



US010384065B2

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

(10) **Patent No.:** **US 10,384,065 B2**  
(45) **Date of Patent:** **\*Aug. 20, 2019**

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

(58) **Field of Classification Search**  
CPC . A61B 5/4836; A61B 5/1118; A61N 1/36139; A61N 1/36053; A61N 1/3621; A61N 1/36114  
See application file for complete search history.

(71) Applicant: **LivaNova USA, Inc.**, Houston, TX (US)  
(72) Inventors: **Imad Libbus**, St. Paul, MN (US); **Badri Amurthur**, Los Gatos, CA (US); **Bruce H. Kenknight**, Maple Grove, MN (US)

(56) **References Cited**  
U.S. PATENT DOCUMENTS

5,330,507 A 7/1994 Schwartz  
5,522,854 A 6/1996 Ideker et al.  
(Continued)

(73) Assignee: **LivaNova USA, Inc.**, Houston, TX (US)  
(\* ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.  
This patent is subject to a terminal disclaimer.

FOREIGN PATENT DOCUMENTS

WO WO-93/21824 11/1993  
WO WO-2010/005482 A1 1/2010

OTHER PUBLICATIONS

US 8,315,702 B2, 11/2012, Chavan et al. (withdrawn)  
(Continued)

(21) Appl. No.: **15/585,958**  
(22) Filed: **May 3, 2017**

*Primary Examiner* — Alyssa M Alter  
(74) *Attorney, Agent, or Firm* — Foley & Lardner LLP

(65) **Prior Publication Data**  
US 2017/0296822 A1 Oct. 19, 2017

(57) **ABSTRACT**

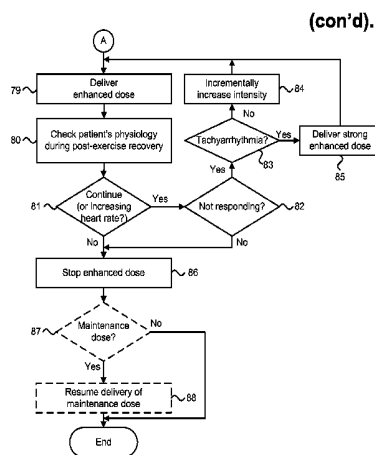
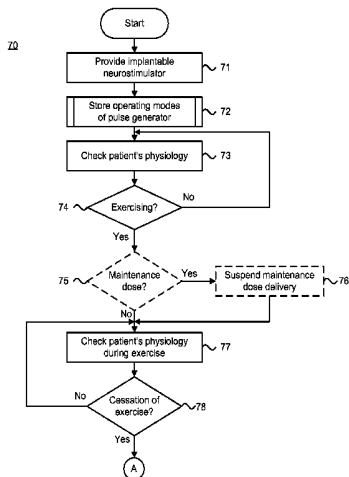
An implantable neurostimulator-implemented method for enhancing post-exercise recovery through vagus nerve stimulation is provided. An implantable neurostimulator, including a pulse generator configured to deliver electrical therapeutic stimulation in a manner that results in creation and propagation (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  
(Continued)

**Related U.S. Application Data**

(63) Continuation of application No. 13/673,795, filed on Nov. 9, 2012, now Pat. No. 9,643,008.

(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)



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)

(56)

### References Cited

#### U.S. PATENT DOCUMENTS

5,707,400	A	1/1998	Terry, Jr. et al.	7,418,292	B2	8/2008	Shafer
5,928,272	A	7/1999	Adkins et al.	7,452,800	B2	11/2008	Sosnowchik et al.
5,978,709	A	11/1999	Begemann et al.	7,480,532	B2	1/2009	Kieval et al.
6,006,134	A	12/1999	Hill et al.	7,481,759	B2	1/2009	Whitehurst et al.
6,266,564	B1	7/2001	Hill et al.	7,485,104	B2	2/2009	Kieval
6,354,991	B1	3/2002	Gross et al.	7,493,167	B2	2/2009	Hussein et al.
6,449,507	B1	9/2002	Hill et al.	7,499,742	B2	3/2009	Bolea et al.
6,473,644	B1	10/2002	Terry et al.	7,499,747	B2	3/2009	Kieval et al.
6,508,771	B1	1/2003	Padmanabhan et al.	7,499,748	B2	3/2009	Moffitt et al.
6,522,926	B1	2/2003	Kieval et al.	7,502,650	B2	3/2009	Kieval
6,600,954	B2	7/2003	Cohen et al.	7,542,800	B2	6/2009	Libbus et al.
6,610,713	B2	8/2003	Tracey	7,548,780	B2	6/2009	Libbus et al.
6,616,624	B1	9/2003	Kieval	7,551,958	B2	6/2009	Libbus et al.
6,622,041	B2	9/2003	Terry, Jr. et al.	7,561,922	B2	7/2009	Cohen et al.
6,652,449	B1	11/2003	Gross et al.	7,561,923	B2	7/2009	Libbus et al.
6,684,105	B2	1/2004	Cohen et al.	7,570,999	B2	8/2009	Libbus et al.
6,690,971	B2	2/2004	Schauerte et al.	7,582,053	B2	9/2009	Gross et al.
6,712,772	B2	3/2004	Cohen et al.	7,584,004	B2	9/2009	Caparso et al.
6,718,208	B2	4/2004	Hill et al.	7,587,238	B2	9/2009	Moffitt et al.
6,838,471	B2	1/2005	Tracey	7,606,622	B2	10/2009	Reeve
6,839,594	B2	1/2005	Cohen et al.	7,613,511	B2	11/2009	Wu et al.
6,850,801	B2	2/2005	Kieval et al.	7,613,516	B2	11/2009	Cohen et al.
6,862,480	B2	3/2005	Cohen et al.	7,616,990	B2	11/2009	Chavan et al.
6,892,098	B2	5/2005	Ayal et al.	7,617,003	B2	11/2009	Caparso et al.
6,896,651	B2	5/2005	Gross et al.	7,623,926	B2	11/2009	Rossing et al.
6,904,318	B2	6/2005	Hill et al.	7,627,384	B2	12/2009	Ayal et al.
6,907,295	B2	7/2005	Gross et al.	7,628,750	B2	12/2009	Cohen et al.
6,963,773	B2	11/2005	Waltman et al.	7,630,760	B2	12/2009	Libbus et al.
6,963,779	B1	11/2005	Shankar	7,634,315	B2	12/2009	Cholette
6,985,774	B2	1/2006	Kieval et al.	7,634,317	B2	12/2009	Ben-David et al.
7,010,345	B2	3/2006	Hill et al.	7,640,057	B2	12/2009	Libbus et al.
7,072,720	B2	7/2006	Puskas	7,647,101	B2	1/2010	Libbus et al.
7,123,961	B1	10/2006	Kroll et al.	7,647,114	B2	1/2010	Libbus
7,136,705	B1	11/2006	Park	7,650,190	B2	1/2010	Zhou et al.
7,139,607	B1	11/2006	Shelchuk	7,657,312	B2	2/2010	Pastore et al.
7,158,832	B2	1/2007	Kieval et al.	7,660,628	B2	2/2010	Libbus et al.
7,184,828	B2	2/2007	Hill et al.	7,664,548	B2	2/2010	Amurthur et al.
7,184,829	B2	2/2007	Hill et al.	7,668,602	B2	2/2010	Ben-David et al.
7,189,204	B2	3/2007	Ni et al.	7,672,633	B2	3/2010	Kondoh
7,218,964	B2	5/2007	Hill et al.	7,672,733	B2	3/2010	Zhou et al.
7,221,979	B2	5/2007	Zhou et al.	7,676,275	B1	3/2010	Farazi et al.
7,225,017	B1	5/2007	Shelchuk	7,684,866	B2	3/2010	Fowler et al.
7,225,019	B2	5/2007	Jahns et al.	7,689,286	B2	3/2010	Pastore et al.
7,237,320	B2	7/2007	Lam	7,711,415	B1	5/2010	Farazi et al.
7,245,967	B1	7/2007	Shelchuk	7,711,421	B2	5/2010	Shafer et al.
7,260,431	B2	8/2007	Libbus et al.	7,734,355	B2	6/2010	Cohen et al.
7,269,457	B2	9/2007	Shafer et al.	7,751,884	B2	7/2010	Ternes et al.
7,277,761	B2	10/2007	Shelchuk	7,769,442	B2	8/2010	Shafer
7,295,881	B2	11/2007	Cohen et al.	7,769,446	B2	8/2010	Moffitt et al.
7,305,265	B2	12/2007	Fukui	7,778,702	B2	8/2010	Ben-David et al.
7,321,793	B2	1/2008	Ezra et al.	7,778,703	B2	8/2010	Gross et al.
7,324,853	B2	1/2008	Ayal et al.	7,778,711	B2	8/2010	Ben-David et al.
7,336,997	B2	2/2008	Fukui	7,783,353	B2	8/2010	Libbus et al.
7,346,398	B2	3/2008	Gross et al.	7,797,041	B2	9/2010	Libbus et al.
7,387,603	B2	6/2008	Gross et al.	7,801,603	B2	9/2010	Westlund et al.
7,389,149	B2	6/2008	Rossing et al.	7,801,604	B2	9/2010	Brockway et al.
7,395,119	B2	7/2008	Hagen et al.	7,801,614	B2	9/2010	Rossing et al.
7,403,819	B1	7/2008	Shelchuk et al.	7,805,193	B2	9/2010	Libbus et al.
				7,805,203	B2	9/2010	Ben-David et al.
				7,813,805	B1	10/2010	Farazi
				7,813,812	B2	10/2010	Kieval et al.
				7,835,797	B2	11/2010	Rossing et al.
				7,840,266	B2	11/2010	Libbus et al.
				7,840,271	B2	11/2010	Kieval et al.
				7,844,346	B2	11/2010	Cohen et al.
				7,848,812	B2	12/2010	Crowley et al.
				7,848,816	B1	12/2010	Wenzel et al.
				7,869,869	B1	1/2011	Farazi
				7,885,709	B2	2/2011	Ben-David
				7,885,711	B2	2/2011	Ben-Ezra et al.
				7,890,185	B2	2/2011	Cohen et al.
				7,894,907	B2	2/2011	Cowan et al.
				7,904,151	B2*	3/2011	Ben-David ..... A61N 1/36114 607/2
				7,904,175	B2	3/2011	Scott et al.
				7,904,176	B2	3/2011	Ben-Ezra et al.
				7,908,008	B2	3/2011	Ben-David et al.
				7,916,013	B2	3/2011	Stevenson
				7,925,342	B2	4/2011	Amurthur et al.

