monitored via a physiological sensor included in the implantable neurostimulator, and upon sensing a condition indicative of tachyarrhythmia, the intensity of the enhanced dose can be increased. The increase can be progressive based on the patient's heart rate trajectory, with the intensity increasing multiple times as the tachyarrhythmia fails to respond to the VNS stimulation or the delivery of the enhanced dose can be maximized based on the patient's heart rate trajectory. If the physiological sensors detect a condition indicative of bradyarrhythmia, the enhanced dose is suspended. Upon an expiration of the period of time for delivery of the enhanced dose, the maintenance dose can be delivered if the patient is not experiencing a tachyarrhythmic episode at the moment. If the patient is experiencing tachyarrhythmia at the time the period for delivery ends, the restorative dose can be delivered.

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. In short term, the delivery of the enhanced dose following the patient's awakening helps decrease the risk of having a sudden cardiac death due to a diurnal peak in VT.

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 managing tachyarrhythmias upon awakening through vagus nerve stimulation, in accordance with one embodiment.

FIG. **7** is a flow diagram showing a routine for delivering an enhanced dose of VNS stimulation upon the patient's awakening for use with the method of FIG. **6**, in accordance with one embodiment.

FIG. **8** is a flow diagram showing a routine for storing operating modes for use with the method of FIG. **6**.

## 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. The imbalance is accompanied by pronounced elevation of basal heart rate arising from chronic sympathetic hyperactivation along the neurocardiac axis, which is exacerbated during awakening by the surge in sympathetic activity that is a part of natural human circadian rhythms.

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.

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 chronic cardiac dysfunction during patient awakening through therapeutic bi-directional vagal stimulation. 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. Pat. No. 8,600,505, entitled "Implantable Device For Facilitating Control Of Electrical Stimulation Of Cervical Vagus Nerves For Treatment Of Chronic Cardiac Dysfunction," U.S. Ser. No. 13/314,130, filed on Dec. 7, 2011, the disclosure of which is incorporated by reference, for basic patient control; and an electromagnetic controller, such as described in commonly-assigned U.S. Pat. No. 8,571,654, entitled "Vagus Nerve Neurostimulator With Multiple Patient-Selectable Modes For Treating Chronic Cardiac Dysfunction," Ser. No. 13/352,244, filed on Jan. 17, 2012, 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, the stimulation device **11** delivers VNS while the patient **10** is awake. 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. Upon patient awakening, an enhanced dose of VNS is delivered to counter the increased tachyarrhythmic risk caused by the natural circadian rhythm-triggered surge of sympathetic activity and increased heart rate. In a further embodiment, tachyarrhythmias outside of awakening 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. Pat. No. 8,688,212, entitled "Implantable Neurostimulator-Implemented Method for Managing Bradycardia through Vagus Nerve Stimulation," Ser. No. 13/554,656, filed on Jul. 20, 2012, the disclosure of which is incorporated by reference.

Both sympathetic and parasympathetic nerve 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. In a maintenance mode, the neurostimulator **12** is parametrically programmed to deliver continuously-cycling, intermittent and periodic ON-OFF cycles of VNS are delivered that produce action potentials in the underlying nerves that propagate bi-directionally. In a restorative mode, the neurostimulator **12** is parametrically programmed to deliver VNS tuned to prevent initiation of or disrupt tachyarrhythmia through continuously-cycling, intermittent and periodic ON-OFF cycles of VNS delivered at higher intensity, which could be higher output current, higher duty cycle, higher frequency, longer pulse width, or a combination of the foregoing parameters, than the maintenance dose are delivered in response to the onset or progression of tachyarrhythmias. In an enhanced mode, which is further described with reference to FIGS. **6** and **7**, the neurostimulator **12** is parametrically programmed to deliver the VNS tuned to prevent initiation of or disrupt tachyarrhythmia specifically upon patient awakening through continuously-cycling, intermittent and periodic ON-OFF cycles of VNS is delivered at delivered at a higher intensity than the maintenance mode, higher output current, higher duty cycle, higher frequency, longer pulse width, or a combination of the foregoing parameters.

