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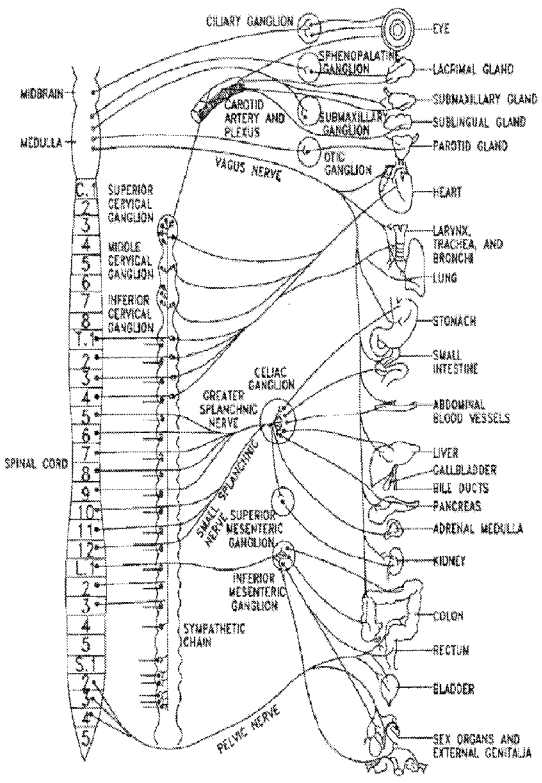
(54) Title: IMPROVED METHODS OF CONTROLLING CARDIOVASCULAR HEALTH

FIG. 1



(57) Abstract: The description provides devices and methods of using such devices to electrically stimulate autonomic nerves to control and improve blood pressure and/or hypertension. These methods can be used to treat subjects that have high blood pressure, are hypertensive or are exercise impaired.

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Improved Methods of Controlling Cardiovascular Health

Cross-Reference to Related Applications

This application claims priority from U.S. provisional patent application number 61/089,709 filed August 18, 2008 and U.S. provisional patent application number 61/164,458 filed March 29, 2009, both of which are incorporated by reference in their entirety.

Field of the Invention

The description provides devices and methods of using such devices to electrically stimulate autonomic nerves to control and/or improve cardiovascular metrics.

Background

The autonomic nervous system is a subsystem of the human nervous system that controls involuntary actions of the smooth muscles (blood vessels and digestive system), the heart, and glands, as shown in FIG. 1. The autonomic nervous system is divided into the sympathetic and parasympathetic systems. The parasympathetic system prepares the body for rest. The sympathetic nervous system generally prepares the body for action by increasing heart rate, increasing blood pressure, and increasing metabolism. Neuromodulation therapies that involve stimulating the sympathetic nervous system have, therefore, been challenging to implement because stimulation of the sympathetic system could in theory cause unsafe cardiovascular results.

Therefore, there is a need for improved neuromodulation methods that are safe and beneficial to the cardiovascular system and in some instances also provide treatments for other medical conditions.

Summary

Improved methods of electrically stimulating the sympathetic nervous system (SNS) are described herein. These methods provide improving one or more cardiovascular metrics. In some examples, the methods involve electrically stimulating the SNS and lowering blood pressure below a baseline blood pressure. Such methods also allow for more effective use of neurostimulation therapies for the treatment of various disorders, such as obesity, metabolic syndrome (e.g., insulin resistance, abnormal cholesterol profiles, as well as others), diabetes, and related abnormalities. These methods include using a stimulation pattern that includes at least two doses. Additionally, some of these methods involve electrical stimulation of a sympathetic nerve with a simulation pattern that includes at least one soft transition, at least one dose ramp, and combinations thereof. The stimulation patterns can be delivered for at least one, two, three, or four weeks. In some examples, stimulation patterns are delivered for months and years. Such stimulation patterns can vary over the time that they are administered and can be referred to as therapeutic regimes. Typically, stimulation patterns can vary in current, frequency and pulse width, as well as overall ON and OFF times. Moreover, OFF times include

time when no electrical stimulation is delivered, as well as times when minimal electrical stimulation is delivered.

In some examples, subjects having hypertension are treated with the therapeutic regimes described herein. These subjects are electrically stimulated with a simulation pattern having at least one soft transition, at least one dose ramp or combinations thereof. After completion of a therapeutic regime, the hypertensive state of the subject is improved.

In yet other examples, the cardiovascular health of a subject that is exercise compromised can be improved. As described in further detail below, exercise compromised subjects include subjects that are incapable of cardiovascular exercise or otherwise should exercise under doctor supervision. There are various metrics of cardiovascular health that can be used to establish a baseline level for a particular metric. A stimulation pattern can be administered to the subject. The pattern can include at least one soft transition, at least one dose ramp, or combinations thereof. After a therapeutic regime is complete, the cardiovascular metric is improved.

One of ordinary skill in the art will appreciate that the stimulation patterns described herein can include electrical stimulation at a variety of different frequencies. For example, frequencies of less than 50, 25, 20, 10, 5, 3, 2, or 1 Hz can be used. Similarly, the current used can vary. Exemplary currents include less than 5 mA, 4 mA, 3 mA, 2 mA and 1 mA. Other variations in the electrical stimulation can include varying pulse widths (PW). For example, pulse widths of less than 1 millisecond, less than 700 microseconds, less than 600 microseconds, less than 300 microseconds, or less than 100 microseconds can be used.

In some of the examples provided herein, the soft transitions will have both a leading soft transition and an ending soft transition. These soft transitions can last for less than 5, 10, 20, 30, 40, or 60 seconds. Moreover, the rate of change during a soft transition can be from about 0.1 mA/second to about 1 mA/second.

In some of the examples provided herein dose ramping is included. Dose ramping is further described below and includes ramping the signal intensity at the beginning of the ON portion of a dose (i.e., leading dose ramp) and in some cases decreasing the signal intensity at the end of a dose (i.e., ending dose ramp). Stimulation patterns including a dose ramp have a MAX dose and the doses are ramped from the initial signal intensity to the MAX dose during the ON portion of a dose. Exemplary dose ramping includes ramping from 1 to 5 mA over 5, 10 or 20 minutes with, or without, a similar rate of decrease at the end of the ON portion of the dose. Similarly, dose ramping can include ramping PW and/or current.