(56)

## References Cited

## U.S. PATENT DOCUMENTS

- 7,925,352 B2 4/2011 Stack et al.  
7,974,693 B2 7/2011 Ben-David et al.  
8,005,542 B2 8/2011 Ben-Ezra et al.  
8,005,545 B2 8/2011 Ben-David et al.  
8,036,745 B2 10/2011 Ben-David et al.  
8,060,197 B2 11/2011 Ben-David et al.  
8,065,021 B2 11/2011 Gross et al.  
8,083,663 B2 12/2011 Gross et al.  
8,116,881 B2 2/2012 Cohen et al.  
8,131,362 B2 3/2012 Moffitt et al.  
8,160,701 B2 4/2012 Zhao et al.  
8,160,705 B2 4/2012 Stevenson et al.  
8,195,290 B2 6/2012 Brockway et al.  
8,224,436 B2 7/2012 Libbus et al.  
8,249,711 B2 8/2012 Libbus et al.  
8,369,943 B2 2/2013 Shuros et al.  
8,386,038 B2 2/2013 Bianchi et al.  
8,401,640 B2 3/2013 Zhao et al.  
8,417,354 B2 4/2013 Zhang et al.  
8,571,654 B2 10/2013 Libbus et al.  
8,577,458 B1 11/2013 Libbus et al.  
8,600,505 B2 12/2013 Libbus et al.  
8,634,921 B2 1/2014 Chavan et al.  
8,688,212 B2 4/2014 Libbus et al.  
8,918,190 B2 12/2014 Libbus et al.  
9,452,290 B2 9/2016 Libbus et al.  
2002/0107553 A1 8/2002 Hill et al.  
2003/0018113 A1 1/2003 Nakahama et al.  
2003/0040774 A1 2/2003 Terry et al.  
2003/0099373 A1 5/2003 Joo et al.  
2003/0099377 A1 5/2003 Hanawa  
2003/0153954 A1 8/2003 Park et al.  
2003/0171781 A1 9/2003 Florio et al.  
2004/0110549 A1 6/2004 Pope et al.  
2004/0110550 A1 6/2004 Pope et al.  
2004/0199210 A1 10/2004 Shelchuk  
2004/0210261 A1 10/2004 King et al.  
2004/0215265 A1 10/2004 Keizer  
2005/0011805 A1 1/2005 Lyons et al.  
2005/0049655 A1 3/2005 Boveja et al.  
2005/0065553 A1 3/2005 Ezra et al.  
2005/0125044 A1 6/2005 Tracey  
2005/0131467 A1 6/2005 Boveja  
2005/0165465 A1 7/2005 Pianca et al.  
2005/0267542 A1 12/2005 David et al.  
2006/0015153 A1 1/2006 Gliner et al.  
2006/0019764 A1 1/2006 Gegelys  
2006/0100668 A1 5/2006 Ben-David et al.  
2006/0190053 A1 8/2006 Dobak, III  
2006/0206155 A1 9/2006 Ben-David et al.  
2006/0253161 A1 11/2006 Libbus et al.  
2007/0067004 A1 3/2007 Boveja et al.  
2007/0093870 A1 4/2007 Maschino  
2007/0179543 A1 8/2007 Ben-David et al.  
2007/0213773 A1 9/2007 Hill et al.  
2007/0233194 A1 10/2007 Craig  
2007/0255320 A1 11/2007 Inman et al.  
2007/0276453 A1 11/2007 Hill et al.  
2008/0015659 A1 1/2008 Zhang et al.  
2008/0021503 A1 1/2008 Whitehurst et al.  
2008/0033511 A1 2/2008 Dobak  
2008/0051839 A1 2/2008 Libbus et al.  
2008/0058874 A1 3/2008 Westlund et al.  
2008/0061240 A1 3/2008 Heuft  
2008/0091240 A1 4/2008 Ben-David et al.  
2008/0132983 A1 6/2008 Cohen et al.  
2008/0147140 A1 6/2008 Ternes et al.  
2008/0183258 A1 7/2008 Inman  
2008/0243196 A1 10/2008 Libbus et al.  
2008/0319513 A1 12/2008 Pu et al.  
2009/0024186 A1 1/2009 Brockway et al.  
2009/0030493 A1 1/2009 Colborn et al.  
2009/0118777 A1 5/2009 Iki et al.  
2009/0124848 A1 5/2009 Miazga  
2009/0149900 A1 6/2009 Moffitt et al.  
2009/0248097 A1 10/2009 Tracey et al.  
2009/0270953 A1 10/2009 Ecker et al.  
2009/0275956 A1 11/2009 Burnes et al.  
2010/0010556 A1 1/2010 Zhao et al.  
2010/0010603 A1 1/2010 Ben-David et al.  
2010/0016919 A1 1/2010 Hill et al.  
2010/0042173 A1 2/2010 Farazi et al.  
2010/0114197 A1 5/2010 Burnes et al.  
2010/0114203 A1 5/2010 Burnes et al.  
2010/0114227 A1 5/2010 Cholette et al.  
2010/0174341 A1 7/2010 Bolea et al.  
2010/0286740 A1 11/2010 Libbus et al.  
2010/0331908 A1 12/2010 Farazi  
2011/0015692 A1 1/2011 Libbus et al.  
2011/0082514 A1 4/2011 Libbus et al.  
2011/0098796 A1 4/2011 Ben-David et al.  
2011/0224749 A1 9/2011 Ben-David et al.  
2011/0257708 A1 10/2011 Kramer et al.  
2011/0313488 A1 12/2011 Hincapie Ordenez et al.  
2012/0143286 A1 6/2012 Hahn et al.  
2012/0172742 A1 6/2012 Arcot-Krishnamurthy et al.  
2012/0185007 A1 7/2012 Ziegler et al.  
2012/0185010 A1 7/2012 Zhou et al.  
2012/0192874 A1 8/2012 Bolea et al.  
2012/0271374 A1 10/2012 Nelson et al.  
2012/0303080 A1 11/2012 Ben-David et al.  
2013/0158616 A1 6/2013 Libbus et al.  
2013/0158617 A1 6/2013 Libbus et al.  
2013/0158618 A1 6/2013 Libbus et al.  
2013/0238047 A1 9/2013 Libbus et al.  
2013/0289646 A1 10/2013 Libbus et al.  
2014/0025132 A1 1/2014 Libbus et al.  
2014/0135862 A1 5/2014 Libbus et al.  
2014/0135863 A1 5/2014 Libbus et al.  
2014/0135864 A1 5/2014 Libbus et al.  
2014/0228905 A1 8/2014 Bolea  
2014/0277232 A1 9/2014 Libbus et al.  
2015/0073511 A1 3/2015 Libbus et al.  
2015/0073512 A1 3/2015 Libbus et al.  
2015/0094962 A1 4/2015 Hoegh et al.  
2015/0119956 A1 4/2015 Libbus et al.  
2015/0119959 A1 4/2015 Libbus et al.  
2015/0196762 A1 7/2015 Amurthur et al.  
2015/0273214 A1 10/2015 Kenknight et al.  
2015/0306394 A1 10/2015 Libbus et al.  
2015/0306395 A1 10/2015 Libbus et al.  
2015/0321001 A1 11/2015 Libbus et al.

## OTHER PUBLICATIONS

- Zhang, et al., "Chronic Vagus Nerve Stimulation Improves Autonomic Control and Attenuates Systemic Inflammation and Heart Failure Progression in a Canine High-Rate Pacing Model," *Journal of the American Heart Association, Circ Heart Fail*, 2, pp. 692-699 (2009).  
Abraham, et al., "Devices in the management of advanced, chronic heart failure," *Nature Reviews*, vol. 10, pp. 98-110 (Feb. 2013) (Published online Dec. 11, 2012).  
Adamson, et al., "Continuous Autonomic Assessment in Patients with Symptomatic Heart Failure: Prognostic Value of Heart Rate Variability Measured by an Implanted Cardiac Resynchronization Device," *Circulation, Journal of the American Heart Association*, 110, pp. 2389-2394 (2004).  
Agostoni, et al., "Functional and Histological Studies of the Vagus Nerve and its Branches to the Heart, Lungs and Abdominal Viscera in the Cat," *J. Physiol.* 135, pp. 182-205 (1957).  
Ajani, et al., "Prevalence of High C-Reactive Protein in Persons with Serum Lipid Concentrations within Recommended Values," *Chemical Chemistry*, 50:9, pp. 1618-1622 (2004).  
Akiyama, et al., "Effects of right and left vagal stimulation on left ventricular acetylcholine levels in the cat," *Acta Physiol Scand*, 172, pp. 11-16 (2001).  
Anand, et al., "C-Reactive Protein in Heart Failure: Prognostic Value and the Effect of Valsartan," *Circulation, Journal of the American Heart Association*, 112, pp. 1428-1434 (2005).