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 monoflouride 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** can also contain 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 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 monitor whether the patient **10** is awake or asleep, as further described infra with reference to FIG. **6** and determine the presence of possible tachyarrhythmias, particularly VT.

In a further embodiment, the housing **21** contains a minute ventilation sensor **32** 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., the disclosure of which is incorporated by reference, measures the patient's respiratory rate and tidal volume, and calculates the patient's minute ventilation volume. The minute ventilation sensor **32** provides the minute ventilation volume to the control and logic circuitry as sensory inputs that can be used to determine whether the patient is awake.

In a still further embodiment, the housing **21** contains an accelerometer **33** that is electrically interfaced with the logic and control circuitry, which receives the patient's physical movement as sensory inputs. The minute ventilation sensor **32** may be combined into a blended sensor with at least one accelerometer **33**. The accelerometer **33** 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 **33** provides sensory inputs that can be used to determine the patient's posture and rate of movement and whether the patient has fallen or awakened from sleep. In a further embodiment, the accelerometer **33** can be located separately from the minute ventilation sensor **32**, either on the interior or exterior of the housing **21**.

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. Pat. Nos. 8,60,505 and 8,571,654, 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. Pat. No. 8,630,709, 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, 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 could 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 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 maintenance dose 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 a restorative dose at a higher level of intensity than the maintenance dose, which could be higher output current, higher duty cycle, higher frequency, longer pulse width, or a combination of the foregoing parameters, in response to the presence of tachyarrhythmias. Finally, the therapeutic doses also include an enhanced dose of VNS tuned to prevent initiation of or disrupt tachyarrhythmia upon awakening through continuously-cycling, intermittent and periodic ON-OFF cycles of VNS delivered at a higher intensity than the maintenance dose, which could be higher output current, higher duty cycle, higher frequency, longer pulse width, or a combination of the foregoing parameters, in response to the presence of tachyarrhythmias upon the patient's **10** awakening.

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. Pat. No. 8,577,458, 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, 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, published as US 2013/0158616 A1, pending, 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, published as US 2013/0158617 A1, pending, the disclosures of which are incorporated by reference. Finally, the neurostimulator **12** can be used to ameliorate heart rate increase and decrease tachyarrhythmic risk following exercise, such as 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 on Nov. 9, 2012, published as US 2014/0135864 A1, pending, the disclosure of which is incorporated by reference.

Therapeutically, VNS is delivered during the period following awakening 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, or following the patient's awakening from sleep, VNS is delivered 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. In the hours following awakening, the risk of tachyarrhythmia is even higher. Although delivered in an enhanced dose upon patient awakening and, in a further embodiment, in a maintenance dose while the patient is awake, 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 awakening 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.

While therapeutic VNS maintenance dose delivery can be suspended upon the occurrence of tachyarrhythmia and replaced with the delivery of a higher intensity VNS restorative dose that is tuned to prevent initiation of or disrupt tachyarrhythmia, neither of the doses are appropriate for the increased period of risk that a patient experiences upon waking up. The maintenance dose may be too low to prevent the occurrence of tachyarrhythmia during the diurnal peak, while the restorative dose may subject the patient to a high

dose of VNS needlessly on occasions that a tachyarrhythmic event does not occur. FIG. **6** is a flow diagram showing an implantable neurostimulator-implemented method for managing tachyarrhythmias upon the patient's **10** awakening through vagus nerve stimulation **70**, in accordance with one embodiment. The method **70** is implemented on the stimulation device **11**, the operation of which is parametrically defined through stored stimulation parameters and timing cycles. The method **70** can be used for treatment of both CHF and non-CHF patients suffering from other forms of chronic cardiac dysfunction.

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. In a further embodiment, the integrated heart rate sensor **31** could be omitted in lieu of other types of sensing mechanisms for measuring the patient's physiology.