Surprisingly, the weight of the subjects can remain substantially the same over the course of a therapeutic regime. However, in some instances, it may increase or decrease.

Also included in the disclosure are devices programmed to provide the various therapies described herein.

Detailed Description

I. Definitions

"Baseline" as used herein refers to the measure of a physiological state when a subject is not treated with a specific therapy. Physiological states are typically assessed using physiological markers including biological markers and cardiovascular metrics. Exemplary biological markers include, for example, hormones, carbohydrates, vitamins, minerals, receptors, ligands, as wells as many other molecules known in the art. Baseline can be assessed while a subject is medicated, or is otherwise undergoing a therapeutic regime that does not contain a stimulation pattern that include doses having soft transitions, dose ramping, or combinations thereof. For instance, a subject that is taking oral medication to control blood pressure can have a baseline blood pressure that is measured while on that medication. The baseline measure is generally tested over the course of days to establish an average of at least two time points, thus, minimizing the possibility that the baseline measurement will reflect an unusually high or low temporary value for a subject. The baseline, once established, can then be used in comparison to a post therapy measurement of that same physiological state to determine the benefit of a specific therapy. For example, baseline blood pressure can be established by taking an average of two or more blood pressure readings over the course of one or more days. A therapeutic regime, as described below, can be administered to the subject and after the termination of stimulation, or post stimulation, blood pressure can be measured again and compared to baseline. The comparison allows one to determine the effectiveness of a particular therapeutic regime.

"Cardiovascular health" as used herein refers to the health of a subject's heart or blood vessels (arteries and veins). One of ordinary skill in the art will appreciate that there are many known metrics that can be used to characterize cardiovascular health. These metrics include, for example, blood pressure (BP), veinous return, atrial fill rate, heart rate (HR), cardiac rhythm, and cardiac output (Q). Q is the volume of blood being pumped by the heart, in particular, by a ventricle in one minute. This is measured in cubic decimeters/min (1 cubic decimeter equals 1000 cubic centimeters or 1 liter). An average cardiac output for a healthy human would be 5 L/min for a human male and 4.5 L/min for a female. HR can vary by a factor of approximately 3, between 60 and 180 beats per minute, while stroke volume (SV) can vary between 70 and 120 mL, a factor of only 1.7. A parameter related to SV is Ejection Fraction (EF). EF is the fraction of blood ejected by the Left Ventricle (LV) during the contraction or ejection phase of the cardiac cycle or systole. Prior to the start of systole, the LV is filled with blood to the capacity known as End Diastolic Volume (EDV) during the filling phase or diastole. During systole, the LV contracts and ejects blood until it reaches its minimum capacity known as End Systolic Volume (ESV), it does not empty completely. Clearly, the EF is dependent on the ventricular EDV, which can vary with ventricular disease associated with ventricular dilatation. Even with LV dilatation and impaired contraction the Q can remain constant due to an increase in EDV. These cardiovascular metrics relate to each other as follows:

Stroke Volume (SV) = EDV – ESV

Ejection Fraction (EF) = (SV / EDV) × 100%

Cardiac Output (Q) = SV × HR

Cardiac Index (CI) = Q / Body Surface Area (BSA) = SV × HR/BSA

HR is Heart Rate, expressed as BPM (Beats Per Minute)

BSA is Body Surface Area in square meters.

Cardiovascular health improvement can be observed by measuring one or more of these metrics to establish a baseline and then measuring metric again to determine the percentage change from baseline. Depending upon the measured metric an improvement will be represented by an increase or decrease in the measured value. One of ordinary skill in the art will appreciate that even a slight improvement can provide health benefits. For example, an improvement at least 0.01% from the baseline metric or at least 0.02%, at least 0.5%, at least 0.7%, at least 1%, at least 3%, at least 5% or at least 7% from the baseline metric is an improvement in cardiovascular health.

"Blood Pressure" as described herein includes diastolic, systolic, or mean arterial blood pressure (MAP, i.e., the average pressure in one complete cardiac cycle or several cycles such as cycles within a 10 minute period). One of ordinary skill in the art will appreciate that mmHg are the units most commonly used to describe blood pressure and that a standard cuff and stethoscope can be used to measure blood pressure. An improvement in blood pressure can be observed by measuring diastolic, systolic or MAP to establish a baseline and after therapy measuring that same pressure again. A decrease in at least 0.01% from baseline, at least 0.05%, at least 0.1%, at least 1.0%, or at least 3% from baseline is an improvement. As mentioned above blood pressure can be used as an indicator of cardiovascular health.

"Pulse" as used herein describes a unit of electric energy delivered. Pulses have a certain pulse width and amplitude (see FIGS. 3A-3C). One of ordinary skill in the art will understand that each pulse is normally followed by a recharge and a possible idle period. A series of pulses including the recharge and idle, if present, is termed a pulse train. Pulse trains are usually measured in units of time from about 1 millisecond to about 60 seconds. However, pulse trains having a longer duration are possible. The characteristics of a pulse or pulse train are chosen so that the desired action potentials can be triggered in the nerve fibers within the nerve.

"Soft transition" refers to the increase or escalation of, the amplitude of pulses during the initial part of a pulse train (i.e., leading soft transition). See, FIGS. 3A-3C. The term soft transition also can include a stepwise decrease in amplitude of pulses at the end of a pulse train (i.e., ending soft transition). When used in a therapeutic regime the soft transition generally occurs every time a pulse train occurs. The use of soft transitions within a therapeutic regime can be used to decrease cardiovascular stress.

"Duty cycle" refers to the amount of "ON" time and "OFF" time. A pulse train is considered the "ON" time in a duty cycle and the "OFF" time within a duty cycle indicates a period in which little or no stimulation occurs. Duty cycle is reflected in the percentage ON time within a cycle. Therefore, a 50% duty cycle lasting 2 minutes includes 60 seconds ON and 60 seconds OFF (see, exemplary program interface in FIG. 10).

