Title: APPLICATIONS OF HEART RATE VARIABILITY ANALYSIS IN BAROREFLEX ACTIVATION THERAPY AFFECTING AUTONOMIC NERVOUS SYSTEM RESPONSE

Abstract: A method of operating a baroreflex therapy system includes providing an implantable baroreflex activation device, providing a sensing arrangement, and providing a controller in operable communication with the baroreflex activation device and the sensing arrangement. The sensing arrangement is used to measure cardiac electrical activity of a patient to generate cardiac electrical activity data. The cardiac electrical activity data is communicated to the controller, wherein the controller performs heart rate variability analysis based on the cardiac electrical activity data. An indication of results of the heart rate variability analysis are provided, upon which a determination may be made to adjust a baroreflex therapy to be delivered by the implantable baroreflex activation device.
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APPLICATIONS OF HEART RATE VARIABILITY ANALYSIS IN BAROREFLEX ACTIVATION THERAPY AFFECTING AUTONOMIC NERVOUS SYSTEM RESPONSE

FIELD OF THE INVENTION

The invention relates generally to medical devices and methods, and more particularly, to baroreflex activation therapy devices, methods, and systems incorporating heart rate variability analysis for modulating a therapy.

BACKGROUND OF THE INVENTION

Cardiovascular disease is a major contributor to patient illness and mortality. It also is a primary driver of health care expenditure, costing more than $326 billion each year in the United States. Hypertension, or high blood pressure, is a major cardiovascular disorder that is estimated to affect over 65 million people in the United States alone. Of those with hypertension, it is reported that fewer than 30% have their blood pressure under control. Hypertension is a leading cause of heart failure and stroke. It is the primary cause of death for tens of thousands of patients per year and is listed as a primary or contributing cause of death for hundreds of thousands of patients per year in the U.S. Accordingly, hypertension is a serious health problem demanding significant research and development for the treatment thereof.

Hypertension occurs when the body's smaller blood vessels (arterioles) constrict, causing an increase in blood pressure. Because the blood vessels constrict, the heart must work harder to maintain blood flow at the higher pressures. Although the body may tolerate short periods of increased blood pressure, sustained hypertension may eventually result in damage to multiple body organs, including the kidneys, brain, eyes and other tissues, causing a variety of maladies associated therewith. The elevated blood pressure may also damage the lining of the blood vessels, accelerating the process of atherosclerosis and increasing the likelihood that a blood clot may develop. This could lead to a heart attack and/or stroke. Sustained high blood pressure may eventually result in an enlarged and damaged heart (hypertrophy), which may lead to heart failure.

Heart failure is the final common expression of a variety of cardiovascular disorders, including ischemic heart disease. It is characterized by an inability of the heart to pump enough blood to meet the body's needs and results in fatigue, reduced exercise capacity and poor survival. Heart failure results in the activation of a number of body systems to compensate for the heart's inability to pump sufficient blood. Many of these responses are mediated by an increase in the level of activation of the sympathetic nervous system, as well as by activation of
multiple other neurohormonal responses. Generally speaking, this sympathetic nervous system activation signals the heart to increase heart rate and force of contraction to increase the cardiac output; it signals the kidneys to expand the blood volume by retaining sodium and water; and it signals the arterioles to constrict to elevate the blood pressure. The cardiac, renal and vascular responses increase the workload of the heart, further accelerating myocardial damage and exacerbating the heart failure state. Accordingly, it is desirable to reduce the level of sympathetic nervous system activation in order to stop or at least minimize this vicious cycle and thereby treat or manage the heart failure.

It has been known for decades that the wall of the carotid sinus, a structure at the bifurcation of the common carotid arteries, contains stretch receptors (baroreceptors) that are sensitive to the blood pressure. These receptors send signals via the carotid sinus nerve to the brain, which in turn regulates the cardiovascular system to maintain normal blood pressure (the baroreflex), in part through activation of the sympathetic and/or parasympathetic nervous system (collectively, the autonomic nervous system). Electrical stimulation of the carotid sinus nerve has previously been proposed to reduce blood pressure and the workload of the heart in the treatment of high blood pressure and angina. For example, U.S. Pat. No. 6,073,048 to Kieval et al. discloses a baroreflex modulation system and method for stimulating the baroreflex based on various cardiovascular and pulmonary parameters. Implantable devices for treating high blood pressure or hypertension by stimulating various nerves and tissue in the body are known and described, for example, in U.S. Patent No. 3,650,277 (stimulation of carotid sinus nerve), U.S. Patent No. 5,707,400 (stimulation of vagal nerve), and U.S. Patent No. 6,522,926 (stimulation of baroreceptors).

Implantable baroreflex activation devices and systems for treating hypertension generally include a pulse generator that stimulates the patient’s baroreceptors by applying an electric field to the arterial wall of the carotid sinus artery via an electrode assembly intimately attached to the artery. The pulse generator is controlled by a microprocessor-based controller that may receive feedback from a sensed physiological parameter.