The pulse generator stores a set of one or more operating modes (step **72**) that parametrically defines a low level maintenance dose, an enhanced dose, and a restorative dose of VNS stimulation, the latter two of which are higher in intensity than the maintenance dose, as further described infra with reference to FIG. **8**. A sleeping patient's **10** physiological state is regularly monitored to determine whether the patient **10** has awakened from sleep (step **73**). In a further embodiment, the risk of cardiac arrhythmias during or attendant to sleep, particularly sleep apneic episodes, can be managed by the implantable neurostimulator **12**, such as described in commonly-assigned U.S. Patent Application, entitled "Implantable Neurostimulator-Implemented Method For Managing Tachyarrhythmic Risk During Sleep Through Vagus Nerve Stimulation," Ser. No. 13/828,486, filed Mar. 14, 2013, published as US 2014/0277232 A1, pending, the disclosure of which is incorporated by reference. In one embodiment, heart rate is used to check the patient's physiology using the heart rate sensor **31**. A normative heart rate during sleep is generally considered to fall between 60 to 70 beats per minute (bpm). Upon awakening, the heart rate naturally rises to an awake range generally somewhere under 100 bpm, depending upon patient condition. The normative heart rate of the patient **10** is monitored and recorded periodically while asleep to determine whether the patient **10** is awakening.

In general, awakening is characterized by the gradual onset of an increased heart rate, which can be sensed by the neurostimulator **12**, 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 recorded during sleep, for instance, a heart rate that gradually increases over a seven-minute period and is then maintained for a non-transitory period of time, the patient **10** is considered to be awakening. In contrast, abrupt onset of increased heart rate could be indicative of a non-sinus tachyarrhythmia.

In a still further embodiment, a minute ventilation sensor **32** can be used to determine patient awakening. Minute ventilation is closely tied to heart rate during sleep, as ventilatory volume (tidal volume) and breathing frequency (respiratory rate) decrease synchronously, as does heart rate, as the patient falls asleep, then settles into a regular pattern. Tidal volume at rest is measured by the minute ventilation sensor **32**. 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 **32**. 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 activity. A normative activity level while asleep is established by determining means of the tidal volume and respiratory rate. 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 awakening. In a still further embodiment, the heart rate sensor **31** and the accelerometer **32** can be used in combination with the minute ventilation sensor **32**. Still other measures and indications of awakening are possible.

In a still further embodiment, the neurostimulator **12** can use a multiple forms of sensory data in determining whether the patient **10** has awakened. 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 **33** data, which would discount a rise in heart rate that occurs while the patient **10** remains recumbent and otherwise still. Other ways of preferentially weighting the data are possible.

If the physiological state indicates that the patient **10** has not awakened from sleep (step **74**), the patient's state is checked again periodically. If the monitored physiological state is indicative of the patient **10** having awakened (step **74**), therapeutic VNS, as parametrically defined by the enhanced dose operating mode, is delivered to at least one of the vagus nerves through continuously-cycling, intermittent and periodic electrical pulses to tuned to prevent initiation of or disrupt tachyarrhythmia upon the patient's awakening (step **75**), as further described infra with reference to FIG. **7**.

Following a completion of the enhanced dose delivery (step **75**), a set of optional follow-up stimulation doses can be delivered as follows. The patient's normative physiology is monitored (step **76**). If a condition indicative of tachyarrhythmia is present (step **77**), a restorative dose of VNS stimulation is initiated (step **78**), such as further described in the commonly-assigned U.S. Patent application, entitled "Implantable Neurostimulator-Implemented Method for Managing Tachyarrhythmia Through Vagus Nerve Stimulation," Ser. No. 13/673,766, filed Nov. 9, 2012, published as US 2014/0135862 A1, pending, the disclosure of which is incorporated by reference. Contrarily, in the absence of tachyarrhythmia, the presence of bradyarrhythmia is assessed (step **79**). If a condition indicative of bradyarrhythmia is detected (step **79**), the method **70** is terminated and the bradyarrhythmia is addressed, such as described in commonly-assigned U.S. Pat. No. 8,688,212, entitled "Implantable Neurostimulator-Implemented Method for Managing Bradycardia through Vagus Nerve Stimulation," Ser. No. 13/554,656, filed on Jul. 20, 2012, the disclosure of which is incorporated by reference. If a condition indicative of a bradyarrhythmia is absent (step **79**), a maintenance dose of VNS stimulation is initiated (step **80**), such as further described in the commonly-assigned U.S. Patent application, entitled "Implantable Neurostimulator-Implemented Method for Managing Tachyarrhythmia Through Vagus Nerve Stimulation," Ser. No. 13/673,766, filed Nov. 9, 2012, published as US 2014/0135862 A1, pending, the disclosure of which is incorporated by reference.