"Dose" is used to refer to the repeating pattern of ON times and OFF times, with ON times pulses having certain amplitudes, frequencies, and pulse widths (PW). The ON time within a dose can have a leading and ending ramp and can be repeated in various patterns (see, Exemplary 30 ramped dose shown in FIG. 9). Dose ramping is an additional method of controlling cardiovascular metrics, such as improving blood pressure. Inter-dose ramping can also be used in a stimulation pattern. Inter-dose ramping includes increasing/decreasing stimulation between doses. Exemplary doses include a pattern of one hour ON and two hours OFF, one hour ON and one hour OFF, 30 minutes ON and one hour OFF. Doses are usually measured in units of time from about 5, 10, 15, 20, 25, or 30 minutes, or as long as up to 1, 2, 3, 4, 5, 6, 8, 10 or 24 hours. It is typical to give multiple doses in a day, such as at least 1, 3, 5, 6, 7, 9, 12, or more doses.

"Therapeutic regime" refers to the stimulation pattern designed to bring a subject to a clinical goal. For example, a therapeutic regime is a sequencing of doses that can include a variety of variations in duty cycle, ramping, frequency (Hz) and stimulation intensity (see, FIGS. 3A-3C). Therapeutic regimes can last from one day to as long as years. In some instances, subjects will need to be chronically on a therapeutic regime. Dynamic stimulation patterns change (e.g., have doses and can change in Hz, PW and/or current) over an identified period of time. The choice of therapeutic regime will depend on the subject and end goal of the therapy. For example, if a subject is treated for obesity the therapeutic regime will be designed to induce weight loss over the course of months. The stimulation pattern is chosen such that therapeutic effectiveness is maintained over a desired length of time.

"Tolerability threshold" is established by providing a stimulation intensity and/or a duty cycle while observing the reaction of the subject. In the case of dogs, tolerability can be established by observing behaviors such as whining, pacing, repetitive behaviors, or muscle twitch. In the case of humans, the subject can provide verbal feedback regarding the discomfort caused by a particular stimulation pattern. The amplitude, frequency and/or pulse width can be either decreased or increased until the subject indicates (indication will depend upon the species of the subject) that the stimulation is not tolerable, then the amplitude, frequency and/or pulse width can be readjusted to a level that allows the subject to conduct daily activities without a serious negative impact caused by the therapeutic regime. One of ordinary skill in the art will appreciate that the tolerability threshold may change for a given subject and that treatment can be titrated throughout a treatment regime to accommodate the subject's tolerability threshold.

Tolerability can also be established using physiological markers, such as biomarkers (e.g., circulating hormones, carbohydrates, and fatty acids) or changes in cardiovascular metrics. Therapy can

then be titrated to those markers. In other words, electrical stimulation can be administered until a given biomarker reaches a desired level.

"Hypertensive/hypertension" refers to subjects that display blood pressure profiles that are elevated compared to the normal population. For example, in humans normal systolic pressures range from about 90 to about 119 mmHg and normal diastolic pressures range from about 60-79 mmHg. Humans can be classified as having varying degrees of hypertension if one or more of these pressures exceed these normal ranges. Additionally, hypertensive subjects may or may not display additional physical problems including for example, obesity, diabetes, elevated triglycerides, elevated cholesterol, as well as breathing and sleep disorders.

"Modulation" refers to the excitation (elicitation of one or more action potentials), inhibition, or a combination of excitation and inhibition of a nerve or nerve fibers. Electrical "activation" generally includes excitation, but can also include blocking (e.g., high frequency stimulation).

Definition clarifications.

Where a range of values is provided, it is understood that each intervening value between the upper and lower limit of that range and any other stated or intervening value in that stated range is encompassed within the invention. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the invention.

It must be noted that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a pulse generator" includes a plurality of different pulse generators unless context clearly requires otherwise.

The term "or" refers to a single element of stated alternative elements or a combination of two or more elements, unless the context clearly indicates otherwise. For example, the phrase "biomarker or cardiovascular metric" refers to biomarkers, cardiovascular metrics, or a combination of both cardiovascular metrics and biomarkers.

The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided may be different from the actual publication dates, which may need to be independently confirmed.

Before the present invention is further described, it is to be understood that this invention is not limited to particular embodiments described. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

Other terms and definitions are defined throughout the text as necessary for providing a detailed description.

II. Figure Descriptions

FIG. 1 is a diagrammatic view of an efferent autonomic nervous system anatomy.

FIG. 2 is a diagrammatic view of a sympathetic nervous system anatomy.

FIGS. 3A -3C is a diagram showing the relationship of a pulse, duty cycle, dose and therapeutic regime. One of ordinary skill in the art will appreciate that the ON time described in a therapeutic regime does not actually reflect that amount of time electrical energy is delivered to a splanchnic nerve. Therapeutic ON time refers to the amount of time that a dose is run during a therapeutic course. Similarly, one of ordinary skill in the art will appreciate that the ON time within a dose does not represent the amount of time electrical energy is delivered to a splanchnic nerve. The ON time in a dose actually refers to the amount of time a duty cycle is run during a dose. This same pattern also holds true for the ON time within a duty cycle. The ON time within a duty cycle actually represents the amount of time a pulse or pulse train is running within the duty cycle and within the pulse train there may be an OFF period that includes a recharge and/or an idle period. Therefore, one of ordinary skill in the art will appreciate that the true measure of electrical energy delivered over the course of a therapeutic regime needs to be calculated taking all of these relationships into consideration.

FIG. 4 shows a diagram of a quadrapolar blocking electrode.

FIG. 5 shows a diagram of an implantable pulse generator (IPG) with a lead.

FIG. 6 shows a flow schematic of an IPG.

FIG. 7A is a bar graph showing the results of a comparison of mean arterial blood pressure (MAP) changes caused by static stimulation and dose ramping compared to baseline. These results indicate that dose ramping mitigates rises in BP compared to static stimulation. FIG. 7B is a line graph showing the impact of ON and OFF time on BP. In FIG. 7A the diamonds indicate changes in BP caused by static stimulation (stimulation that initiates at the maximum intensity and holds that intensity during the whole ON time) and the squares indicate changes in MAP caused by a ramped dose. These results indicate that dosing including dose ramping mitigates the highs and lows compared to static stimulation.