Since baroreflex activation therapy has conventionally been targeted to treating elevated blood pressure in the patient, the physical parameter most often considered for use in a feedback control scheme in BAT devices is blood pressure. Typical BAT devices would sense blood pressure directly, or indirectly, then adjust baroreflex activation accordingly. To this end, known methods for measuring pressure may include measuring the arterial blood pressure directly with an implanted blood pressure sensing device, or monitoring blood pressure indirectly, through measurement vessel wall dilation and contraction, blood flow volume or velocity, vascular resistance, and so on.
Measurements of arterial blood pressure for controlling automatic baroreflex activation devices can be difficult to obtain accurately by an implantable system having one or more sensors and measurement circuitry interfaced therewith. Although the cardiac rhythm is more readily measurable, such as with known electrocardiogram (ECG) measuring techniques, or with pulse timing, cardiac rhythm alone is only an indirect indicator of blood pressure. Additionally, an absolute measurement of a physiological parameter, that is, a measurement taken at a single moment in time, may be an incomplete indicator of the effectiveness of the therapy being delivered. Factors such as patient activity and/or environmental conditions may contribute to the sensed physiological parameter providing an incomplete representation of the condition of the patient and the effectiveness of the therapy.

One approach to monitoring heart rate during baroreflex therapy is to use a lead inserted into the heart of the patient. This approach can be overly complex, requiring additional invasive surgery to place the lead. Further, in many cases, the surgeon implanting the baroreflex therapy device is not trained to insert the lead in the heart, thereby requiring the services of an additional surgeon.

As various techniques are employed for treating cardiopulmonary and other diseases by medical devices to influence the body’s autonomic nervous system, there is an increasing need for assessing the effectiveness of, and controlling, the therapy to produce certain desirable effects, and to minimize certain undesirable effects on the autonomic nervous system and on other bodily systems responsive to control via the autonomic nervous system.

SUMMARY OF THE INVENTION

According to one aspect of the invention, heart rate variability (HRV) analysis is utilized to quantify the efficacy of baroreflex activation therapy (BAT) for modulating the Autonomic Nervous System (ANS) in the treatment of hypertension or other physiological condition or disease. In a related embodiment, the HRV analysis is further used to determine the need for increasing, decreasing, adjusting, stopping, or otherwise adjusting the BAT.

In various embodiments, the cardiac rhythm information collected for HRV analysis is gathered by a variety of sensing arrangements. For example, the cardiac rhythm can be sensed electrically such as according to known electrocardiogram (ECG) methods. In another example embodiment, the cardiac rhythm is detected by a pulse detection arrangement.

In a related embodiment, a combination of sensing arrangements of different types are used in concert, such as the combination of electrical cardiac rhythm sensing correlated to detected arterial pulses. This latter hybrid type of measuring arrangement can provide cardiac electrophysiology information in relation to heart contractility information, from which
analytical inferences might be made about the patient's condition. For example, differences between the HRV as computed based on an ECG type measurement, versus the HRV as computed by a pulse detection arrangement may provide important diagnostic insight.

In a related embodiment, the BAT device is communicatively interfaced as part of a system capable of reporting physiologic conditions measured by the device to an output apparatus having a user interface. This type of system arrangement can facilitate providing diagnostic information to a user such as a physician, nurse, technician, the patient, or other individual.

In one embodiment, the baroreflex activation device is configured with performance target information that is expressed in terms of HRV analysis output. If the actual measured patient condition (also in terms of HRV analysis output) is outside of a performance target range, the baroreflex stimulation device responds in some preconfigured manner. Responses include, for example, communicating the fact that the detected patient condition is out of a desirable range to an physician interface device; or adjusting the therapy in an attempt to improve the patient's condition through activation of the baroreflex system.

According to another aspect of the invention, HRV analysis is performed by a controller of a baroreflex activation device as part of a feedback system for controlling the administered therapy. In one type of embodiment, HRV-based feedback information can provide a more practicable ongoing measurement arrangement than a measurement of a sign (e.g. arterial blood pressure) that is the subject of treatment. In a related type of embodiment, HRV analysis is used in concert with other measured physiological responses or conditions. For example, HRV analysis can be considered by the BAT device or system together with one or more of: heart rate measurements, blood pressure measurements, respiration rate measurements, pulse oximetry measurements, blood chemistry measurements, ECG waveform analysis, end-tidal measurements, and any other parameter that is indicative of a heart beat.

In another type of embodiment, the autonomic nervous system response measurable by the HRV analysis is itself the subject of the treatment. In studying or treating diseases and conditions that have been correlated with certain autonomic nervous system conditions, or with one or more conditions expressed in terms of HRV analysis results, a BAT system can influence the body's physiology to achieve and maintain a certain state of the HRV as the target result.

One aspect of the invention recognizes that BAT effects the parasympathetic nervous system in addition to the sympathetic nervous system. Also, the baroreflex activation can affect the sympathetic/parasympathetic balance. According to one such embodiment, HRV analysis is performed in conjunction with BAT to measure effectiveness of the therapy on different parts of the autonomic nervous system. For example, the HRV analysis can be utilized to distinguish the
sympathetic response to the baroreflex activation from the parasympathetic response.

In a related embodiment, the BAT can be tuned or adjusted to emphasize a certain type of measured effect on the autonomic nervous system's response. For example, in one embodiment, the BAT can be controlled to produce a maximum suppressive effect on the sympathetic response, and a maximum enhancement effect on the parasympathetic response. In another embodiment, the therapy can be adjusted to emphasize parasympathetic tone without regard to the effect on the sympathetic tone.