(56) **References Cited**

## OTHER PUBLICATIONS

- Anholt, et al., "Recruitment and blocking properties of the CardioFit stimulation lead," *Journal of Neural Engineering*, 8, pp. 1-6, (2011).
- Ardell, et al.; "Selective vagal innervation of sinoatrial and atrioventricular nodes in canine heart," *Am. J. Physiol.* 251 (Heart Circ. Physiol. 20), pp. H764-H773 (1986).
- Armour, "Cardiac neuronal hierarchy in health and disease," *Am J Physiol Regul Integr Comp Physiol*, 287, pp. R262-R271 (2004).
- Armour, "Myocardial ischaemia and the cardiac nervous system," *Cardiovascular Research*, 41, pp. 41-54 (1999).
- Armour, "The little brain on the heart," *Cleveland Clinic Journal of Medicine*, vol. 74, supp. 1, pp. S48-S51 (Feb. 2007).
- Armour, et al., "Functional anatomy of canine cardiac nerves," *Acta anat.*, 91, pp. 510-528 (1975).
- Armour, et al., "Localized myocardial responses to stimulation of small cardiac branches of the vagus," *American Journal of Physiology*, vol. 228, No. 1 pp. 141-148 (Jan. 1975).
- Armour, JA, "Potential clinical relevance of the 'little brain' on the mammalian heart," *Experimental Physiology*, vol. 1 93, No. 2, pp. 165-176 (Feb. 2008). Online Publication Date: Nov. 2, 2007. Available at: <http://ep.physoc.org/content/93/2/165.long>.
- Asala, et al., "An electron microscope study of vagus nerve composition in the ferret," *Anat Embryol*, 175, pp. 247-253 (1986).
- Aukrust, et al., "Inflammatory and anti-inflammatory cytokines in chronic heart failure: Potential therapeutic implications," *Annals of Medicine*, 37, pp. 74-85 (2005).
- Author Unknown, "Nerve fiber—Types and Function," [www.boddunan.com](http://www.boddunan.com) Available at [www.boddunan.com/education/20-medicine-a-surgery/12730-nerve-fiber-types-and-function.html](http://www.boddunan.com/education/20-medicine-a-surgery/12730-nerve-fiber-types-and-function.html) (Apr. 19, 2010).
- Author Unknown, American Diabetes Association, "Standards of Medical Care in Diabetes—2012," *Diabetes Care*, vol. 35, supplement 1, pp. S11-S63 (Jan. 2012).
- Author Unknown, Staff of ADInstruments, "Principles of Nerve Stimulation," Application Note, ADInstruments (Apr. 2002).
- Bae, et al., "Gliosis in the Amygdala Following Myocardial Infarction in the Rat," *J Vet Med Sci*, 72(8), pp. 1041-1045 (2010).
- Bernik, et al., "Pharmacological Stimulation of the Cholinergic Antiinflammatory Pathway," *J. Exp. Med*, vol. 195, No. 6, pp. 781-788 (Mar. 18, 2002).
- Berthoud, et al., "Functional and chemical anatomy of the afferent vagal system," *Autonomic Neuroscience: Basic and Clinical*, 85, pp. 1-17 (2000).
- Bhagat, et al., "Differential Effect of Right and Left Vagal Stimulation on Right and Left Circumflex Coronary Arteries," *S A Medical Journal*, 50, pp. 1591-1594 (1976).
- Biasucci, et al., "Elevated Levels of C-Reactive Protein at Discharge in Patients with Unstable Angina Predict Recurrent Instability," *Circulation, Journal of the American Heart Association*, 99, pp. 855-860 (1999).
- Bibeovski, et al., "Evidence for impaired vagus nerve activity in heart failure," *Heart Fail Rev*, 16, pp. 129-135 (2011).
- Bibeovski, et al., "Ganglionic Mechanisms Contribute to Diminished Vagal Control in Heart Failure," *Circulation, Journal of the American Heart Association*, 99, pp. 2958-2963 (1999).
- Bilgutay, et al., "Vagal Tuning a new concept in the treatment of supraventricular arrhythmias, angina pectoris, and heart failure," *Journal of Thoracic and Cardiovascular Surgery*, vol. 56, No. 1, pp. 71-82 (Jul. 1968).
- Binkley, et al., "Parasympathetic Withdrawal is an Integral Component of Autonomic Imbalance in Congestive Heart Failure: Demonstration in Human Subjects and Verification in a Paced Canine Model of Ventricular Failure," *JACC*, vol. 18, No. 2, pp. 464-472 (Aug. 1991).
- Bois, et al., "Mode of action of bradycardic agent, S 16257, on ionic currents of rabbit sinoatrial node cells," *Abstract, British Journal of Pharmacology*, 118(4):1051-7 (1996).
- Bonaz, et al., "Vagus nerve stimulation: From epilepsy to the cholinergic anti-inflammatory pathway," *Neurogastroenterology & Motility*, pp. 1-14 (2013).
- Borggreve, et al., "Vagal Stimulation Devices," *ESC Congress 2010* (2010).
- Borovilkova, et al., "Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin," *Nature*, vol. 405, pp. 458-462 (May 25, 2000).
- Brack, et al., "Mechanisms underlying the autonomic modulation of ventricular fibrillation initiation tentative prophylactic properties in vagus nerve stimulation on malignant arrhythmias in heart failure," *Heart Fail Rev* (Published online Jun. 8, 2012).
- Bronzino, "Biomedical Engineering Fundamentals," CRC Press, Chapter 30, pp. 30-10-30-15 (Apr. 2006).
- Buschman, et al., "Heart Rate Control via Vagus Nerve Stimulation," *Neuromodulation*, vol. 9, No. 3, pp. 214-220 (2006).
- Butterwick, et al., "Tissue Damage by Pulsed Electrical Stimulation," *IEEE Transactions on Biomedical Engineering*, vol. 54, No. 12, pp. 2261-2267 (Dec. 2007).
- Calkins, et al., "Comparison of Responses to Isoproterenol and Epinephrine During Head-Up Tilt in Suspected Vasodepressor Syncope," *The American Journal of Cardiology*, vol. 67 pp. 207-209 (Jan. 15, 1991).
- Castoro et al., "Excitation properties of the right cervical vagus nerve in adult dogs," *Experimental Neurology*, vol. 227, iss. 1, pp. 62-68 (Jan. 2011). Online Publication Date: Sep. 17, 2010. Available at: <http://www.sciencedirect.com/science/article/pii/S001448861000347X>.
- Chapleau, et al., "Methods of assessing vagus nerve activity and reflexes," *Heart Fail Rev*, 16, pp. 109-127 (2011).
- Chen, et al., "National and Regional Trends in Heart Failure Hospitalization and Mortality Rates for Medicare Beneficiaries, 1998-2008," *JAMA*, vol. 306, No. 15 (Oct. 19, 2011).
- Chen, et al., "Role of Atrial Electrophysiology and Autonomic Nervous System in Patients with Supraventricular Tachycardia and Paroxysmal Atrial Fibrillation," *J Am Coll Cardiol*, vol. 32, No. 3, pp. 732-738 (Sep. 1998).
- Cheng, et al., "Long-term Outcomes in Individuals with Prolonged PR Interval or First-Degree Atrioventricular Block," *JAMA*, vol. 301, No. 24 pp. 2571-2577 (Jun. 24, 2009).
- Chiou, et al., "Effects of Continuous Enhanced Vagal Tone and Dual Atrioventricular Node and Accessory Pathways," *Circulation, Journal of the American Heart Association*, 107, pp. 2583-2588 (2003).
- Cohen, et al., "Histopathology of the stimulated Vagus nerve: Primum non nocere," *Heart Fail Rev*, 16, pp. 163-169 (2011).
- Colombo, et al., "Comparison between spectral analysis and the phenylephrine methods for the assessment of baroreflex sensitivity in chronic heart failure," *Clinical Science*, 97, pp. 503-513 (1999).
- Cryan, et al., "Animal models and mood disorders: recent developments," *Current Opinion in Psychiatry*, 20, pp. 1-7 (2007).
- Das, "Vagal nerve stimulation in prevention and management of coronary heart disease," *World J. Cardiol*, 3(4), pp. 105-110 (Apr. 26, 2011).
- De Castro, et al., "Parasympathetic-mediated atrial fibrillation during tilt test associated with increased baroreflex sensitivity," *The European Society of Cardiology, Europace*, 8, pp. 349-351 (2006).
- De Ferrari et al., "Chronic vagus nerve stimulation: a new and promising therapeutic approach for chronic heart failure," *European Heart Journal*, vol. 32, iss. 7, pp. 847-855 (Apr. 2011). Online publication date: Oct. 28, 2010. Available at: <http://eurheartj.oxfordjournals.org/content/32/7/847.long>.
- De Ferrari, et al., "Baroreflex Sensitivity Predicts Long-Term Cardiovascular Mortality After Myocardial Infarction Even in Patients with Preserved Left Ventricular Function," *Journal of the American College of Cardiology*, vol. 50, No. 24, pp. 2285-2290 (2007).
- De Ferrari, et al., "Chronic Vagal Stimulation in Patients with Congestive Heart Failure," 31st Annual International Conference of the IEE EMBS (2009).
- De Ferrari, et al., "Vagus nerve stimulation: from pre-clinical to clinical application: challenges and future directions," *Heart Fail Rev*, 16, pp. 195-203 (2011) (Published Online Dec. 17, 2010).
- De Jonge, et al., "Stimulation of the vagus nerve attenuates macrophage activation by activating the Jak2-STAT3 signaling pathway," *Nature Immunology*, vol. 6, No. 8, pp. 844-852 (Aug. 2005).

(56)

## References Cited

## OTHER PUBLICATIONS

- Desai, et al., "Pharmacologic modulation of parasympathetic activity in heart failure," *Heart Fail Rev*, 16, pp. 179-193 (Published online: Oct. 6, 2010) (2011).
- Dickerson, et al., "Parasympathetic neurons in the cranial medial ventricular fat pad on the dog heart selectively decrease ventricular contractility," *Journal of the Autonomic Nervous System*, 70, pp. 129-141 (1998).
- Dunlap, et al., "Mechanisms of altered vagal control in heart failure: influence of muscarinic receptors and acetylcholinesterase activity," *Am J Physiol Heart Circ Physiol*, 285, pp. H1632-H1640 (Jun. 26, 2003).
- Elsenbruch, et al., "Heart Rate Variability During Waking and Sleep in Healthy Males and Females," *Sleep*, vol. 22, No. 8, pp. 1067-1071 (1999).
- Euler, et al., "Acetylcholine release by a stimulus train lowers atrial fibrillation threshold," *Am. J Physiol.* 253 (Heart Circ. Physiol., 22), pp. H863-H868 (1987).
- Evans, et al., "Histological and functional studies on the fibre composition of the vagus nerve of the rabbit," *Journal of Anatomy*, 130, pp. 139-151 (1954).
- Fallen, "Vagal Afferent Stimulation as a Cardioprotective Strategy? Introducing the Concept," *A.N.E.*, vol. 10, No. 4 (Oct. 2005).
- Fan, et al., "Transvenous vagus nerve stimulation: A potential heart failure therapy is feasible in humans," *JACC*, vol. 55, issue 10A, pp. E152-E153 (2010).
- Fazan, et al., "Diabetic Peripheral Neuropathies: A Morphometric Overview," *Int. J. Morphol.*, 28(1), pp. 51-64 (2010).
- Feinauer, et al., "Ouabain enhances release of acetylcholine in the heart evoked by unilateral vagal stimulation," *Arch Pharmacol*, 333, pp. 7-12 (1986).
- Fonarow, et al., "Incremental Reduction in Risk of Death Associated with Use of Guideline-Recommended Therapies in Patients with Heart Failure: A Nested Case-Control Analysis of Improve HF," *J Am Heart Assoc*, 1, pp. 16-26 (2012).
- Ford, et al., "The effects of electrical stimulation of myelinated and non-myelinated vagal fibres on heart rate in the rabbit," *J. Physiol.* 380, pp. 341-347 (1986).
- Furukawa, et al., "Effects of Verapamil, Zatebradine, and E-4031 on the Pacemaker Location and Rate in Response to Sympathetic Stimulation in Dog Hearts," *the Journal of Pharmacology and Experimental Therapeutics*, vol. 289, No. 3, pp. 1334-1342 (1999).
- Furukawa, et al., "Selective inhibition by zatebradine and discrete parasympathetic stimulation of the positive chronotropic response to sympathetic stimulation in anesthetized dogs," *Abstract, Journal of Pharmacology & Experimental Therapeutics*, 272(2):744-9 (1995).
- Gatti, et al., "Can neurons in the nucleus ambiguus selectively regulate cardiac rate and atrioventricular conduction?" *Journal of the Autonomic Nervous System*, 57, pp. 123-127 (1996).
- Gatti, et al., "Vagal control of left ventricular contractility is selectively mediated by a cranioventricular intracardiac ganglion in the cat," *Journal of the Autonomic Nervous System*, 66, pp. 138-144 (1997).
- Gibbons, et al., "Neuromodulation targets intrinsic cardiac neurons to attenuate neuronally mediated atrial arrhythmias," *Am J Physiol Regul Integr Comp Physiol* 302: R357-R364 (2012) (First published Nov. 16, 2011).
- Gottdiener, et al., "Predictors of Congestive Heart Failure in the Elderly: the Cardiovascular Health Study," *Journal of the American College of Cardiology*, vol. 35, No. 6, pp. 1628-1637 (2000).
- Gray, et al., "Parasympathetic control of the Heart. II. A novel interganglionic intrinsic cardiac circuit mediates neural control of heart rate," *J. Appl Physiol*, 96, pp. 2273-2278 (2004).
- Gray, et al., "Parasympathetic control of the Heart. III. Neuropeptide Y—immunoreactive nerve terminals synapse on three populations of negative chronotropic vagal preganglionic neurons," *J. Appl Physiol*, 96, pp. 2279-2287 (2004).
- Grill, "Chapter 14—Principles of Electric Field Generation for Stimulation of the Central Nervous System," *Neuromodulation*, Academic Press (2009).
- Guilleminault, et al., "Cyclical Variation of the Heart Rate in Sleep Apnea Syndrome," *The Lancet*, pp. 126-131 (Jan. 21, 1984).
- Hardwick, et al., "Chronic myocardial infarction induces phenotypic and functional remodeling in the guinea pig cardiac plexus," *Am J Physiol Regulatory Integrative Comp Physiol*, 295, pp. 1926-1933 (2008).
- Hardwick, et al., "Remodeling of the guinea pig intrinsic cardiac plexus with chronic pressure overload," *Am J Physiol Regulatory Integrative Comp Physiol*, 297, pp. 859-866 (2009).
- Hauptman, et al., "The vagus nerve and autonomic imbalance in heart failure: past, present, and future," *Heart Fail Rev*, 16, pp. 97-99 (2011).
- Hellyer, et al., "Autonomic nerve activity and blood pressure in ambulatory dogs," *Heart Rhythm*, vol. 11(2), pp. 307-313 (Feb. 2014).
- Hirooka, et al., "Imbalance of central nitric oxide and reactive oxygen species in the regulation of sympathetic activity and neural mechanisms of hypertension," *Am J Physiol Regulatory Integrative Comp Physiol*, 300, pp. 818-826 (2011).
- Hoffman, et al., "Vagus Nerve Components," *Anat Rec*, 127, pp. 551-568 (1957).
- Hu, et al., "Role of sympathetic nervous system in myocardial ischemia injury: Beneficial or deleterious?" *Letters to the Editor*, Elsevier Ireland Ltd. (Mar. 27, 2012).
- Hua, et al., "Left vagal stimulation induces dynorphin release and suppresses substance P release from the rat thoracic spinal cord during cardiac ischemia," *Am J Physiol Regulatory Integrative Comp Physiol*, 287, pp. 1468-1477 (2004).
- Huston, et al., "Splenectomy inactivates the cholinergic anti-inflammatory pathway during lethal endotoxemia and polymicrobial sepsis," *J. Exp. Med*, vol. 203, No. 7 pp. 1623-1628 (Jun. 19, 2006).
- Huston, et al., "Transcutaneous vagus nerve stimulation reduces serum high mobility group box 1 levels and improves survival in murine sepsis," *Crit Care Med*, vol. 35, No. 12, pp. 2762-2768 (2007).
- Ingemansson, et al., "Autonomic modulation of the atrial cycle length by the head up tilt test: noninvasive evaluation in patients with chronic atrial fibrillation," *Heart*, 80, pp. 71-76 (1998).
- Ito, et al., "Efferent sympathetic and vagal innervation of the canine right ventricle," *Circulation, Journal of the American Heart Association*, vol. 90, pp. 1469-1468 (1994).
- Jacques, et al., "Spinal Cord Stimulation Causes Potentiation of Right Vagus Nerve Effects on Atrial Chronotropic Function and Repolarization in Canines," *Journal of Cardiovascular Electrophysiology*, vol. 22, No. 4, pp. 440-447 (Apr. 2011).
- Jaenisch, et al., "Respiratory muscle training improves baroreceptor sensitivity, decrease sympathetic tonus and increase vagal effect in rats with heart failure," *European Heart Journal*, 32 (Abstract Supplement, pp. 976 (2011)).
- Jammes, et al., "Afferent and efferent components of the bronchial vagal branches in cats," *Journal of the Autonomic Nervous System*, 5, pp. 165-176 (1982).
- Janabi, et al., "Oxidized LDL—Induced NF-kB Activation and Subsequent Expression of Proinflammatory Genes are Defective in Monocyte-Derived Macrophages from CD36-Deficient Patients," *Arterioscler Thromb Vase Biol.*, 20:1953-1960 (2000).
- Janse, et al., "Effects of unilateral stellate ganglion stimulation and ablation on electrophysiologic changes induced by acute myocardial ischemia in dogs," *Circulation, Journal of the American Heart Association*, 72, pp. 585-595 (1985).
- Jessup, et al., "2009 Focused Update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults," *Circulation, Journal of the American Heart Association*, vol. 119, pp. 1977-2016 (2009).
- Johnson, et al., "Parasympathetic control of the heart. I. An interventriculo-septal ganglion is the major source of the vagal intracardiac innervation of the ventricles," *J Appl Physiol*, 96, pp. 2265-2272 (2004).
- Kakinuma, et al., "Cholinoceptive and cholinergic properties of cardiomyocytes involving an amplification mechanism for vagal efferent effects in sparsely innervated ventricular myocardium," *FEBS Journal*, 276, pp. 5111-5125 (2009).