The enhanced dose of VNS stimulation helps ameliorate tachyarrhythmia vulnerability during awakening. FIG. **7** is a flow diagram showing the routine **90** for providing an enhanced dose that is engaged upon the patient's **10** awakening for use in the method **70** of FIG. **6**. An enhanced dose, which has a higher intensity than the maintenance dose, is therapeutically delivered (step **91**). In one embodiment, the enhanced dose is parametrically defined with a pulse width in the range of 250 to 500 μsec, delivering between 1.0 and 1.5 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.

The patient's **10** normative physiology is monitored during delivery of the enhanced dose (step **92**). The enhanced dose ameliorates, but does not fully eliminate, the risk of tachyarrhythmias. 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. If a condition indicative of tachyarrhythmia is detected (step **93**), the intensity of the enhanced dose is progressively increased (step **94**) and delivered (step **95**). The neurostimulator **12** checks whether the time period for the delivery of the enhanced dose has expired (step **96**), terminating the routine **90** upon the period's expiration. In one embodiment, a fixed period of one to three hours is used, although the time period can be adjusted by a physician. In a further embodiment, the time period can be extended if a tachyarrhythmic condition occurs.

If the time period has not expired (step **96**), the responsiveness of the tachyarrhythmia to the enhanced dose is assessed (step **97**). Non-responsiveness to the delivery of VNS stimulation can occur during 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. Depending on the patient's **10** heart response trajectory, the intensity of the enhanced dose can be progressively increased by the same or similar amount each cycle (step **94-97**), or, for life-threatening or paroxysmal arrhythmias, immediately increased to a strongly enhanced dose of significantly higher intensity (step **94**), due to the lack of time to ramp up the intensity progressively. The amount by which the intensity of the enhanced dose is progressively increased can also depend on the heart rate trajectory. In one embodiment, the strongly enhanced dose delivery (step **94**) maximizes the VNS stimulation, delivering the maximum intensity of stimulation that the neurostimulator **12** can produce.

If the tachyarrhythmia is responding to the enhanced dose delivery (step **97**), therapeutic delivery of the enhanced dose at default intensity is resumed (step **91**) upon the termination of the tachyarrhythmia. In a further embodiment, the intensity of the enhanced dose can be increased continuously, independently of the heart response trajectory, for the duration of the period of time.

On the other hand, as the delivery of the enhanced dose is both preventative and precautionary, heart rate could decrease in response to the enhanced dose delivery as an unintended side-effect. If a condition indicative of bradyarrhythmia is detected (step **98**), the enhanced dose delivery is suspended (step **99**), terminating the routine **90**.

Finally, in the absence of tachyarrhythmia (step **93**) or bradyarrhythmia (step **98**), the neurostimulator **12** checks whether the time period for delivery of the enhanced dose has expired (step **100**), terminating the routine **90** if the period has expired. Otherwise, enhanced dose delivery continues (step **91**).

In a still further embodiment, delivery of the enhanced, as well as the restorative 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. Pat. Nos. 8,600,505 and 8,571,654, 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. **8** is a flow diagram showing a routine **110** for storing operating modes for use with the method **70** of FIG. **6**. Three operating modes are stored, which include a maintenance dose of VNS tuned to restore cardiac autonomic balance (step **111**) through continuously-cycling, intermittent and periodic electrical pulses; an enhanced dose of VNS tuned to prevent initiation of or disrupt tachyarrhythmia upon awakening through continuously-cycling, intermittent and periodic ON-OFF cycles of VNS delivered at a higher intensity than the maintenance dose (step **112**); and a restorative dose tuned to prevent initiation of or disrupt tachyarrhythmia (step **113**) through periodic electrical pulses delivered at a 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, maintenance dose, or restorative 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 change in form and detail may be made therein without departing from the spirit and scope.