According to another aspect of the invention, BAT is applied to treating conditions that are affected by modulation of the body's sympathetic and parasympathetic activities. For example, according to various embodiments, the therapy is tuned or adjusted to slow or increase the heart rate, decrease or increase intestinal and gland activity, or relax or tighten sphincter muscles in the gastrointestinal tract. Examples of conditions that may be treatable by such modulation of the autonomic nervous system include, without limitation, sleep apnea, irritable bowel syndrome, Crohn's disease, incontinence, pain, and other disorders besides blood pressure-related conditions.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a diagram illustrating various components of an example baroreflex activation device that is implantable in a patient, according to one aspect of the invention.

Fig. 2 illustrates one embodiment of a central processing unit (CPU) of the baroreflex activation device of Fig. 1.

Fig. 3 illustrates an example control system according to one embodiment for regulating the autonomic nervous system based on patient monitoring and heart rate variability analysis.

While the invention is amenable to various modifications and alternative forms, specifics thereof have been shown by way of example in the drawings and will be described in detail. It should be understood, however, that the intention is not to limit the invention to the particular embodiments described. On the contrary, the intention is to cover all modifications, equivalents, and alternatives falling within the spirit and scope of the invention.

DETAILED DESCRIPTION

Changes in blood pressure, heart rate, respiration, etc., are each an observable manifestation of the autonomic nervous system's response. Moreover, each named sign (or measure) is caused by a complex combination of physical responses. For example, blood pressure changes can be caused by arteriole constriction, cardiac rhythm activity, and numerous other mechanisms. As further research is conducted to study the root causes of hypertension and
associated diseases, one type of treatment approach can be directed to targeting the greater autonomic nervous system response, rather than selected observable symptoms such as high blood pressure, heart rate, and the like.

Baroreflex activation therapy (BAT) is known to affect the body's autonomic nervous system, which in turn regulates the blood pressure, heart rate, respiration, and other systems. BAT may be used to activate baroreceptors and/or nerves to provide the brain with signals indicating an increase in blood pressure. These signals cause the brain to reduce the body's blood pressure and level of sympathetic nervous system and neurohormonal activation, and increase parasympathetic nervous system activation. The efficiency or effectiveness of BAT may be influenced by when it is delivered relative to the cardiac, respiratory and other cycles. For example, BAT may be more or less effective when delivered during the contraction vs. relaxation phase of the heart or during the expiratory vs. inspiratory phase of respiration. Accordingly, absolute measurements of arterial pressure or heart rate do not entirely reflect the full effects of baroreflex activation.

Furthermore, because the end result of successful baroreflex activation therapy is to prevent these physical parameters from reaching extreme levels, e.g., reduce hypertension, prior efforts focused on the absolute measurement of such parameters as an indication of BAT effectiveness. Because of this prior focus, no one has previously confirmed or utilized the relationship between the variability of such parameters, especially as they indicate variability of heart rate, and BAT effectiveness.

The parasympathetic nervous system has a complementary relationship with the sympathetic nervous system. The body uses these two systems to regulate blood pressure. Stimulation or enhancement of the parasympathetic nervous system generally causes a decrease in blood pressure. Stimulating or enhancing the sympathetic nervous system, on the other hand, generally causes blood pressure to increase. If cardiac output is insufficient to meet demand (i.e., the heart is unable to pump sufficient blood), the brain activates a number of body systems, including the heart, kidneys, blood vessels, and other organs/tissues to correct this.

Baroreceptor signals in the arterial vasculature are used to activate a number of body systems which collectively may be referred to as the baroreflex system. For the purposes of the present invention, it will be assumed that the "receptors" in the venous and cardiopulmonary vasculature and heart chambers function analogously to the baroreceptors in the arterial vasculature, but such assumption is not intended to limit the present invention in any way. In particular, the methods described herein will function and achieve at least some of the stated therapeutic objectives regardless of the precise and actual mechanism responsible for the result. Moreover, the present invention may activate baroreceptors, mechanoreceptors, pressoreceptors,
stretch receptors, chemoreceptors, or any other venous, heart, or cardiopulmonary receptors which affect the blood pressure, nervous system activity, and neurohormonal activity in a manner analogous to baroreceptors in the arterial vasculature. For convenience, all such venous receptors will be referred to collectively herein as "baroreceptors" or "receptors" unless otherwise expressly noted.

While there may be small structural or anatomical differences among various receptors in the vasculature, for the purposes of some embodiments of the present invention, activation may be directed at any of these receptors and/or nerves and/or nerve endings from these receptors so long as they provide the desired effects. In particular, such receptors will provide afferent signals, i.e., signals to the brain, which provide the blood pressure and/or volume information to the brain. This allows the brain to cause "reflex" changes in the autonomic nervous system, which in turn modulate organ activity to maintain desired hemodynamics and organ perfusion. Activation of the baroreflex system may be accomplished by stimulating such receptors, nerves, nerve fibers, nerve endings, or any combination thereof.

Techniques are known for measuring the sympathetic and parasympathetic nervous system responses. Beat-to-beat fluctuations which occur around a person's mean heart rate are known as heart rate variability (HRV). The fluctuations from beat-to-beat are attributed, in part, to the nonlinear interaction between the sympathetic and parasympathetic branches of the autonomic nervous system. The sympathetic autonomic and parasympathetic autonomic nervous systems regulate, to some extent, the sinoatrial (SA) node and atrioventricular (AV) node of the heart and, thus, largely influence the control of the heart rate. These two nervous systems operate somewhat reciprocally to effect changes in the heart rate. In this regard, parasympathetic stimulation decreases the firing rate of the pacemaker cells located in the sinus node of the heart. Sympathetic stimulation, on the other hand, increases this firing rate.