FIG. 8 is a line graph showing the BP response to both a frequency ramped dose and a current ramped dose. The control is a static stimulation. The frequency ramped dose is shown as triangles with a light dashed line and the current ramped dose is shown as triangles with a dark dashed line. The results indicate that both frequency ramping and current ramping favorably mitigate BP changes as compared to the unramped control.

FIG. 9 shows a diagram reflecting the components of a dose ramp in comparison to a inter dose ramp. The dose ramp shown reflects 30 minute dose that includes a 10 minute leading dose ramp and a 5 minute ending dose ramp. Also shown is the plateau within the dose that lasts 15 minutes at which signal intensity is maintained. This is in contrast to the inter dose ramping shown as a series of 30 minute doses that increase in intensity and then decrease.

FIG. 10 is a diagram reflecting the characteristics of a soft transition. Pulses having 519 microsecond lengths are delivered in a 60 second ON and 60 second OFF pattern. The soft transition is programmed such that maximum current amplitude for a given pulse train is reached in 5 seconds. The soft transition can also include an ending soft transition.

FIG. 11 shows a graph of data generated from a 45-day study in which various stimulation patterns were run in dogs to determine the impact of the stimulation pattern on mean arterial blood pressure (MAP). The results indicate that initially MAP increased over baseline, but over time, it decreased to baseline and below. Over the course of a therapeutic regime, this pattern is useful for beneficially altering cardiovascular health.

FIG. 12 shows various diagrams depicting exemplary algorithms (stimulation patterns) described below, in Examples 3 and 4. These stimulation patterns contain both soft transitions (i.e., 2 sec ramp up) and dose ramping (i.e., one-hour ramp up).

FIG. 13 shows a more detailed view of the stimulation patterns shown in FIG. 12, above.

FIG. 14 shows a line graph of MAP changes from baseline on a daily basis throughout the stimulation portion of the study (see Example 3 below). The results indicate that MAP changes related to algorithms used and that by the end of the stimulation MAP had decreased below baseline for the majority of the algorithms.

FIG. 15 shows a line graph of heart rate (HR) changes from baseline on a daily basis throughout the stimulation portion of the study (see Example 3, below). The results indicate that HR stayed below baseline for all of the algorithms during the stimulation portion of the study, with the exception of a spike in the algorithm A group on day 6. One of ordinary skill in the art will appreciate that given the sample size deviations, such as that seen on day 6, are expected, however, the overall results indicate a favorable impact on HR.

FIG. 16 shows a bar graph of depicting the post-stimulation impact on BP that resulted from the stimulation algorithms described below in Example 3. These results indicate that BP remains below baseline for at least two weeks post-stimulation (Post-Stim1 and Post-Stim2).

FIG. 17 shows a bar graph of depicting the post-stimulation impact on HR that resulted from the stimulation algorithms described below in Example 3. These results indicate that HR remains below baseline for at least two weeks post-stimulation (Post-Stim1 and Post-Stim2).

III. Stimulation Patterns

The stimulation patterns described herein include two or more doses and a soft transition, a dose ramp or combinations thereof. One of ordinary skill in the art will appreciate that the choice of the pattern, and the intensity thereof, will be impacted by the anatomy and physiology of the nerve fibers that are being targeted by the therapy.

FIGS. 1 and 2 provide an overview of the autonomic nervous system. The hypothalamus controls the sympathetic nervous system via descending neurons in the ventral horn of the spinal cord, as shown in FIG. 2. These neurons synapse with preganglionic sympathetic neurons that exit the spinal cord and form the white communicating ramus. The preganglionic neuron will either synapse in the paraspinous ganglia chain or pass through these ganglia and synapse in a peripheral, or collateral, ganglion such as the celiac or mesenteric. After synapsing in a particular ganglion, a postsynaptic neuron continues to innervate the organs of the body (heart, intestines, liver, pancreas, etc.) or to innervate the adipose tissue and glands of the periphery and skin. Preganglionic neurons of the sympathetic system can be both small-diameter unmyelinated fibers (type C-like) and small-diameter myelinated fibers (type B-like). Postganglionic neurons are typically unmyelinated type C neurons.

The greater splanchnic nerve (GSN) is formed by efferent sympathetic neurons exiting the spinal cord from thoracic vertebral segment numbers 4 or 5 (T4 or T5) through thoracic vertebral segment numbers 9, 10, or 11 (T9, T10, or T11). The lesser splanchnic (lesser SN) nerve is formed by preganglionic fibers sympathetic efferent fibers from T10 to T12 and the least splanchnic nerve (least SN) is formed by fibers from T12. The GSN is typically present bilaterally in animals, including humans, with the other splanchnic nerves having a more variable pattern, present unilaterally or bilaterally and sometimes being absent. The splanchnic nerves run along the anterior lateral aspect of the vertebral bodies, pass out of the thorax, and enter the abdomen through the crus of the diaphragm. The nerves run in proximity to the azygous veins. Once in the abdomen, neurons of the GSN synapse with postganglionic neurons primarily in celiac ganglia. Some neurons of the GSN pass through the celiac ganglia and synapse on in the adrenal medulla. Neurons of the lesser SN and least SN synapse with post-ganglionic neurons in the mesenteric ganglia.

Postganglionic neurons, arising from the celiac ganglia that synapse with the GSN, innervate primarily the upper digestive system, including the stomach, pylorus, duodenum, pancreas, and liver. In addition, blood vessels and adipose tissue of the abdomen are innervated by neurons arising from the celiac ganglia/greater splanchnic nerve. Postganglionic neurons of the mesenteric ganglia, supplied by preganglionic neurons of the lesser and least splanchnic nerve, innervate primarily the lower intestine, colon, rectum, kidneys, bladder, and sexual organs, and the blood vessels that supply these organs and tissues.

Action potentials are initiated when a voltage potential across the cell membrane exceeds a certain threshold. This action potential is then propagated down the length of the neuron. The action potential of a nerve is complex and represents the sum of action potentials of the individual neurons in it.