What is claimed is:

**1**. A method for aiding awakening-induced tachyarrhythmias through vagus nerve stimulation, comprising the steps of:

providing an implantable neurostimulator comprising a sensor and a pulse generator configured to deliver electrical therapeutic stimulation to a vagus nerve of a patient;

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

a first dose of the electrical therapeutic simulation comprising a first intensity; and

a second dose of the electrical therapeutic stimulation comprising a second intensity lower than the first intensity;

monitoring a physiological state of the patient to sense a patient's awakening from a sleep state via the sensor; and

upon sensing the patient's awakening, delivering the first dose to the vagus nerve.

**2**. A method according to claim **1**, further comprising delivering the second dose to the vagus nerve via the pulse generator through a pair of helical electrodes following the delivery of the first dose.

**3**. A method according to claim **1**, wherein the sensor comprises a heart rate sensor, the method further comprising the steps of:

establishing a normative heart rate of the patient with the heart rate sensor as a mean heart rate sensed during the sleep state;

sensing a heart rate of the patient with the heart rate sensor; and

confirming that the patient is awakening from the sleep state when the heart rate gradually rises and is sustained at an elevated heart rate above the normative heart rate.

**4**. A method according to claim **1**, wherein the sensor comprises an accelerometer, the method further comprising the steps of:

establishing a normative activity level of the patient with the accelerometer as a mean frequency of movement sensed during the sleep state;

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

confirming that the patient is awakening from the sleep state when the patient's activity level rises and is sustained at an elevated activity level above the normative activity level.

**5**. A method according to claim **1**, wherein the sensor comprises a minute ventilation sensor, the method further comprising the steps of:

establishing a normative tidal volume and normative respiratory rate of the patient with the minute ventilation sensor sensed during the sleep state;

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

confirming that the patient is awakening from the sleep state with the patient's tidal volume and respiratory rate rise and are sustained at elevated levels respectively above the normative tidal volume and the normative respiratory rate by a threshold amount.

**6**. A method according to claim **1**, further comprising monitoring the physiological state through delivery of the first dose and, upon sensing a condition indicative of an onset of tachyarrhythmia, intensifying the electrical therapeutic stimulation as specified in the operating mode.

**7**. A method according to claim **6**, further comprising progressively intensifying the electrical therapeutic stimulation as specified in the operating mode as the tachyarrhythmia continues.

**8**. A method according to claim **6**, further comprising increasing the electrical therapeutic stimulation to a highest level specified in the operating mode in response to the tachyarrhythmia failing to respond to the intensified electrical therapeutic stimulation.

**9**. A method according to claim **1**, further comprising extending a period of time of the first dose delivery based on a heart response trajectory of the patient determined by a processor of the neurostimulator using data from the sensor.

**10**. A method according to claim **1**, further comprising progressively intensifying the electrical therapeutic stimulation as specified in the operating mode independently of the patient's heart response trajectory.

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

electrically stimulating the vagus nerve after an expiration of a period of time, comprising the steps of:

monitoring the physiological state of the patient to detect a presence or an absence of the condition indicative of tachyarrhythmia;

upon detecting the presence of the condition indicative of the tachyarrhythmia after an expiration of the period of time, switching to delivering a third dose to the vagus nerve via the pulse generator; and

upon detecting the absence of the condition indicative of the tachyarrhythmia after an expiration of the period of time, switching to delivering the second dose to the vagus nerve via the pulse generator,

wherein the storing of the operating modes of the pulse generator further comprises defining the third dose of the electrical therapeutic simulation tuned to prevent initiation of or disrupt tachyarrhythmia.