Many clinicians agree that the parasympathetic and sympathetic inputs to the SA node mediate low frequency heart rate fluctuations (i.e., generally below 0.15 Hz), whereas modulation of parasympathetic outflow mediates higher frequency fluctuations. Studies have further shown that a decrease in heart rate variability correlates with a decrease in parasympathetic nervous activity and an accompanied increase in sympathetic nervous activity. See J. Thomas Bigger, et al, "Components of Heart Rate Variability Measured During Healing of Acute Myocardial Infarction" American Journal of Cardiology, Vol. 61 (1988), pp. 208-215. In a healthy, resting heart, for instance, the parasympathetic activity dominates to maintain the heart rate. However, in an unhealthy heart, for example one having heart disease, sympathetic activity may more influence and control the heart rate.

HRV analysis can be performed in at least two ways, such as by using time domain or
frequency domain measures of variability. In the case of ECG techniques that measure cardiac activity in terms of electrical parameters, or characteristics, intervals between heart beats (measured, for example, as the interval between successive R waves of an ECG) with a normal sinus mechanism (NN intervals) are measured and analyzed. Two commonly used measures are the standard deviation of NN intervals (SD), which increases with a reduction in sympathetic tone; and the root mean square of successive differences between adjacent NN intervals (rMSSD), which increases as parasympathetic tone is enhanced.

In another embodiment, HRV may be captured through the measurement of other physical parameters. Various mechanical, electromechanical, chemical, ultrasonic, optical, or other techniques may be used to measure parameters such as vessel wall expansion and contraction, changes in arterial impedance, varying levels of blood oxygenation, and so on. Though the type of measured data will vary according to measurement technique and parameter, each data set will represent a series of heart beats, from which HRV can be determined.

With respect to frequency domain measures of HRV, these may be obtained by performing Fourier analysis, such as fast Fourier transformation (FFT) on sampled sets of heart rate data, then analyzing changes in the content of certain frequency bins as a function of time.

For example, where ECG measuring techniques are used, two peaks are typically present in the FFT of five-minute ECG recordings. High frequency (HF) (0.15-0.40 Hz) peaks reflect modulation of the efferent parasympathetic activity, and low frequency (0.04-0.15 Hz) (LF) peaks reflect modulation of the efferent parasympathetic vagal and efferent sympathetic nervous system.

The amplitude of LF or HF power is a measure of autonomic nervous system modulation of sinus node firing, and not a measure of global sympathetic and parasympathetic nervous system tone; however, the LF/HF ratio is used as an index of sympathetic parasympathetic balance. In normal subjects the amplitude of LF power exceeds that of HF; however, during controlled respiration there is a marked increase in HF and a reduction in the LF components and of the LF/HF ratio.

A similar Fourier analysis of non-electrical physical parameters indicative of HRV may yield a different frequency-power spectrum, depending on the measured parameter, as compared to ECG recordings. For example, the frequency-power spectrum derived from measurements of the expansion and contraction of the carotid artery may demonstrate power spread across a wider frequency spectrum. However, the LF/HF ratio derived from the measurement of non-electrical physical parameters provides a similarly useful measure for understanding sympathetic parasympathetic balance.

Following acute beta-adrenergic blockade with the nonselective betablocker propranolol,
which would be expected to result in peripheral sympathoinhibition, there is typically an increase in the HF component and a reduction in the LF component of the FFT of five-minute ECG recordings. This is associated with a reduction in the LF/HF ratio. When blood pressure is reduced by an intravenous infusion of nitroglycerine, or tilt testing, there is typically an increase in the LF component indicating sympathetic activation.

FIG. 1 is a diagram illustrating an example baroreflex activation device 100 that is optionally implantable in a patient 102. Persons of ordinary skill in the art will recognize that the aspects of the invention can be suitably applied to non-implantable, i.e. external baroreflex activation devices. Device 100 includes a central processor unit (CPU) 104, which may include one or more microprocessors or microcontrollers, for example, that is configured to control the operation of the device. CPU 104 is configured to cause the device to administer the therapy via therapy circuit 106 and electrodes 108. A communications circuit 110 is interfaced with CPU 104 and is used for communicating information between CPU 104 and equipment external to the patient 102, such as a device programmer, external processor, external or remote sensors, or a remote transmission device such as a telecom/IT device. Baroreflex activation device 100 also includes a power source such as a battery 112, and power conditioning circuitry 114 for converting the battery power into various power supplies suitable for powering each component or sub-system of the device. CPU 104 can detect at least one physiologic condition of patient 102 via patient monitoring circuitry 116 and at least one sensor 118. In one embodiment, CPU 104 detects at least one physiologic parameter indicative of the heart rate of patient 102 via patient monitoring circuitry 116 and at least one sensor 118.

FIG. 2 illustrates one embodiment of CPU 104. CPU 104 includes a microprocessor core 200; read-only memory (ROM) 202 for storing instructions; random access memory (RAM) 204 for use as data gathering, or scratchpad memory during operation; input/output (I/O) bus driving circuitry 206 for transmitting and receiving information via, and controlling the use of, I/O bus 207; analog-to-digital (A/D) converter 208 for converting analog signals received via analog inputs 209 into a digital format for use by microprocessor core 200; and clock 210 for providing a time base for use by microprocessor core 200. In one type of embodiment, CPU 104 has signal processing capability (such as that provided by a DSP core) to perform computations on relatively long sequences of sampled data. An internal CPU interconnect 212 provides an interface between the various CPU components, and can include conventional data exchange hardware, such as a data bus, an address bus, and control lines (not shown).