Neurons can be myelinated and unmyelinated and of large axonal diameter and small axonal diameter. In general, the speed of action potential conduction increases with myelination and with neuron axonal diameter. Accordingly, neurons are classified into type A, B and C neurons based on myelination, axon diameter, and axon conduction velocity. In terms of axon diameter and conduction velocity, A is greater than B, which is greater than C.

Each neuronal type (i.e., type A, B, or C neurons) has a characteristic pulse amplitude-duration profile (energy pulse signal or stimulation intensity) that leads to activation. The stimulation intensity can be described as the product of the current amplitude and the pulse width. Myelinated neurons (types A and B) can be stimulated with relatively low current amplitudes, approximately 0.1 to 5.0 milliamperes, and short pulse widths, approximately about 50 microseconds to about 200 microseconds. Unmyelinated type C fibers typically require longer pulse widths approximately about 300 microseconds to about 1,000 microseconds and higher current amplitudes for stimulation. Thus, in certain embodiments, the stimulation intensity for efferent activation of a nerve can be in the range of about 0.005 mAmp-msec to about 5.0 mAmp-msec. In certain embodiments, the stimulation intensity for efferent activation of a nerve can be in the range of about 0.001 mAmp-msec to about 10.0 mAmp-msec.

Three characteristics, among other things, can be used to describe stimulation intensity. These characteristics are the pulse width (PW), current (amplitude) and frequency. As is evident from the description provided herein the choice of the stimulation pattern and the characteristics of the stimulation intensity will be driven by which nerve fibers, nerves, end organs, or tissues are the target of the therapy, as well as by whether signal blocking is included.

The stimulation patterns described herein can use a variety of PWs. For example, PWs from about 50 microseconds to about 1 second can be used, from about 100 microseconds to about 500 milliseconds, or from about 100 microseconds to about 900 microseconds can be used. In some examples, the PW is less than 600 microseconds. The pulse widths can be varied during both leading and ending soft transitions, as well as during dose ramping and intra dose ramping. Moreover, pulse widths can be varied at the same time, prior to, or after changes in current and frequency are made during a therapeutic regime.

The stimulation patterns described herein can use a variety of currents. For example, currents of from about .5 mA to about 10 mA, from about 1.5 mA to about 7 mA, or from about 2 mA to about 5 mA can be used. In some examples, the current is less than 6 mA. The current can be varied during both leading and ending soft transitions, as well as during dose ramping and intra dose ramping. Moreover, current can be varied at the same time, prior to, or after changes in PW and frequencies are made during a therapeutic regime.

The stimulation patterns described herein can use a variety of frequencies. For example, frequencies of from about .5 Hz to about 100 Hz, from about 1.0 Hz to about 20 Hz, or from about 2 Hz to about 5 Hz can be used. In some examples, the current is less than 3 Hz. The frequency can be varied during both leading and ending soft transitions, as well as during dose ramping and intra dose ramping. Moreover, the frequency can be varied at the same time, prior to, or after changes in PW and current are made during a therapeutic regime.

Doses have ON times and OFF times and typically, multiple doses are given during a day. In some instances two or more, three or more, four or more, five or more, 6 or more, 9 or more, or 10 or

more doses are given within a 24 hour period. Moreover, some of the doses given within a 24-hour period can contain dose ramping, soft transitions, or combinations thereof. The distribution of multiple doses within a given time period can also vary. For example, within a 24-hour period 6 doses having a one hour ON duration can be given. The ON times can be distributed substantially evenly over the 24 hours, for example in a pattern of one hour ON and three hours OFF, or the pattern can be shifted to abbreviate the OFF times during the day and increase them at night. Similar changes can be made to tailor the dosing pattern for various purposes. In instances where the therapy is designed to target cardiovascular health in combination with the treatment of obesity, doses can be given prior to or at the time of meals. In other examples, doses can be given over the course of weeks and months. Such doses can be given such that 25% of the doses occur in the first half of the therapeutic time and then the remaining 75% of the doses can be given in the last half of the therapeutic time. As described in more detail below, the use of doses with a therapeutic regime has been seen to improve cardiovascular metrics during therapy as well as post stimulation.

In some examples it is beneficial to escalate the stimulation intensity between doses (inter-dose ramping) until the peak stimulation intensity is reached. For example, the doses on day one in a therapeutic regime can be set to reach a maximum of 1 mA for each dose and then starting on day two the maximum can be changed to 2 mA. Frequency can also be ramped on an inter-dose ramping scheme and therefore, is included in the term inter-dose ramping.

As previously mentioned ramping within a dose (i.e., dose ramping) causes an escalation in signal intensity to a maximum (leading dose ramp) and when present a decrease in signal intensity at the end of the dose (ending dose ramp). For example, if a specific dose has a maximum intensity of 5 mA the first pulse train of that dose can be delivered at 1 mA, the second pulse train at 2 mA, the third at 3 mA, the fourth at 4 mA and finally the fifth at 5 mA. Several pulse trains can then be delivered at this maximum intensity and then the dose can be ramped down or up again in a similar fashion. One of ordinary skill in the art will appreciate that doses can be ramped using incremental changes in current, frequency, pulse widths and combinations thereof. Typically dose ramping is referred to as a specified change over time. For example, pulse width can be ramped from a 100 microsecond pulse to a 1000 microsecond pulse at the beginning of a dose and a similar ramp down can be used. In other examples, a frequency dose ramp can be included. Frequency can ramp from 1 Hz to 3, 5, 10 or 20 Hz at the beginning of a dose and a similar ramp can be used at the end of the dose. Similarly, current can be ramped from .1 mA to about 5 mA at the beginning of a dose and a similar ramp down can be used at the end of a dose. The rate will then depend upon the amount of time within a specific dose that is dedicated to the ramp.

Dose ramping can be used to slowly condition the cardiovascular system and ease a subject into and out of a series of ON times within a therapeutic regime.