(56)

## References Cited

## OTHER PUBLICATIONS

- Kalman, "Specific effects of zatebradine on sinus node function: suppression of automaticity, prolongation of sinoatrial conduction and pacemaker shift in the denervated canine heart," *Abstract, Journal of Pharmacology & Experimental Therapeutics*, 272(1):85-93 (1995).
- Kaneko, et al., "C-Reactive Protein in Dilated Cardiomyopathy," *Cardiology*, 91, pp. 215-219 (1999).
- Katare, et al., "Vagal nerve stimulation prevents reperfusion injury through inhibition of opening of mitochondrial permeability transition pore independent of bradycardiac effect," *The Journal of Thoracic and Cardiovascular Surgery*, vol. 137, No. 1, pp. 223-231 (2009).
- Katz, et al., "Diseases of the heart in the Works of Hippocrates," *Br Heart J*, 24, pp. 257-264 (1962).
- Kawada, et al., "High-frequency dominant depression of peripheral vagal control of heart rate in rats with chronic heart failure," *Acta Physiol* 207, 494-502 (2013).
- Kawada, et al., "Vagal stimulation suppresses ischemia-induced myocardial interstitial norepinephrine release," *Life Sciences*, 78, pp. 882-887 (2006).
- Kawashima, "The autonomic nervous system of the human heart with special reference to its origin, course, and peripheral distribution," *Anat Embryol*, 209, pp. 425-438 (2005).
- Klein et al., "Vagus nerve stimulation: A new approach to reduce heart failure," *Cardiology Journal*, vol. 17, iss. 6, pp. 638-643 (2010).
- Kliks, et al., "Influence of Sympathetic Tone on Ventricular Fibrillation Threshold During Experimental Coronary Occlusion," *The American Journal of Cardiology*, vol. 36, pp. 45-49 (Jul. 1975).
- Kolman, et al., "The effect of vagus nerve stimulation upon vulnerability of the canine ventricle: role of sympathetic-parasympathetic interactions," *Journal of the American Heart Association*, 52, pp. 578-585 (1975).
- Kong, et al., "Optimizing the Parameters of Vagus Nerve Stimulation by Uniform Design in Rats with Acute Myocardial Infarction," *PLOS One*, vol. 7, issue 11 (Nov. 2012).
- Koopman, et al., "Pilot study of stimulation of the cholinergic anti-inflammatory pathway with an implantable vagus nerve stimulation device in patients with rheumatoid arthritis," *Abstract* (2012).
- Kulbertus, et al., ed., "Neurocardiology," Futura Publishing Co., pp. 13 ("Anatomy of the Cardiac Efferent Innervation"); 61-63 ("Autonomic Neural Control"); 87, 89, 9293 ("Sympathetic-Parasympathetic Interactions"); 183, 187 ("Parasympathetic Nervous System"); 104 (1988).
- La Rovere, et al., "Baroreflex Sensitivity and Heart Rate Variability in the Identification of Patients at Risk for Life-Threatening Arrhythmias: Implications for Clinical Trials," *Circulation, Journal of the American Heart Association*, 103, pp. 2072-2077 (2001).
- La Rovere, et al., "Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators," *Lancet*, 351(9101), pp. 478-484 (Feb. 14, 1998).
- Lane, et al., "Prediction and Prevention of Sudden Cardiac Death in Heart Failure," *Heart*, 91, pp. 674-680 (2005).
- Lechat, et al., "Heart rate and Cardiac Rhythm Relationships with Bisoprolol Benefit in Chronic Heart Failure in CIBIS II Trial," *Circulation, Journal of American Heart Association*, 103, pp. 1428-1433 (2001).
- Lewis, et al., "Vagus nerve stimulation decreases left ventricular contractility in vivo in the human and pig heart," *Journal of Physiology*, 534, pp. 547-552 (2001).
- Li et al., "Vagal Nerve Stimulation Markedly Improves Long-Term Survival After Chronic Heart Failure in Rats," *Circulation: Journal of the American Heart Association*, vol. 109, iss. 1, pp. 120-124 (Jan. 2004). Online publication date: Dec. 8, 2003. Available at: <http://circ.ahajournals.org/cgi/pmidlookup?view=long&pmid=14662714>.
- Li, et al., "Early vagal stimulation markedly prevented cardiac dysfunction in rats after acute myocardial infarction in addition to suppressing arrhythmic death," *European Heart Journal*, 32 (Abstract Supplement), pp. 297-298 (2011).
- Li, et al., "Inflammatory cytokines and nitric oxide in heart failure and potential modulation by vagus nerve stimulation," *Heart Fail Rev*, 16, pp. 137-145 (2011).
- Li, et al., "Low-Level Vagosympathetic Stimulation. A Paradox and Potential New Modality for the Treatment of Focal Atrial Fibrillation," *Gire Arrhythm Electrophysiol, Journal of American Heart Association*, 2, pp. 645-651 (2009).
- Li, et al., "Restoration of vagal tone by donepezil, on top of losartan treatment, markedly suppresses ventricular dysfunction and improves long-term survival in chronic heart failure rats," *European Heart Journal*, 32 (Abstract Supplement), pp. 642 (2011).
- Libby, et al., "Inflammation and Atherosclerosis," *Circulation, Journal of the American Heart Association*, 105, pp. 1135-1143 (2002).
- Liu, et al., "Differing sympathetic and vagal effects on atrial fibrillation in dogs: role of refractoriness heterogeneity," *Am. J. Physiol.* 273 (Heart Circ. Physiol. 42), pp. H805-H816 (1997).
- Lo, et al., "Paradoxical long-term proarrhythmic effects after ablating the 'head station' ganglionated plexi of the vagal innervation to the heart," *Heart Rhythm*, vol. 10, No. 5, pp. 751-757 (May 2013).
- Lohmeier, et al., "Prolonged Activation of the Baroreflex Produces Sustained Hypotension," *Hypertension, Journal of the American Heart Association*, 43, pp. 306-311 (2004).
- Lu, et al., "Vagal nerve stimulation produces cardiac injury by attenuating mitochondrial dysfunction in a murine burn injury model," *J. Cell. Mol. Med.*, vol. 17, No. 5, pp. 664-671 (2013).
- Ma, et al., "Analysis of afferent, central, and efferent components of the baroreceptor reflex in mice," *Am J Physiol Regulatory Integration Comp Physiol*, 283, pp. 1033-1040 (2002).
- Maj, et al., "P5775: Autonomic imbalance and circulating androgens and estrogens in men with systolic heart failure," *European Heart Journal*, 32 (Abstract Supplement), pp. 1090 (2011).
- Malkin, et al., "Life-saving or life-prolonging? Interpreting trial data and survival curves for patients with congestive heart failure," *The European Journal of Heart Failure*, 7, pp. 143-148 (2005).
- Mann, "Chapter 12—Peripheral Nerves," *The Nervous System in Action*, [michaeldmann.net/mann12.html](http://michaeldmann.net/mann12.html), (Jul. 2011).
- Mann, "Inflammatory Mediators and the Failing Heart. Past, Present, and the Foreseeable Future," *Circ Res.*, 91, pp. 988-998 (2002).
- Mann, "Stress-Activated Cytokines and the Heart: From Adaptation to Maladaptation," *Annu. Rev. Physiol.*, 65, pp. 81-101 (2003).
- Martin-Portugues, et al., "Histopathologic features of the vagus nerve after electrical stimulation in swine," *Histol Histopathol*, 20, pp. 851-856 (2005).
- Martins, et al., "Distribution of Local Repolarization Changes Produced by Efferent Vagal Stimulation in the Canine Ventricles," *JACC*, vol. 2, No. 6, pp. 1191-1199 (Dec. 1983).
- Massari, et al., "Neural control of left ventricular contractility in the dog heart: synaptic interactions of negative inotropic vagal preganglionic neurons in the nucleus ambiguus and tyrosine hydroxylase immunoreactive terminals," *Brain Research*, 802, pp. 205-220 (1998).
- May, et al., "P564: Long-term prediction of all-cause mortality in diabetic autonomic neuropathy: simple function tests or 24-hour heart rate variability (HRV)?" *European Heart Journal*, 32 (Abstract Supplement), pp. 64 (2011).
- Mei, et al., "The Composition of the Vagus Nerve of the Cat," *Cell Tissue Res.*, 209, pp. 423-431 (1980).
- Merrill, et al., "Electrical stimulation of excitable tissue: design of efficacious and safe protocols," *Journal of Neuroscience Methods*, 141, pp. 171-198 (2005).
- Mortara, et al., "Arterial Baroreflex Modulation of Heart Rate in Chronic Heart Failure," *Circulation, Journal of the American Heart Association*, vol. 96, No. 10, pp. 3450-3458 (Nov. 18, 1997).
- Murakawa, et al., "Effect of Cervical Vagal Nerve Stimulation on Defibrillation Energy," *Jpn Heart J*, 44, pp. 91-100 (Jan. 2003).
- Naito, "Effects of zatebradine and propranolol on canine ischemia and reperfusion-induced arrhythmias," *European Journal of Pharmacology*, 388, pp. 171-176 (2000).
- Nakajima, et al., "Autonomic Control of the Location and Rate of the Cardiac Pacemaker in the Sinoatrial Fat Pad of Parasympatheti-