Referring again to Fig. 1, in a related embodiment, the patient monitoring circuitry 116, or at least a portion of the signal processing circuitry of CPU 104 is situated remotely from device 100 and communicatively coupled with device 100. Similarly, sensor 118 can be
remotely situated from patient monitoring circuitry 116 or from device 100. In a further related embodiment, electrodes 108 may be remotely situated from device 100.

Sensor 118 can take many forms within the spirit of the invention. For example, sensor 118 can include an intravascular or external pressure transducer, arterial pulse detector ultrasonic activity detector, or any suitable device, internal or external to the patient, for sensing or detecting physiological events or activity of the patient. In another embodiment sensor 118 can be a chemical or optical sensor, such as a sensor for measuring a degree of blood oxygenation. Sensor 118 may also comprise a cardiac electrical activity detector, such as one or a set of ECG probes, whether internal or external to the patient. The ECG probes can be of the near-field type that are situated proximally (within 1-2 cm) of the heart or inside the heart. The ECG probes can also be of the far-field or extracardial type, such as external patches or implanted electrodes. Sensor 118 can also comprise a set of individual sensors of the same type or of different types. Sensor 118 may be implanted in whole or in part, or may be disposed outside the body. Furthermore, sensor 118 may be incorporated into a BAT electrode 108, or alternatively, may be a separate sensor, placed at a location some distance from a BAT electrode 108. Sensor 118 may also comprise a set of individual sensors of the same type or of different types.

Similarly, sensor 118 may comprise any suitable device or arrangement that senses, measures, or monitors a physical parameter from which heart rate, and ultimately HRV, may be derived. As used herein, physical parameter refers to any measure other than cardiac electrical activity that correlates with a heart beat. For example, sensor 118 may comprise a transducer or gauge that measures physical parameters such as blood pressure (systolic, diastolic, average or pulse pressure), blood volumetric flow rate, blood flow velocity, vessel dilation and constriction, vasoactivity, nerve activity, tissue activity, heart or body movement, activity levels, respiration, or any other physical parameter that indicates the occurrence of a heart beat. Examples of suitable transducers or gauges for sensor 118 include a piezoelectric pressure transducer, an ultrasonic flow velocity transducer, an ultrasonic volumetric flow rate transducer, a thermodilution flow velocity transducer, a capacitive pressure transducer, a membrane, an optical detector (SVO2), tissue impedance (electrical), or a strain gauge. Although only one sensor 118 is depicted, multiple sensors 118 of the same or different type at the same or different locations may be utilized.

Sensor 118 may be implanted inside the body as, for example, in an extracardiac location, such as in or on an artery, a vein, or a nerve. Sensor 118 may also be disposed outside the body. In one embodiment, sensor 118 may be implanted transluminally. Transluminal implantation of sensor 118 may be desired when the parameter is to be measured acutely and a non-invasive surgical implantation procedure is preferred.
When sensor 118 measures a physical parameter, it generates a sensor signal. The signal generated by sensor 118 may correspond directly to the measured physical parameter or a reference value from which the physical parameter can be accurately derived. In one embodiment, sensor 118 only generates a signal when the measured physical parameter reaches a pre-determined threshold or occurs within a certain range. In other embodiments, sensor 118 generates a signal continuously such that the physical parameter can be measured continuously.

As an illustrative example, in one embodiment, sensor 118 may comprise a foil strain gauge or force sensing resistor device disposed about, or wrapped around, an artery. In this embodiment, the physical parameter measured is the expansion and contraction of the vessel wall, detected as a series of forces exerted by the vessel wall upon sensor 118. As a patient's heart beats, the vessel walls expand and contracts, and such forces are measured by sensor 118. Although a time delay exists between heart beats and expansion and contraction of the vessel, the measured data indicates, or correlates, to heart rate. As such, timing, frequency, and other HRV information, may be determined by the data collected by sensor 118, and used to modify, or determine the effectiveness of, BAT.

According to one embodiment of the invention, patient monitoring circuitry 116 operates in cooperation with sensor 118 to collect cardiac activity information for CPU 104. CPU 104 processes this cardiac activity information to produce a characterization of the patient's condition being monitored. In one embodiment, monitoring circuitry 116 and sensor 118 collect cardiac rhythm information, such as the time difference between R-wave peaks, or the period or frequency of detected arterial pulses or heart beats. Such data may be communicated from sensor 118 to patient monitoring circuitry and/or CPU 104 in a variety of ways, including direct communication through cables and wires, via wireless communication methods, such as radio frequency, infrared, and other technologies, or through other techniques known in the art, and depending upon type and location of sensor 118. CPU 104 analyzes this cardiac rhythm information according to heart rate variability (HRV) analysis techniques, such as those described above, and produces an evaluated score or some other quantitative assessment of the HRV analysis. The HRV score or quantitative assessment may then be used to determine the need for increasing or decreasing, modulating, stopping, or otherwise adjusting the BAT.