Therapeutic regimes can also include time OFF that lasts for as long as one, two or three days. One of ordinary skill in the art will appreciate the time OFF does not necessarily mean that no stimulation is occurring. In some instances, a low level of stimulation can be provided during the time

OFF. When present in a therapeutic regime time off can be dispersed evenly or at regular intervals within a therapeutic regime. For example, every 3rd day, 4th day, or 5th day can be OFF. Time off can also be more random and distributed throughout a therapeutic regime, for instance at times chosen by the subject or doctor.

Soft transitions can be used with or without being accompanied by dose ramping within a therapeutic regime. Similar to dose ramping, soft transitions can be on a steep slope or a shallow slope, meaning that the intensity of the pulses can increase quickly or over a longer period of time. For example, a soft transition can increase/decrease at a rate of about .01 mA/microsecond to about .1 mA/microsecond. In other examples, a soft transition ramps from 0.1 mA to 5 mA in 2, 5, 10 or 30 seconds. The choice of the duration of the increase will depend upon the goal of the therapeutic regime.

The duty cycle can range from about 1% to about 100%. Peripheral nerve stimulation is commonly conducted at nearly a continuous, or 100%, duty cycle. However, an optimal duty cycle for splanchnic nerve stimulation to treat cardiovascular health can be less than 75% in some embodiments, less than 50% in some embodiments, or even less than 30% in certain embodiments. This can reduce problems associated with muscle twitching as well as reduce the chance for blood pressure or heart rate elevations caused by the stimulation energy. The on-time can also be important for splanchnic nerve stimulation in the treatment of cardiovascular health. Because some of the desired effects of nerve stimulation can involve the release of hormones, on-times sufficiently long enough to allow plasma levels to rise are important.

The stimulation intensity (current (mAmp or mA) multiplied by pulse width (mSec)) can be varied throughout a therapeutic regime. In can be successively increased or randomly increase and decrease. A maximum tolerable intensity can be established through subject feedback or through observation of physical parameters such as muscle twitch or changes in one or more cardiovascular metrics. In some examples, therapy is increased by about 20% each day thereafter (i.e. during each subsequent portion of the simulation time period) until the stimulation intensity reaches a therapeutic optimum. One of ordinary skill in the art will appreciate that the therapeutic optimum will vary depending upon the desired therapeutic outcome. For instance, if cardiac strength is the end goal of the therapy the stimulation intensity can be increased until the heart is working at a level of moderate exercise. Once this level has been reached, stimulation can be repeated much like a normal exercise regime.

In certain embodiments, a stimulation intensity increase of about 20% from one portion of the stimulation ON period to the next portion is achieved by increasing the pulse width by about 20%. In certain embodiments, the stimulation intensity increase of about 20% is achieved by changing both the current and pulse width such that the product of the new values is about 20% greater that the product of the previous day's values for those parameters. In certain embodiments, the stimulation intensity increase of about 20% is achieved by increasing both the current and pulse width such that the product of the new values is about 20% greater that the product of the previous day's values for those

parameters. In certain embodiments, the stimulation intensity increase of about 20% is achieved by increasing the current amplitude of the stimulation signal by about 20%.

In certain embodiments, the stimulation intensity increase of about 20% in a 24-hour period is achieved by an approximately continuous change in either the current amplitude, pulse width, or both. In certain embodiments, the stimulation signal intensity increase of about 20% in a 24 hour period is achieved by changing the current amplitude, pulse width, or both, at irregular intervals within each 24-hour period. In certain embodiments, the stimulation signal intensity increase of about 20% in a 24-hour period is achieved by changing the current amplitude, pulse width, or both, at regular intervals within each 24-hour period. In certain embodiments, the stimulation intensity increase of about 20% in a 24-hour period is achieved by changing the current amplitude, pulse width, or both, at regular intervals and in a stepwise manner within each 24-hour period. In certain embodiments, stimulation intensity increase of about 20% in a 24 hour period is achieved by changing the current amplitude, pulse width, or both, once during each 24-hour period. In certain embodiments, the stimulation intensity increase of about 20% in a 24 hour period is achieved by increasing the current amplitude once during each 24 hour period.

IV. Devices

Any device capable of providing electrical stimulation to autonomic nerves can be used to deliver a desired therapeutic regime. One of ordinary skill in the art will appreciate that there are a variety of pulse generators, electrodes and software configurations known in the art and that can be used in the methods described herein. The following description is therefore, offered as a non-limiting description of potential device choices.

Devices can be used to provide electrical stimulation in an afferent direction (from the peripheral nerves to the central nervous system), efferent direction (from the central nervous system to the periphery) or combinations thereof. One of ordinary skill in the art will appreciate that the type of pulse generator and lead chosen will impact the functionality of the device and that devices specific for afferent, efferent and combinations of afferent and efferent stimulation can be chosen and are well known in the art. A description of such devices is provided in WO2009020581A1, IKI et al. (priority number US2007000955018P, filed 2007-08-09), US2007000955018Pwhich is herein incorporated by reference in its entirety.

In some examples, efferent stimulation will be used to primarily stimulate the sympathetic nervous system that innervates the digestive system, adrenals, abdominal adipose tissue, and splanchnic vascular bed. In instances were the primary goal is efferent stimulation the afferent signal from the sympathetic nervous system can be partially (e.g., blocked intermittently or allowing for selective nerve fiber stimulation) or fully blocked using various anode and cathode configurations known in the art. An exemplary quadrapolar blocking electrode is shown in FIG. 4, however, as previously mentioned other designs can be used.

In one example, afferent stimulation can be used to provide input into the central nervous system. For example, signals relating to satiety can be used in a therapy designed to improve cardiovascular metrics and treat obesity and co-morbidities thereof. In instances were the primary goal is afferent stimulation the efferent signal from the central nervous system can be partially (e.g., blocked intermittently or allowing for selective nerve fiber stimulation) or fully blocked using various anode and cathode configurations known in the art.