(56)

## References Cited

## OTHER PUBLICATIONS

- cally Denervated Dog Hearts," *Journal of Cardiovascular Electrophysiology*, vol. 13, No. 9 pp. 896-901 (Sep. 2002).
- Nearing, et al., "Crescendo in Depolarization and Repolarization Heterogeneity Heralds Development of Ventricular Tachycardia in Hospitalized Patients with Decompensated Heart Failure," *Circulation Arrhythmia and Electrophysiology*, *Journal of the American Heart Association*, 5, pp. 84-90 (2012).
- Nihei, et al., "Decreased Vagal Control Over Heart Rate in Rats with Right-Sided Congestive Heart Failure—Downregulation of Neuronal Nitric Oxide Synthase," *Gire J*, 69, pp. 493-499 (2005).
- Nihei, et al., "Decreased Vagal Control Over Heart Rate in Rats with Right-Sided Congestive Heart Failure—Downregulation of Neuronal Nitric Oxide Synthase," *Oirc J*, 69, pp. 493-499 (2005).
- Ninomiya, "Direct Evidence of Nonuniform Distribution of Vagal Effects on Dog Atria," *Circulation Research*, vol. XIX, pp. 576-583 (Sep. 1966).
- Nolan, et al., "Prospective Study of Heart Rate Variability and Mortality in Chronic Heart Failure: Results of the United Kingdom Heart Failure Evaluation and Assessment of Risk Trial (UK-Heart)," *Circulation*, *Journal of the American Heart Association*, 98, pp. 1510-1516 (1998).
- Ochoa, et al., "P2497: Effects of insulin resistance on resting heart rate, baroreflex sensitivity and indices of autonomic cardiovascular modulation in individuals with high blood pressure levels," *European Heart Journal*, 32 (Abstract Supplement), pp. 431-432 (2011).
- Ogawa, et al., "Left Stellate Ganglion and Vagal Nerve Activity and Cardiac Arrhythmias in Ambulatory Dogs with Pacing-Induced Congestive Heart Failure," *Journal of the American College of Cardiology*, vol. 50, No. 4, pp. 335-444 (2007).
- Okada, et al., "Cyclic Stretch Upregulates Production of Interleukin-8 and Monocyte Chemoattractant and Activating Factor/Monocyte Chemoattractant Protein-1 in Human Endothelial Cells," *Arterioscler Thromb Vase Biol.*, 18, pp. 894-901 (1998).
- Oliveira, et al., "Effects of vagal stimulation on induction and termination of atrial fibrillation in an in vivo rabbit heart model," *Rev Port Cardiol*, 29(03), pp. 375-389 (2010).
- Olshansky, et al., "Parasympathetic Nervous System and Heart Failure: Pathophysiology and Potential Implications for Therapy," *Circulation*, *Journal of the American Heart Association*, 118, pp. 863-871 (2008).
- Onkka, et al., "Sympathetic nerve fibers and ganglia in canine cervical vagus nerves: Localization and quantitation," *Heart Rhythm*, vol. 10, No. 4, pp. 585-591 (Apr. 2013).
- Ordelman, et al., "Selectivity for Specific Cardiovascular Effects of Vagal Nerve Stimulation with a Multi-Contact Electrode Cuff," *IEEE*, pp. 1-6 (2011).
- Packer, et al., "Effect of Carvedilol on Survival in Severe Chronic Heart Failure," *The New England Journal of Medicine*, vol. 344, No. 22, pp. 1651-1658 (May 31, 2001).
- Pavlov, et al., "Central muscarinic cholinergic regulation of the systemic inflammatory response during endotoxemia," *Pnas*, vol. 103, No. 13, pp. 5219-5223 (Mar. 28, 2006).
- Pavlov, et al., "Controlling inflammation: the cholinergic anti-inflammatory pathway," *Biochemical Society Transactions*, vol. 34, part 6, pp. 1037-1040 (2006).
- PCT Application No. PCT/US2012/068205, Search Report and Written Opinion dated Feb. 8, 2013, 15 pages.
- PCT Application No. PCT/US2012/068211, Search Report and Written Opinion dated Jun. 13, 2013.
- PCT Application No. PCT/US2012/068213, Search Report and Written Opinion dated Mar. 15, 2013, 11 pages.
- PCT Application No. PCT/US2012/068223, Search Report and Written Opinion dated Apr. 3, 2013, 11 pages.
- PCT Application No. PCT/US2013/021964, Search Report and Written Opinion dated Jul. 25, 2013, 9 pages.
- PCT Application No. PCT/US2013/050390, Search Report and Written Opinion dated Nov. 5, 2013.
- PCT Application No. PCT/US2013/068541, International Preliminary Report on Patentability dated May 21, 2015, 9 pages.
- PCT Application No. PCT/US2013/068541, Search Report and Written Opinion dated Jan. 7, 2014.
- PCT Application No. PCT/US2014/024827, Search Report and Written Opinion dated Nov. 11, 2014, 18 pages.
- PCT Application No. PCT/US2015/020116, Search Report and Written Opinion dated Jul. 6, 2015, 12 pages.
- Peckham, et al., "Chapter 18—Implantable Neural Stimulators," *Neuromodulation*, Academic Press (2009).
- Pina, et al., "The Predictive Value of Biomarkers in Heart Failure," *Medscape Education Cardiology*, Available at <http://www.medscape.org/viewarticle/765328> (CME Released: Jun. 15, 2012).
- Pitzalis, et al., "Comparison Between Noninvasive Indices of Baroreceptor Sensitivity and the Phenylephrine Method in Post-Myocardial Infarction Patients," *Circulation*, *Journal of the American Heart Association*, 97, pp. 1362-1367 (1998).
- Poole-Wilson, "Relation of Pathophysiologic Mechanisms to Outcome in Heart Failure," *JACC*, vol. 22, No. 4 (supplement A), pp. 22A-29A (Oct. 1993).
- Pye, et al., "Study of serum C-reactive protein concentration in cardiac failure," *Br Heart J*, 63, pp. 228-30 (1990).
- Rademacher, et al., "P5878: Multidimensional halter-based analysis of cardiac autonomic regulation predicts early AF recurrence after electrical cardioversion," *European Heart Journal*, 32 (Abstract Supplement), pp. 1116-1117 (2011).
- Randall, et al., "Regional vagosympathetic control of the heart," *American Journal of Physiology*, vol. 227, No. 2, pp. 444-452 (1974).
- Randall, et al., "Selective Vagal Innervation of the Heart," *Annals of Clinical and Laboratory Science*, vol. 16, No. 3, pp. 198-208 (1986).
- Raymond, et al., "Elevated interleukin-6 levels in patients with asymptomatic left ventricular systolic dysfunction," *American Heart Journal*, vol. 141, No. 3, pp. 435-438 (Mar. 2001).
- Rhee, et al., "Effects of suprathreshold vagal stimulation on stellate ganglion nerve activity in ambulatory dogs," 33rd Annual Scientific Sessions, *Heart Rhythm*, Presentation Abstract (2012).
- Rhee, et al., "Presentation Abstract—Effects of suprathreshold vagal stimulation on stellate ganglion nerve activity in ambulatory dogs," 33rd Annual Scientific Sessions, *Heart Rhythm* (2012).
- Riccio, et al., "Interganglionic segregation of distinct vagal afferent fibre phenotypes in guinea-pig airways," *Journal of Physiology*, 495.2, pp. 521-530 (1996).
- Riddle, et al., "Epidemiologic Relationships Between A1C and All-Cause Mortality During a Median 3.4-Year Follow-up of Glycemic Treatment in the Accord Trial," *Diabetes Care*, vol. 33, No. 5, pp. 983-990 (May 2010).
- Ridker, C-Reactive Protein: A Simple Test to Help Predict Risk of Heart Attack and Stroke, *Journal of the American Heart Association*, 108, pp. e81-e85 (2003).
- Ridker, et al., "Comparison of C-Reactive Protein and Low-Density Lipoprotein Cholesterol Levels in the Prediction of First Cardiovascular Events," *New England Journal of Medicine*, vol. 347, No. 20, pp. 1557-1566 (Nov. 14, 2002).
- Ridker, et al., "C-Reactive Protein and Other Markers of Inflammation in the Prediction of Cardiovascular Disease in Women," *The New England Journal of Medicine*, vol. 342, No. 12, pp. 836-841 (Mar. 23, 2000).
- Ridker, et al., "Inflammation, Pravastatin, and the Risk of Coronary Events After Myocardial Infarction in Patients With Average Cholesterol Levels," *Circulation*, *Journal of the American Heart Association*, 98, pp. 839-844 (1998).
- Roger, et al., "Heart Disease and Stroke Statistics—2011 Update: A Report from the American Heart Association," *Circulation*, *Journal of the American Heart Association*. Available at <http://cir.ahajournals.org/content/123/4/e18> (2010).
- Romanovsky, et al., "The vagus nerve in the thermoregulatory response to systemic inflammation," *Am. J. Physiol.*, 273, pp. R407-R413 (1997).
- Rossi, et al., "Epicardial ganglionated plexus stimulation decreases postoperative inflammatory response in humans," *Heart Rhythm*, vol. 9, No. 6, pp. 943-950 (Jun. 2012).
- Rouse, et al., "The haemodynamic actions of Zenca ZD7288, a novel sino-atrial node function modulator, in the exercising beagle:

(56)