Such data may be communicated from sensor 118 to patient monitoring circuitry and/or CPU 104 in a variety of ways, including direct communication through cables and wires, via wireless communication methods, such as radio frequency, infrared, and other technologies, or through other techniques known in the art, and depending upon type and location of sensor 118. CPU 104 analyzes this data according to heart rate variability (HRV) analysis techniques, such as those described above, and produces an evaluated score or some other quantitative
assessment of the HRV analysis. The HRV score or quantitative assessment may then be used to
determine the need for increasing or decreasing, modulating, stopping, or otherwise adjusting the
BAT.

In some embodiments, the BAT device is communicatively interfaced as part of a system
capable of reporting physiologic conditions measured by the device to an output apparatus
having a user interface. This type of system arrangement can facilitate providing diagnostic
information to a physician, medical doctor, nurse, medical technician, patient, or other such user.

In one embodiment, the BAT device is configured with performance target information
that is expressed in terms of HRV analysis output. If the actual measured patient condition (also
in terms of HRV analysis output) is outside of a performance target range, the BAT device
responds in some preconfigured manner. Responses include, for example, communicating the
fact that the detected patient condition is out of a desirable range to a physician interface device;
or adjusting the therapy in an attempt to improve the patient's condition through activation of the
baroreflex.

In one embodiment, a combination of electrical cardiac rhythm sensing is correlated to
detected arterial pulses. This type of scheme can provide cardiac electrophysiology information
in relation to heart contractility information. Processor 104 can use this information to make
additional inferences or diagnoses of the patient's condition. For example, differences between
the HRV as computed based on by an ECG type measurement, versus the HRV as computed by
a pulse detection arrangement may provide important diagnostic insight in to a systemic cause of
an observable disease. For example, the timing of pulse detection relative to electrical
depolarization detection can be an important measure.

In a related embodiment, processor 104 conducts HRV analysis so as to distinguish the
effectiveness of the BAT as affecting the sympathetic nervous system response, or as affecting
the parasympathetic nervous system response. This degree of analytical insight can be instituted
in concert with other, symptomatic-oriented, physiological sensing such as blood pressure, pulse
oximetry, and the like. Processor 104 can further process these various physiological
measurements or characterizations to synthesize the different types of information into a
comprehensive patient condition assessment. Analytical methods can include regression
analysis, morphology, and other computational techniques that are known in the art.

In one embodiment, as described above, baroreflex activation device 100 operates a
closed-loop control system for adjusting one or more therapy characteristics to achieve a desired
result as measured by patient monitoring circuitry 116 and sensor 118. FIG. 3 illustrates an
example control system 300 for regulating the therapy characteristics to produce a desired effect
on a monitored physiological parameter. A set point 302 representing the desired physiological
condition is provided to the system as depicted. Set point 302 is a target that system 300 will strive to achieve by adjusting the level, waveform, or any other characteristic or combination of characteristics of the therapy administration. The adjustment can be conducted according to a predetermined regime or algorithm. Set point 302 can be stable, or time-variable, depending on the nature of the physiologic condition to be controlled. For additional disclosure pertaining to therapy characteristics that can be adjusted by system 300 to achieve set point target 302 such as therapy signal characteristics, see U.S. Patent No. 6,985,774 to Kieval et al., the disclosure of which is hereby incorporated by reference in its entirety.

Control system 300 compares set point 302 with an actual measurement 304 and analytical assessment 305 of the measurement 304 to produce an error signal 306. The error signal 306 is operated on by proportional-integral-differential controls 308, 310, and 312, respectively. Proportional control 308 includes a proportional weighting constant KP; integral control 310 includes an integral weighting constant KI; and differential control 312 includes differential weighting constant KD. The output of each control type is aggregated to produce a control signal 314. The baroreflex activation device administers a therapy dosage 316 according to the control signal 314, which results in a controlled effect 318 in the patient.

In one example embodiment, the feedback loop includes the analytical result of the HRV analysis. Thus, for example, in an embodiment where the control objective is to operate the baroreflex stimulation signal in a mode that produces the greatest parasympathetic tone enhancement in the patient, a measured and computed rMSSD is produced by analytical assessment 305 and used as the feedback signal to compare against a desired set point 302 expressed in terms of rMSSD.

Various techniques for BAT can be applied according to embodiments of the invention to achieve different types of effects on the patient's autonomic nervous system. For example, in one embodiment, in addition to or in place of stimulating baroreceptors in the carotid sinus artery at the carotid bifurcation, baroreflex therapy can be applied to the carotid body to stimulate chemoreceptors. Stimulation of the carotid body can produce an effect on the autonomic nervous system that generally opposes the effects resulting from stimulation of the baroreceptors.

In another type of embodiment, the autonomic nervous system response measurable by the HRV analysis is itself the subject of the treatment. Thus, according to one aspect of the invention, autonomic nervous system condition or response is used as part of a control loop capable of (a) suppressing sympathetic tone and enhancing parasympathetic tone; (b) enhancing sympathetic tone and suppressing parasympathetic tone; (c) enhancing or suppressing sympathetic tone; or (d) enhancing or suppressing parasympathetic tone. Embodiments of this aspect include treatment of patients with sleep disorders such as sleep apnea, in which it may be
desirable to increase the patient's sympathetico-adrenal response during the day, or during active
times, and to decrease it during times of rest.