A simple design of one possible device that can be used in the methods described herein is shown in FIG. 5. An electrical tissue modulation energy source in the form of an implantable pulse generator (IPG) 28 is coupled to a cuff electrode 30 by a conductive lead 32. Embodiments of the conductive lead 32 can include a central conductor or bundle of central conductors, braided or otherwise, surrounded by an insulation layer. The conductive lead 32 can generally be a flexible thin member capable of transmitting electrical energy of a variety of types and can be electrically insulated and shielded in order to prevent energy from escaping into surrounding tissue. The conductive lead 32 can be configured to transmit direct current, alternating current including radiofrequency current and the like. The length of embodiments of the conductive lead 32 can be from about 10 cm to about 100 cm. Pins at a proximal end 34 of the electrode lead 32 plug into a receptacle 36 in the IPG 28. The various circuitry components of the IPG 28 can be housed in an epoxy-titanium shell 38. The IPG shell 38 is generally disc shaped and can have an outer transverse dimension of about 3 cm to about 15 cm and a thickness of about 3 mm to about 15 mm.

Referring to the schematic representation of an embodiment of an impulse generator (IPG 28) in FIG. 6, the IPG 28 contains a battery 40 that is coupled to and supplies power to a logic and control unit 42 that can include a central processing unit and memory unit (not shown). The battery 40 itself can be of a rechargeable variety that can be recharged either by direct electric coupling with a recharge voltage supply or by remote inductive coupling. If inductive coupling is to be used, a recharge signal can be generated external to a patient's body and coupled to a receiver, which is in turn in electrical communication with the battery 40. A tissue stimulation pattern, which, for some embodiments, can be a tissue stimulation or treatment algorithm, can be programmed into the memory unit of the logic and control circuit 42. The memory unit can include software or hardware that is configured to store information necessary to carry out a tissue stimulation pattern or regimen in a repeatable and controllable manner. Such information stored in the memory unit can be uploaded or downloaded via non-invasive wireless communication via an antenna 44, which is coupled to the logic and control unit 42.

A voltage regulator 46 is disposed between the battery 40 and logic and control unit 42 and controls the battery output to the logic and control unit 42. A crystal oscillator 48 provides timing signals for output pulse signals and for the logic and control unit 42 generally. The antenna 44 is coupled to an output unit 50 and the logic and control unit 42 and is used for transmitting information to and receiving communications from an external programmer or wand (not shown). The external programmer or wand can also check on the status of the IPG 28. The output unit 50 is coupled to the electric lead 32 of the IPG 28 which can terminate at a receptacle 52 configured to couple electrically with the pins on the

proximal end 34 of the conductive lead 32 of the cuff electrode 30. The output unit 50 can also include a radio transmitter to inductively couple with a wireless electrode embodiment (not shown) of the cuff electrode 30. For such an embodiment, conductive electric leads between the IPG 28 and the cuff electrode 30 would be unnecessary. One embodiment of the IPG 28 can include the Cyberonics Model 101 manufactured by the Cyberonics Company in Houston, Tex.

The logic and control unit 42 controls the tissue stimulation output energy and includes a memory unit that can store machine readable information which allows for programming of desired tissue stimulation patterns or algorithms including the chronological profile of electrical stimulation energy parameters over time including the signal voltage, frequency, pulse width, duty cycle and the like. Such desired tissue stimulation patterns or algorithms can include any of the stimulation patterns or algorithms discussed herein. The tissue stimulation patterns or algorithms can be configured to improve cardiovascular health, as well as improve lipid profiles or aspects of lipid profiles, increase energy expenditure, increase lean tissue or muscle mass or treat any other attendant or contributing condition of metabolic syndrome discussed herein.

In one exemplary embodiment, a patch electrode can also be used. As one of ordinary skill in the art will appreciate, such an electrode does not encircle the nerve, but rather is attached to a structure in close proximity to the nerve. Patch electrodes can be chosen when improvement of cardiovascular health in combination with the treatment of diseases, such as diabetes, is desired.

In addition, one or more sensors (i.e, implantable or external) can be used to detect physiological markers and provide feedback in a closed loop in order to adjust stimulation signal parameters or treatment algorithms. Such sensors can be used to ensure that cardiovascular metrics are maintained within safe parameters. Examples of such feedback or control loop embodiments include achieving predetermined levels of cardiovascular metrics, including for example BP and HR, plasma catecholamine, C-reactive protein, HbA1C as well as those described above. In addition to using, a sensor a subject can be provided with a program modulating device that allows the subject to input certain information relating to pain, fatigue, and the like. Such subject supplied information can then be used to shift the therapeutic regime to either a more strenuous or a less strenuous stimulation pattern.

One of ordinary skill in the art will appreciate that there are multiple methods that can be used to implant the devices described herein. One example includes implanting a lead/electrode assembly for activation of the greater splanchnic nerve (also referred to herein as "the splanchnic nerve") percutaneously using an introducer. The introducer can be a hollow needle-like device that would be placed posteriorly through the skin between the ribs para-midline at the T9-T12 level of the thoracic spinal column. A posterior placement with the patient prone can allow bilateral electrode placement at the splanchnic nerves, if desired. Placement of the needle can be guided using fluoroscopy, ultrasound, or CT scanning. Proximity to the splanchnic nerve by the introducer can be sensed by providing energy pulses to the introducer electrically to activate the nerve while monitoring for a rise in a cardiovascular metric. All but the tip of the introducer can be electrically isolated so as to focus the energy delivered to

the tip of the introducer. Generally, the lower the current amplitude used to cause a rise in a cardiovascular metric, the closer the introducer tip would be to the nerve.

In some embodiments, the introducer tip serves as the cathode for stimulation. In certain embodiments, a stimulation endoscope can be placed into the stomach of the patient for electrical stimulation of the stomach. The evoked potentials created in the stomach can be sensed in the splanchnic nerve by the introducer. To avoid damage to the spinal nerves, the introducer can sense evoked potentials created by electrically activating peripheral sensory nerves. Alternatively, evoked potentials can be created in the lower intercostal nerves or upper abdominal nerves and sensed in the splanchnic. Once the introducer was in proximity to the nerve, a catheter type lead electrode assembly would be inserted through the introducer and adjacent to the nerve. Alternatively, a wireless, radiofrequency battery charged, electrode can be advanced through the introducer to reside alongside the nerve. In either case, stimulating the nerve and monitoring for a rise in MAP or muscle twitch can be used to confirm electrode placement.