**12**. A method according to claim **11**, wherein the third dose comprises periodic electrical pulses delivered at a higher intensity than the second dose.

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

defining the intensity of the first dose as comprising one or more of an output current, a duty cycle, a frequency, and a pulse width;

defining the second dose as comprising one or more of an output current lower than the first dose output current, a duty cycle lower than the first dose duty cycle, a frequency lower than the first dose frequency, and a pulse width shorter than the first dose pulse width; and

defining the third dose as comprising one or more of an output current higher than the second dose output current, a duty cycle higher than the second dose duty cycle, a frequency higher than the second dose frequency, and a pulse width longer than the second dose pulse width.

**14**. A method according to claim **11**, 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 by at least one of:

switching between delivery of the first dose, the second dose, and the third dose;

triggering or increasing delivery of either the first dose, the second dose, and the third dose; and

decreasing or suspending delivery of either of the first dose, the second dose, and the third dose.

**15**. A method according to claim **1**, further comprising titrating the electrical therapeutic stimulation when beginning or suspending delivery of the first dose.

**16**. A method according to claim **1**, wherein defining the first dose further comprises:

monitoring the patient's normative physiology during delivery of the first dose; and

suspending the electrical therapeutic stimulation as specified in the operating mode upon a presence of a bradyarrhythmia.

**17**. A neurostimulator system for aiding awakening-induced tachyarrhythmias through vagus nerve stimulation, comprising:

a sensor; and

a neurostimulator comprising a pulse generator configured to deliver electrical therapeutic stimulation to a patient's vagus nerve and a memory comprising instructions that cause the pulse generator to:

deliver a first dose of the electrical therapeutic stimulation at a first intensity;

deliver a second dose of the electrical therapeutic stimulation at a second intensity lower than the first intensity;

monitor the physiological state of the patient to sense a patient's awakening from a sleep state via the sensor; and

upon sensing the patient's awakening, delivering the first dose to the vagus nerve.

**18**. A system according to claim **17**, wherein the pulse generator further comprises a pair of helical electrodes configured to deliver the first dose and the second dose to the vagus nerve.

**19**. A system according to claim **17**, wherein the memory further comprises instructions that cause the pulse generator to monitor the physiological state throughout the delivery of the first dose and, upon sensing a condition indicative of an onset of tachyarrhythmia, intensifying the electrical therapeutic stimulation.

**20**. A system according to claim **17**, wherein the memory further comprises instructions that cause the pulse generator to:

electrically stimulate the cervical vagus nerve after an expiration of the period of time, comprising the steps of:

upon detecting the presence of the condition indicative of the tachyarrhythmia after an expiration of the period of time, switch to delivering a third dose to the vagus nerve via the pulse generator; and

upon detecting an absence of the condition indicative of the tachyarrhythmia after an expiration of the period of time, switch to delivering the second dose to the vagus nerve via the pulse generator,

wherein the storing of the operating modes of the pulse generator further comprises defining the third dose of the electrical therapeutic simulation tuned to prevent initiation of or disrupt tachyarrhythmia.

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| 专利名称(译) | 植入式神经刺激器实施的方法，用于增强心力衰竭患者通过迷走神经刺激觉醒 | | |
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| 代理机构(译) | FOLEY & Lardner的律师事务所 | | |
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摘要(译)

提供了一种植入式神经刺激器实施的方法，用于在患者通过迷走神经刺激从睡眠中苏醒时控制快速性心律失常。包括脉冲发生器的可植入神经刺激器被配置成以导致在包括患者的颈部迷走神经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）的方式递送电治疗刺激。存储脉冲发生器的操作模式。参数地定义和调整增强剂量的电治疗刺激，以防止患者从睡眠状态苏醒至电脉冲的连续循环，间歇和周期性开-关循环中的至少一个时引发或破坏快速性心律失常。定义了其他操作模式，包括维持剂量和恢复剂量。通过至少一个传感器监测患者的生理状态以检测患者的觉醒，其激活增强剂量的递送。