To selectively enhance or suppress sympathetic vs. parasympathetic response, an
implanted baroreflex activation device with multiple electrode assemblies can be utilized, with
the first electrode assembly positioned to stimulate receptors at a first anatomical location, and
the second electrode assembly is positioned to stimulate receptors at a second anatomical
location. In an example embodiment, the first anatomical location is the carotid bifurcation
wherein baroreceptors are activated, while the second anatomical location is the carotid body
wherein chemoreceptors are activated.

In a related embodiment, a single electrode assembly having a plurality of electrode sets
includes a first electrode set positioned to stimulate receptors in a first area or anatomical
location, while the second electrode set is positioned to stimulate receptors in a second area or
anatomical location. In one embodiment, the receptors stimulated in the first area are of a
different type from the receptors stimulated in the second area, for instance one may be
baroreceptors while the other may be chemoreceptors.

In another embodiment, in which the activity of the digestive system is influenced, for
example, the baroreflex activation device selectively stimulates one or the other of these sensory
mechanisms to produce the desired effect. Thus, to increase digestive activity, baroreflex
activation can be administered to enhance the parasympathetic tone and suppress the sympathetic
tone; and to decrease digestive activity, the carotid body can be stimulated to suppress the
parasympathetic tone while enhancing the sympathetic tone.

In another embodiment of the present invention, multiple baroreflex activation devices
can be provided as part of a baroreflex activation therapy system. In one embodiment, the
sensing arrangement may comprise a separate baroreflex activation device that is capable of
delivering cardiac rhythm management (CRM). Additional disclosure pertaining to the
combination of BAT devices and therapies with CRM devices and therapies that is relevant to
the present invention can be found in Published U.S. Patent Application No. 2006/0004417 to
Rossing et al., and Published U.S. Patent Application No. 2006/0074453 to Kieval et al., the
disclosures of which are hereby incorporated by reference in their entirety.

In another embodiment, a single baroreflex activation device may be configured to
deliver more than one therapy. For example, a single device may deliver two or more distinct
baroreflex therapies. In another embodiment, a single device may deliver a baroreflex therapy
and a drug delivery therapy. In another embodiment, a single device may deliver a baroreflex
therapy and a cardiac rhythm management therapy. In a still further embodiment, multiple
devices may be communicably coupled to a controller, such that a therapy system is capable of
delivering one or more baroreflex therapies, or some combination of baroreflex therapy, drug delivery therapy, and cardiac rhythm management therapy. In the case of such combination devices, one or more therapies and/or devices may be adjusted to achieve the desired effect.

Additional disclosure material that exemplifies at least a portion of the other features and functionality of the range of embodiments within the spirit and scope of the present invention can be found in Published U.S. Patent Application No. 2005/0154418 to Kieval et al., Published U.S. Patent Application No. 2005/0251212 to Kieval et al., and Published U.S. Patent Application No. 2006/0293712 to Kieval et al., the disclosures of which are hereby incorporated by reference in their entireties. Additional disclosure material relating to vascular anatomy and the cardiovascular system as it pertains to the present invention can be found in U.S. Patent No. 6,522,926 to Kieval et al., the disclosure of which is hereby incorporated by reference.

Although the description of the present invention is focused on baroreflex activation therapies based on electrical stimulation of the baroreflex system, other forms of baroreflex activation are fully within the spirit and scope of the invention. For example, various forms of mechanical baroreflex activation and chemical baroreflex activation are applicable to the embodiments disclosed herein. Additional disclosure relating to mechanical and chemical forms of baroreflex therapy can be in U.S. Patent No. 6,522,926, previously incorporated by reference.

Various modifications to the invention may be apparent to one of skill in the art upon reading this disclosure. For example, persons of ordinary skill in the relevant art will recognize that the various features described for the different embodiments of the invention can be suitably combined, un-combined, and re-combined with other features, alone, or in different combinations, within the spirit of the invention. Likewise, the various features described above should all be regarded as example embodiments, rather than limitations to the scope or spirit of the invention. Therefore, the above is not contemplated to limit the scope of the present invention.

For purposes of interpreting the claims for the present invention, it is expressly intended that the provisions of Section 112, sixth paragraph of 35 U.S.C. are not to be invoked unless the specific terms "means for" or "step for" are recited in a claim.
WHAT IS CLAIMED IS:

1. A method of operating a baroreflex therapy system, comprising:
   providing an implantable baroreflex activation device;
   providing a sensing arrangement;
   providing a controller in operable communication with the baroreflex activation device and the sensing arrangement;
   measuring a patient parameter with the sensing arrangement to generate patient parameter data;
   communicating the patient parameter data to the controller;
   performing heart rate variability analysis with the controller based on the patient parameter data; and
   providing an indication of results of the heart rate variability analysis upon which a determination may be made to adjust a baroreflex therapy to be delivered by the implantable baroreflex activation device.

2. The method of claim 1 wherein providing an indication of the results of the heart rate variability analysis is selected from the group consisting of: communicating the results to a physician interface device, and communicating the indication to the implantable baroreflex activation device.

3. The method of claim 1, wherein the controller is configured with a desired performance target range, further comprising:
   comparing the results of the heart rate variability analysis to the desired performance target range; and
   automatically adjusting the baroreflex therapy with the controller if the results of the heart rate variability analysis are outside of the desired performance range.

4. The method of claim 1, wherein the target performance range is set by a physician.

5. The method of claim 1, further comprising:
   sensing a patient second parameter associated with heart rate to generate patient second parameter data;
   communicating the patient second parameter data to the controller; and
providing an indication of the patient second parameter data and results of the heart rate variability analysis, upon which a determination may be made to adjust the baroreflex therapy to be delivered by the baroreflex activation device.