## References Cited

## OTHER PUBLICATIONS

- a comparison with zategradine and propranolol," Abstract, British Journal of Pharmacology, 113(3):1071-7 (1994).
- Rozman, et al., "Heart function influenced by selective mid-cervical left vagus nerve stimulation in a human case study," Hypertension Research, 32, pp. 1041-1043 (2009).
- Rutecki, "Anatomical, Physiological and Theoretical Basis for the Antiepileptic Effect of Vagus Nerve Stimulation," Epilepsia, 31 (suppl. 2), pp. S1-S6 (1990).
- Sabbah et al., "Vagus Nerve Stimulation in Experimental Heart Failure," Heart Failure Reviews, vol. 16, No. 2, Mar. 2011, pp. 171-178.
- Sabbah, et al., "3722: Vagus nerve stimulation improves left ventricular function in heart failure: results of a 6 month investigation with a cross-over design in dogs with experimental heart failure," European Heart Journal, 32 (Abstract Supplement), pp. 642 (2011).
- Sabbah, et al., "Baroreflex Activation Therapy for the Treatment of Heart Failure," Presentation available at <http://www.cvr.com/wp/wp-content/uploads/2012/04/Dr-Sabbah-Slides.pdf> (2012).
- Sabbah, et al., "Chronic Electrical Stimulation of the Carotid Sinus Baroreflex Improves Left Ventricular Function and Promotes Reversal of Ventricular Remodeling in Dogs with Advanced Heart Failure," Circulation Heart Failure, Journal of the American Heart Association, 4, pp. 65-70 (2011).
- Samara, et al., "The Effects of Cardiac Resynchronization Therapy on Chronotropic Incompetence in Patients Intolerant of Beta Antagonist Therapy," Journal of Cardiac Failure, vol. 17, No. 8S, pp. S54-S55 (Aug. 2011).
- Sanner, et al., "P4743: Prediction of cardiovascular risk from nocturnal pulse wave signal using the autonomic state indicator (ASI) technology," European Heart Journal, 32 (Abstract Supplement), pp. 839 (2011).
- Sato, et al., "Serial Circulating Concentrations of C-Reactive Protein, Interleukin (IL)-4, and IL-6 in Patients with Acute Left Heart Decompensation," Clin. Cardiol. 22, pp. 811-813 (1999).
- Schauerte, "Time for Change: Cardiac neurophysiology meets cardiac electrophysiology," Editorial Commentary, Heart Rhythm Society (2013).
- Schiereck, et al., "AV blocking due to asynchronous vagal stimulation in rats," Am J Physiol Heart Circ Physiol, 278, pp. H67-H73 (2000).
- Schocken, et al., "Prevalence and Mortality Rate of Congestive Heart Failure in the United States," JACC, vol. 20, No. 2, pp. 301-306 (Aug. 1992).
- Schwartz, "Vagal Stimulation for Heart Diseases: From Animals to Men," Circulation Journal, vol. 75, pp. 20-27 (Jan. 2011).
- Schwartz, "Vagal stimulation for heart failure," Current Opinion in Cardiology, 26, pp. 51-54 (2011).
- Schwartz, "Vagal stimulation for the treatment of heart failure: a translational success story," Heart, vol. 98, No. 23, pp. 1687-1690 (2012).
- Schwartz, et al. Vagal stimulation for heart failure: Background and first in-man study, Heart Rhythm, 6, 11 suppl., pp. S76-S81 (Nov. 2009).
- Schwartz, et al., "Autonomic mechanisms and sudden death. New insights from analysis of baroreceptor reflexes in conscious dogs with and without myocardial infarction," Circulation, Journal of the American Heart Association, 78, pp. 969-979 (1988).
- Schwartz, et al., "Effects of Unilateral Cardiac Sympathetic Denervation on the Ventricular Fibrillation Threshold," the American Journal of Cardiology, vol. 37, pp. 1034-1040 (Jun. 1976).
- Schwartz, et al., "Long term vagal stimulation in patients with advanced heart failure. First experience in man," European Journal of Heart Failure, 10, pp. 884-891 (2008).
- Schwartz, et al., "Sympathetic-parasympathetic interaction in health and disease: abnormalities and relevance in heart failure," Heart Fail Rev, 16, pp. 101-107 (2011).
- Seta, et al., "Basic Mechanisms in Heart Failure: The Cytokine Hypothesis," Journal of Cardiac Failure, vol. 2, No. 3, pp. 243-249 (1996).
- Sha, et al., "Low-Level Right Vagal Stimulation: Anticholinergic and Antiadrenergic Effects," J Cardiovasc Electrophysiol, pp. 1-7 (Feb. 2011).
- Shamoon, et al., The Diabetes Control and Complications Trial Research Group, "The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus," The New England Journal of Medicine, vol. 329, No. 14, pp. 977-986 (Sep. 30, 1993).
- Shannon, "A Model of Safe Levels for Electrical Stimulation," IEEE Transactions on Biomedical Engineering, vol. 39, No. 4, pp. 424-426 (Apr. 1992).
- Shen, et al., "Continuous Low-Level Vagus Nerve Stimulation Reduces Stellate Ganglion Nerve Activity and Paroxysmal Atrial Tachyarrhythmias in Ambulatory Canines," Circulation, Journal of the American Heart Association, 123, pp. 2204-2212 (2011).
- Shen, et al., "Low-level vagus nerve stimulation upregulates small conductance calcium-activated potassium channels in the stellate ganglion," Heart Rhythm, vol. 10, No. 6, pp. 910-915 (2013).
- Shinohara, et al., "Heart Failure Decreases Nerve Activity in the Right Atrial Ganglionated Plexus," J Cardiovasc Electrophysiol, pp. 1-9 (2011).
- Shioi, et al., "Increased Expression of Interleukin-1B and Monocyte Chemoattractant and Activating Factor/Monocyte Chemoattractant Protein-1 in the Hypertrophied and Failing Heart with Pressure Overload," Gire Res., 81, pp. 664-671 (1997).
- Singal, et al., "The role of oxidative stress in the genesis of heart disease," Cardiovascular Research, 40, pp. 426-432 (1998).
- Spuck, et al., "Right-sided vagus nerve stimulation in humans: An effective therapy?" Epilepsy Research, pp. 1-3 (2008).
- Stein, et al., "A Simple Method to Identify Sleep Apnea Using Holter Recordings," J Cardiovasc Electrophysiol, vol. 14, pp. 467-473 (May 2003).
- Stein, et al., "Feasibility of Using Mobile Cardiac Outpatient Telemetry (MCOT) to Identify Severe Sleep Disorders" (2009).
- Stieber, et al., "Bradycardic and proarrhythmic properties of sinus node inhibitors," Abstract, Molecular Pharmacology, 69(4):1328-37 (2006).
- Taylor, et al., "The unequal influences of the left and right vagi on the control of the heart and pulmonary artery in the rattlesnake, Grata/us durissus," The Journal of Experimental Biology, 212, pp. 145-151 (2009).
- Thayer, et al., "The role of vagal function in the risk for cardiovascular disease and mortality," Biological Psychology, 74, pp. 224-242 (2007).
- Thollon, et al., "Electrophysiological effects of S 16257, a novel sino-atrial node modulator, on rabbit and guinea-pig cardiac preparations: comparison with UL-FS 49," Abstract, British Journal of Pharmacology, 112(1):37-42 (1994).
- Tosato, et al., "Quasi-trapezoidal pulses to selectively block the activation of intrinsic laryngeal muscles during vagal nerve stimulation," J. Neural Eng., 4, pp. 205-212 (2007).
- Tsutsumi, et al., "Modulation of the myocardial redox state by vagal nerve stimulation after experimental myocardial infarction," Cardiovascular Research, 77, pp. 713-721 (2008).
- Tyler, et al., "Chapter 17—Electrodes for the Neural Interface," Neuromodulation, Academic Press (2009).
- Ulphani, et al., "Quantitative analysis of parasympathetic innervation of the porcine heart," Heart Rhythm, 7, pp. 1113-1119 (2010).
- Uthman, et al., "Effectiveness of vagus nerve stimulation in epilepsy patients. A 12-year observation," Neurology, 63, pp. 1124-1126 (2004).
- Van Stee, "Autonomic Innervation of the Heart," Environmental Health Perspectives, vol. 26, pp. 151-158 (1978).
- Vanoli, et al., "Vagal stimulation and prevention of sudden death in conscious dogs with a healed myocardial infarction," Circulation Research, Journal of the American Heart Association, 68, pp. 1471-1481 (1991).
- Vasan, et al., "Inflammatory Markers and Risk of Heart Failure in Elderly Subjects Without Prior Myocardial Infarction," Circulation, Journal of the American Heart Association, 107, pp. 1486-1491 (2003).

(56)