6. A method, comprising:
   providing an implantable baroreflex activation device;
   providing a sensing arrangement;
   providing a controller operably communicable with the baroreflex activation device and the sensing arrangement; and
   providing instructions for operating the device, comprising:
   measuring a patient parameter with the sensing arrangement to generate patient parameter data;
   communicating the patient parameter data to the controller;
   performing heart rate variability analysis with the controller based on the patient parameter data; and
   providing an indication of the results of the heart rate variability analysis to determine an effect on the autonomic nervous system of a patient, upon which a determination may be made to adjust a baroreflex therapy to be delivered by the implantable baroreflex activation device.

7. The method of claim 6, wherein the heart rate variability analysis is used to distinguish a sympathetic nervous system response to the baroreflex therapy from a parasympathetic nervous system response to the baroreflex therapy.

8. The method of claim 6, wherein the baroreflex therapy is adjusted in response to the results of the heart rate variability analysis to increase and/or suppress an effect on the autonomic nervous system.

9. The method of claim 6, wherein the controller is configured with a desired performance target range of an autonomic nervous system response, further comprising:
   comparing the results of the heart rate variability analysis to the desired performance target range; and
   automatically adjusting the baroreflex therapy with the controller if the results of the heart rate variability analysis are outside of the desired performance range.
10. The method of claim 6, wherein the baroreflex therapy is adjusted in response to the results of the heart rate variability analysis to increase an enhancement effect on the parasympathetic nervous system of the patient.

11. The method of claim 6, wherein the baroreflex therapy is adjusted in response to the results of the heart rate variability analysis to increase a suppressive effect on the sympathetic nervous system of the patient.

12. The method of claim 6, wherein providing an indication of the results of the heart rate variability analysis is selected from the group consisting of: communicating the results to a physician interface device, and communicating the results to the implantable baroreflex activation device.

13. The method according to any one of the preceding claims characterized in that the patient parameter comprises a cardiac electrical activity parameter.

14. A system for providing a baroreflex therapy, comprising:
   a baroreflex activation device;
   a sensing arrangement adapted to collect patient parameter data; and
   a controller in communication with the device and the sensing arrangement, wherein the controller is adapted to receive the patient parameter data from the sensing arrangement, perform heart rate variability analysis of the patient parameter data, and provide an indication of results of the heart rate variability analysis upon which a determination may be made to adjust a baroreflex therapy to be delivered by the baroreflex activation device.

15. The system of claim 14, further comprising a physician interface device communicatively coupled to the controller and configured to communicate the results of the heart rate variability analysis to a physician.

16. The system of claim 14, wherein the controller includes a desired performance target range, the results of the heart rate variability analysis are compared to the desired performance target range, and the controller is adapted to automatically adjust the baroreflex therapy if the results of the heart rate variability analysis are outside of the desired performance target range.

17. A system for providing a baroreflex therapy, comprising:
a baroreflex activation device;
means for sensing a patient parameter of a patient, adapted to collect patient parameter data; and
means for controlling the system in communication with the device and the means for sensing patient parameter, wherein the means for controlling is adapted to receive the patient parameter data from the means for sensing, perform a heart rate variability analysis of the patient parameter data, and provide an indication of results of the heart rate variability analysis upon which a determination may be made to adjust a baroreflex therapy to be delivered by the baroreflex activation device.

18. The system of claim 17, further comprising a means for communicating the results of the heart rate variability analysis to a physician.

19. The system of claim 17, wherein the means for controlling includes a desired performance target range, the results of the heart rate variability analysis are compared to the desired performance target range, and the means for controlling is adapted to automatically adjust the baroreflex therapy if the results of the heart rate variability analysis are outside of the desired performance target range.

20. A baroreflex therapy system, comprising:
an implantable baroreflex activation device;
a sensing arrangement;
a controller in operable communication with the baroreflex activation device and the sensing arrangement; and
instructions recorded on a tangible medium for operating the device, comprising:
  measuring a patient parameter with the sensing arrangement to generate patient parameter data;
  communicating the patient parameter data to the controller;
  performing heart rate variability analysis with the controller based on the patient parameter data; and
  providing an indication of the heart rate variability analysis upon which a determination may be made to adjust a baroreflex therapy to be delivered by the implantable baroreflex activation device.

21. The system of claim 20, wherein providing an indication of the results of the heart rate
variability analysis is selected from the group consisting of: communicating the results to a physician interface device, and communicating the results to the implantable baroreflex activation device.

22. The system of claim 20, wherein the controller is configured with a desired performance target range, further comprising:
   comparing the results of the heart rate variability analysis to the desired performance target range; and
   automatically adjusting the baroreflex therapy with the controller if the results of the heart rate variability analysis are outside of the desired performance range.

23. The system of claim 20, wherein the sensing arrangement is selected from the group consisting of:
   at least one sensor integrated with the implantable baroreflex activation device,
   at least one sensor separate from the implantable baroreflex activation device,
   a second implantable medical device that is capable of delivering cardiac rhythm management, and
   a sensor integrated with the baroreflex activation device, the device also capable of delivering cardiac rhythm management.

24. The system according to any one of the claims 14 to 23 characterized in that the patient parameter comprises a cardiac electrical activity parameter.
FIG. 2
FIG. 3