**References Cited**

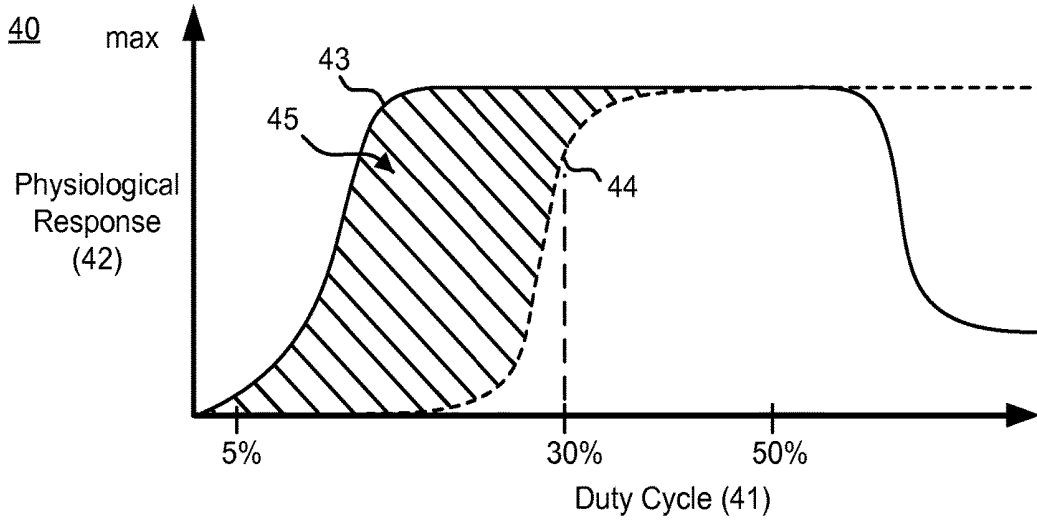
## OTHER PUBLICATIONS

- Vassalle, et al., "An Analysis of Arrhythmias Induced by Ouabain in Intact Dogs," *Circulation Research*, Journal of the American Heart Association, 13, pp. 132-148 (1963).
- Velagaleti, et al., "Long-Term Trends in the Incidence of heart Failure After Myocardial Infarction," 118, pp. 2057-2062 (2008).
- Verrier, et al., "Microvolt T-Wave Alternans," *Journal of the American College of Cardiology*, vol. 58, No. 13, pp. 1309-1324 (2011).
- Vimercati, et al., "Acute vagal stimulation attenuates cardiac metabolic response to B-adrenergic stress," *The Journal of Physiology*, vol. 500, No. 23, pp. 6065-6074 (2012).
- Wang, et al., "Nicotinic acetylcholine receptor alpha-7 subunit is an essential regulator of inflammation," *Nature*, vol. 421, pp. 384-388 (Jan. 23, 2003).
- Wang, et al., "Synaptic and Neurotransmitter Activation of Cardiac Vagal Neurons in the Nucleus Ambiguus," *Annals New York Academy of Sciences*, pp. 237-246 (2001).
- Waninger, et al., "Characterization of Atrioventricular Nodal Response to Electrical Left Vagal Stimulation," *Annals of Biomedical Engineering*, vol. 27, pp. 758-762 (1999).
- Wann, "Behavioural signs of depression and apoptosis in the limbic system following myocardial infarction: effects of sertraline," *Journal of Psychopharmacology*, 23(4), pp. 451-459 (2009).
- Wann, et al., "Vulnerability for apoptosis in the limbic system after myocardial infarction in rats: a possible model for human postinfarct major depression," *J Psychiatry Neurosci*, 32(1):11-6, pp. 11-16 (2007).
- Watkins, et al., "Cytokine-to-Brain Communication: A Review & Analysis of Alternative Mechanisms," *Life Sciences*, vol. 57, No. 11, pp. 1011-1026 (1995).
- Whyte, et al., "Reactive oxygen species modulate neuronal excitability in rat intrinsic cardiac ganglia," *Auton Neurosci*, 150(1-2), pp. 45-52 (Oct. 5, 2009).
- Wieland, et al., "Bradycardic and proarrhythmic properties of sinus node inhibitors," *Abstract, Molecular Pharmacology*, 69(4):1328-37 (2006).
- Yang, et al., "Sustained increases in heart rate induced by time repetition of vagal stimulation in dogs," *Am. J. Physiol.*, 249, pp. H703-H709 (1985).
- Yin, et al., "Independent prognostic value of elevated high-sensitivity C-reactive protein in chronic heart failure," *American Heart Journal*, vol. 147, No. 5, pp. 931-938 (2004).
- Yndestad, et al., "Systemic inflammation in heart failure—the whys and wherefores," *Heart Fail Rev*, 11, pp. 83-92 (2006).
- Yoo, et al., "High-resolution measurement of electrically-evoked vagus nerve activity in the anesthetized dog," *J. Neural Eng.*, 10, pp. 1-9 (2013).
- Yoo, et al., "Selective Control of Physiological Responses by Temporally-Patterned Electrical Stimulation of the Canine Vagus Nerve," 33rd Annual International Conference of the IEEE EMBS (2011).
- Yu, et al., "Interactions between atrial electrical remodeling and autonomic remodeling: How to break the vicious cycle," *Heart Rhythm*, 9, pp. 804-809 (2012).
- Yu, et al., "Low-level transcutaneous electrical stimulation of the auricular branch of the vagus nerve: a noninvasive approach to treat the initial phase of atrial fibrillation," *Heart Rhythm*, 10, pp. 428-435 (2013).
- Yuan, et al., "Gross and Microscopic Anatomy of the Canine Intrinsic Cardiac Nervous System," *The Anatomical Record*, 239, pp. 75-87 (1994).
- Yusuf, et al., "Changes in Hypertension Treatment and in Congestive Heart Failure Mortality in the United States," *Hypertension*, *Journal of the American Heart Association*, 13:174-1179 (1989).
- Zhang, et al., "Arrhythmias and vagus nerve stimulation," *Heart Fail Rev*, 16, pp. 147-161 (2011).
- Zhang, et al., "Involvement of activated astrocyte and microglia of locus coeruleus in cardiac pain processing after acute cardiac injury," *Neurol Res*, 31, pp. 432-438 (2009).
- Zhang, et al., "Relationship between right cervical vagus nerve stimulation and atrial fibrillation inducibility: Therapeutic intensities do not increase arrhythmogenesis," *Heart Rhythm*, 6, pp. 244-250 (2009).
- Zhang, et al., "Therapeutic Effects of Selective Atrioventricular Node Vagal Stimulation in Atrial Fibrillation and Heart Failure," *Journal of Cardiovascular Electrophysiology*, vol. 24, Issue 1, pp. 86-91 (2012).
- Zheng, et al., "Vagal stimulation markedly suppresses arrhythmias in conscious rats with chronic heart failure after myocardial infarction," *Proceedings of the 2005 IEEE* (2005).
- Zipes, et al., "Effects of selective vagal and stellate ganglion stimulation on atrial refractoriness," *Cardiovascular Research*, 8, pp. 647-655 (1974).
- Zucker, et al., "Chronic Baroreceptor Activation Enhances Survival in Dogs with Pacing-Induced Heart Failure," *Journal of the American Heart Association*, *Hypertension* (2007).

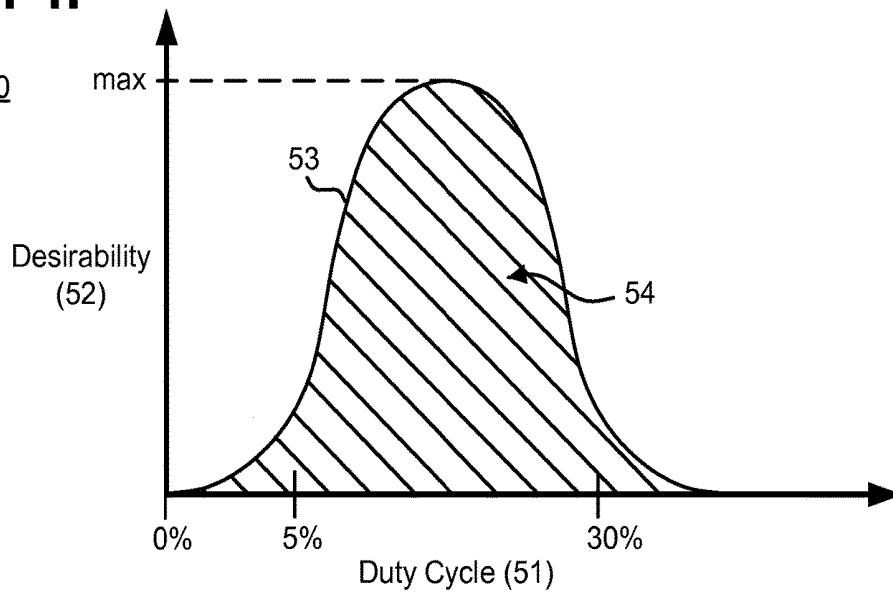
\* cited by examiner



**Fig. 3.**



**Fig. 4.**



**Fig. 5.**

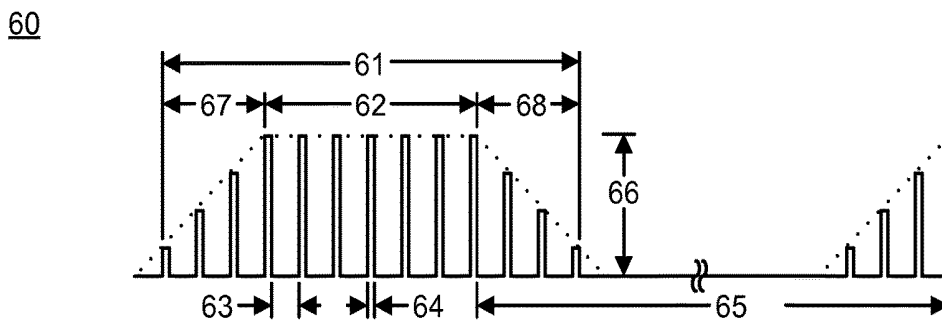


Fig. 6.

70

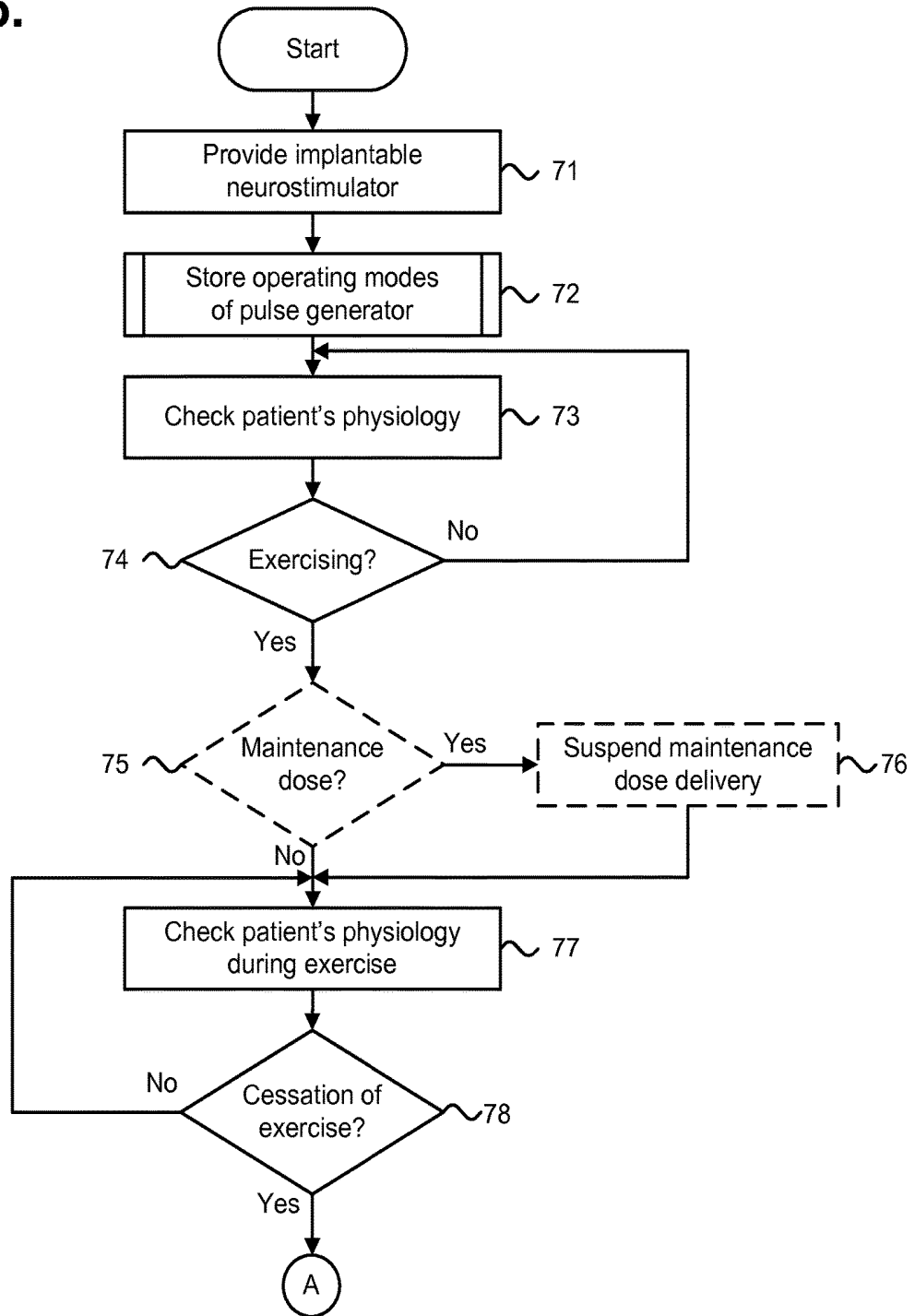


Fig. 6 (con'd).

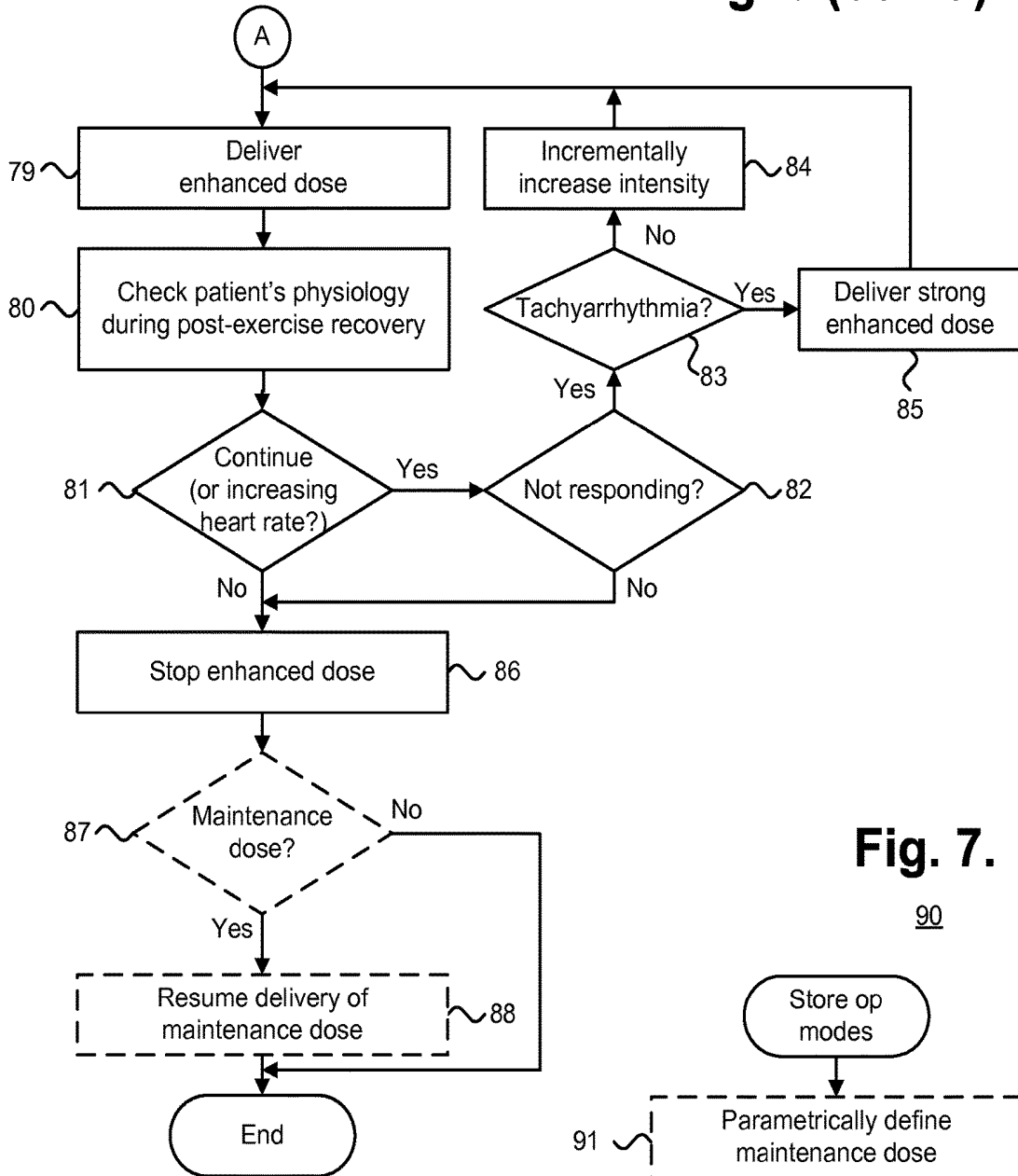
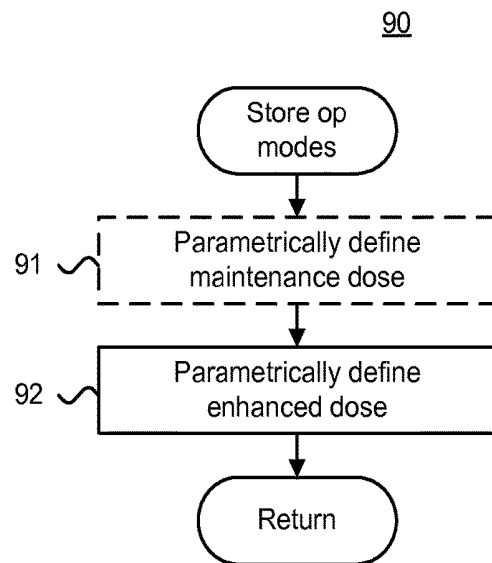


Fig. 7.



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

CROSS-REFERENCE TO RELATED PATENT  
APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 13/673,795, filed Nov. 9, 2012, which is hereby incorporated by reference herein in its entirety.

FIELD OF THE DISCLOSURE

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 neuroexcitatory 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 diam-

eter 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 ranch, 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 OF THE INVENTION

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 autonomic 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. 2A and 2B 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, patented as U.S. Pat. No. 8,600,505, 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, patented as U.S. Pat. No. 8,571,654, 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 19a-b and the mastoid process. The therapy lead 13 and helical electrodes 14 are implanted by first exposing the carotid sheath and chosen vagus nerve 15, 16 through a latero-cervical incision on the ipsilateral side of the patient's neck 18. The helical electrodes 14 are then placed onto the exposed nerve sheath and tethered. A subcutaneous tunnel is formed between the respective implantation sites of the neurostimulator 12 and helical electrodes 14, through which the therapy lead 13 is guided to the neurostimulator 12 and securely connected.

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, patented as U.S. Pat. No. 9,452,290, 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, patented as U.S. Pat. No. 8,688,212, 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. 2A and 2B are diagrams respectively showing the implantable neurostimulator 12 and the stimulation 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. 2A, 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, patented as U.S. Pat. No. 8,630,709, the disclosure of which is incorporated by reference.

Referring next to FIG. 2B, 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-exercising 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, patented as U.S. Pat. No. 8,577,458, 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, patented as U.S. Pat. No. 10/188,856, 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, 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, patented as U.S. Pat. No. 8,918,190, 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 on Nov. 9, 2012, patented as U.S. Pat. No. 8,923,964, and 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, patented as U.S. Pat. No. 9,643,011, 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  $\mu$ sec 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 sensor 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. Pat Nos. 9,452,290 and 8,688,212, 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 effect 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. 15 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. 20

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). 25

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. 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. 40

The recordable memory 29 in the electronic circuitry 22 of the neurostimulator 12 (shown in FIG. 2A) stores the stimulation parameters that control the overall functionality of the pulse generator 11 in providing VNS therapy. FIG. 7 45 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. 50

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  $\mu$ sec 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. 60

Different enhanced doses can be provided to respond to different tachyarrhythmic events. The enhanced dose settings are physician-programmable. For a default enhanced 65

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  $\mu$ sec 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. 15

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. 20

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. A method for enhancing post-exercise recovery 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 cervical vagus nerve of a patient;
  - storing operating modes of the pulse generator in a recordable memory, the operating modes defining:
    - an enhanced dose of the electrical therapeutic stimulation comprising a first intensity; and
    - a maintenance dose of the electrical therapeutic stimulation comprising a second intensity lower than the first intensity;
  - delivering the maintenance dose to the vagus nerve during a non-exertion period of the patient;
  - monitoring a physiological state of the patient during physical exercise via the sensor; and
  - upon sensing a condition indicative of cessation of the physical exercise based on the monitored physiological state, delivering the enhanced dose to the vagus nerve.
2. 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 non-exertion periods exclusive of the physical exercise;
  - periodically sensing a heart rate of the patient with the heart rate sensor;
  - confirming that the patient is undergoing the physical exercise when the 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 heart rate falls below the elevated heart rate by a threshold amount.
3. 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 non-exertion periods exclusive of the physical exercise;

periodically sensing an activity level of the patient with the accelerometer;

confirming that the patient is undergoing the physical exercise when the 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 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, wherein the sensor comprises a minute ventilation sensor, the method further comprising the steps of:

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

periodically sensing a tidal volume and a respiratory rate of the patient with the minute ventilation sensor;

confirming that the patient is undergoing the physical exercise when the 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 tidal volume and respiratory rate fall below the respective elevated levels by a threshold amount.

5. A method according to claim 1, further comprising monitoring the 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 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 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.

8. A method according to claim 1, further comprising 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.

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 by 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. A neurostimulator system for enhancing post-exercise recovery through vagus nerve stimulation, comprising:

a sensor; and

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

deliver a maintenance dose of the electrical therapeutic stimulation during a non-exertion period of the patient;

monitor a physiological state of the patient during physical exercise via the sensor; and

upon sensing a condition indicative of cessation of the physical exercise based on the monitored physiological state, suspend delivery of the maintenance dose and deliver an enhanced dose of the electrical therapeutic stimulation to the vagus nerve, the enhanced dose comprising a first intensity and the maintenance dose comprising a second intensity lower than the first intensity.

12. A system according to claim 11, wherein the sensor comprises a heart rate sensor, and the recordable memory further comprises instructions that cause the pulse generator to:

establish 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 sense a heart rate of the patient with the heart rate sensor;

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

subsequently confirm the cessation of the physical exercise when the heart rate falls below the elevated heart rate by a threshold amount.

13. A system according to claim 11, wherein the sensor comprises an accelerometer, and the recordable memory further comprises instructions that cause the pulse generator to:

establish 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 sense an activity level of the patient with the accelerometer;

confirm that the patient is undergoing the physical exercise when the 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 confirm the cessation of the physical exercise when the activity level falls below the elevated activity level accompanied by a decreased frequency of movement by a threshold amount.

14. A system according to claim 11, wherein the sensor comprises a minute ventilation sensor, and the recordable memory further comprises instructions that cause the pulse generator to:

establish 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 sense a tidal volume and a respiratory rate with the minute ventilation sensor;  
 confirm that the patient is undergoing the physical exercise when the 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 confirm the cessation of the physical exercise when the tidal volume and respiratory rate fall below the respective elevated levels by a threshold amount.

15. A system according to claim 11, wherein the recordable memory further comprises instructions that cause the pulse generator to monitor the 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.

16. A non-transitory computer-readable medium having instructions stored thereon that, when executed by a processor of an implantable medical device, cause the processor to:  
 deliver, via the pulse generator, a maintenance dose of the electrical therapeutic stimulation at a second intensity lower than a first intensity of an enhanced dose during a non-exertion period of the patient;  
 monitor, via a sensor of the implantable medical device, a physiological state of a patient during physical exercise; and  
 upon sensing a condition indicative of cessation of the physical exercise based on the monitored physiological state, suspend delivery of the maintenance dose and deliver the enhanced dose to a vagus nerve of the patient.

17. A non-transitory computer-readable medium according to claim 16, wherein the sensor comprises a heart rate sensor, and wherein the instructions cause the processor to:  
 establish 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 sense a heart rate of the patient with the heart rate sensor;  
 confirm that the patient is undergoing the physical exercise when the heart rate of the patient gradually rises and is sustained at an elevated heart rate above the normative heart rate; and

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

18. A non-transitory computer-readable medium according to claim 16, wherein the sensor comprises an accelerometer, and wherein the instructions cause the processor to:  
 establish 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 sense an activity level of the patient with the accelerometer;  
 confirm that the patient is undergoing the physical exercise when the activity level of the patient gradually rises and is sustained at an elevated activity level above the normative activity level accompanied by an increased frequency of movement; and  
 subsequently confirm the cessation of the physical exercise when the activity level of the patient falls below the elevated activity level accompanied by a decreased frequency of movement by a threshold amount.

19. A non-transitory computer-readable medium according to claim 16, wherein the sensor comprises a minute ventilation sensor, and wherein the instructions cause the processor to:  
 establish a normative tidal volume and a normative respiratory rate of the patient with the minute ventilation sensor sensed during non-exertion periods exclusive of the physical exercise;  
 periodically sense a tidal volume and a respiratory rate of the patient with the minute ventilation sensor;  
 confirm that the patient is undergoing the physical exercise when the tidal volume and respiratory rate of the patient gradually rise and are sustained at elevated levels respectively above the normative tidal volume and the normative respiratory rate; and  
 subsequently confirm the cessation of the physical exercise when the tidal volume and respiratory rate of the patient fall below the respective elevated levels by a threshold amount.

20. A non-transitory computer-readable medium according to claim 16, wherein the instructions further cause the processor to monitor the physiological state of the patient throughout the delivering of the enhanced dose, and upon sensing a condition indicative of an onset of tachyarrhythmia, intensify the electrical therapeutic stimulation.

\* \* \* \* \*

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	<a href="#">US10384065</a>	公开(公告)日	2019-08-20
申请号	US15/585958	申请日	2017-05-03
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 A61N1/3621 A61B5/1118 A61B5/4836		
代理机构(译)	FOLEY & Lardner的律师事务所		
其他公开文献	US20170296822A1		
外部链接	<a href="#">Espacenet</a>		

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。通过可植入神经刺激器中包括的至少一个传感器在体育锻炼期间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。