Once the electrode is in place the current amplitude can be increased at a pulse width of about 50 usec to about 500 usec and a frequency of about 1 Hz, until a BP response is observed. The current amplitude can be set slightly above or slightly below the identified BP threshold. After identifying the desired current amplitude, the pulse width can be increased by as much as 2.5 times and the frequency increased up to about 40 Hz for therapeutic stimulation. The lead (where used) and the IPG can be implanted subcutaneously in the patient's back or side. The lead can be appropriately secured to tissue of the patient to avoid dislodgement. The lesser and least splanchnic nerves can also be activated to some degree by lead/electrode placement according to the above procedure, due to their proximity to the splanchnic nerve.

V. Methods

Generally, the methods described herein relate to modulating cardiovascular metrics using autonomic nerve stimulation. Methods of using combinations of sympathetic and parasympathetic neural stimulation typically can involve a pattern of blocking and signaling, such stimulation can be in parallel or in series (simultaneous blocking of the vagal nerve and stimulation of the splanchnic nerve, or stimulating one first and then the other second). In some instances, the methods described use stimulation profiles having doses and escalating signal intensities which allow a subject to be eased into a stimulation pattern. It is believed that stimulation patterns that include doses, which in turn include soft transitions, dose ramping or combinations thereof, increase the tolerability and effectiveness of the therapy.

A. Reducing Blood Pressure

Generally, unsafe cardiovascular conditions can be controlled by pharmaceutical intervention when diet and exercise fail to offer acceptable solutions. In instances where a subject's blood pressure is elevated typical pharmaceutical intervention can include diuretics to rid the body of excess fluids, beta-blockers to reduce the heart rate and the heart's output of blood, sympathetic nerve inhibitors

causing arterial constriction, vasodilators to cause the muscle in the walls of the blood vessels (especially the arterioles) to relax, allowing the vessel to dilate (widen), angiotensin-converting enzyme (ACE) inhibitors that interfere with the body's production of angiotensin and angiotensioin antagonists. These pharmaceuticals can be used alone or in combination, however, they depend upon patient compliance/tolerance with dosing regimes to keep the subject's blood pressure within safe limits. Therefore, it is desirable to have a therapy that helps control blood pressure and which does not require patient controlled delivery.

As described herein, blood pressure can be controlled during sympathetic nerve stimulation and can be decreased during a stimulation pattern and, moreover that decrease can be maintained post-stimulation. In some examples, blood pressure is controlled during stimulation through the use of one or more doses. During the stimulation the stimulation intensity can be escalated at the pulse train level (soft transition), at the dose level (dose ramping) or a combination thereof. By using escalating signal intensities, the subject's cardiovascular system avoids spikes in cardiovascular metrics such as, for example, heart rate (HR) and/or blood pressure (BP). In the absence of such escalation, BP has been seen to rapidly increase and then decrease at the end of stimulation, thus causing a cycling.

In some examples, high blood pressure mitigating pharmaceuticals are combined with therapeutic regimes to provide a maximum clinical benefit. When a specific stimulation profile is combined with certain classes of BP medications, a synergistic benefit is observed. For example, when combined with diuretics, ACE inhibitors and calcium channel blockers the benefits of both therapies can be realized. In some examples, medication is provided and/or increased during OFF times within a therapeutic regime. In other examples, as a therapeutic regime is initiated medication is started at an initial concentration and then slowly decreased, thus shifting the burden of therapy from the pharmaceutical to the electrical stimulation. The combination of a therapeutic regime with a pharmaceutical can also allow for greater variation within a therapeutic regime so that habituation and/or tachyphalaxis can be avoided, as well as the undesirable side effects associated with pharmaceutical intervention.

As is shown in the examples below various stimulation patterns can improve BP. For example, post stimulation blood pressure can be lowered by at least 0.1% compared to baseline blood pressure. In other examples post stimulation BP can be lower than baseline BP by at least 0.2, 0.5, 0.8, 1.0, 5.0 or 6%.

In some instances after a therapeutic regime is completed, BP remains below baseline. The BP can remain below baseline for at least one week, two weeks, three weeks, four weeks or as long as several months post-stimulation. One of ordinary skill in the art will appreciate that when the primary reason for administration of the therapy is to control BP, the subject can be monitored and upon return to baseline blood pressure, a new therapeutic regime can be initiated. Therefore, the methods provided herein also include administering multiple therapeutic regimes over the course of a subject's life. For example, 1, 2, 3, 4, 10, or 20 or more therapeutic regimes can be provided. Moreover, the stimulation patterns provided in such regimes can be varied to avoid habituation.

In some of the methods described herein, subjects that are hypertensive are selected for therapy. Subjects displaying hypertension can be identified using any method known in the art. In some examples, hypertensive subjects have systolic blood pressures that are greater than 120, 140, 150, 160, or 190 mmHg and in other instances hypertensive subjects have diastolic pressures greater than 80, 90, 100, or 100 mmHg. In many instances, subjects having hypertension will additionally display normal body mass indexes and be capable of normal physical activity.

One of ordinary skill in the art will appreciate that there are many methods of selecting subjects having hypertension. Symptoms associated with hypertension include morning headache, tinnitus - ringing or buzzing in ears, dizziness, confusion, papilloedema, high blood pressure, fatigue, shortness of breath, convulsion, changes in vision, nausea, vomiting, anxiety, increased sweating, nose bleeds, heart palpitations, increased urination frequency, blurred vision, pale skin, and chest pains. These symptoms can be used to select subjects as hypertensive and in some instances, further clinical testing can be performed to identify the subject as hypertensive. After selection of a subject that is hypertensive, an appropriate therapy can be administered to improve the subject's condition.

B. Exercise Compromised

Exercised compromised subjects, as described herein, are individuals that cannot physically exercise themselves due to mental and/or physical impairment or individuals that have physical conditions that lead to a recommendation of exercise under doctor supervision. These people are selected for the stimulation therapy described herein and stimulation profiles are established based upon their overall physical condition. The therapeutic regimes that are designed for exercise compromised subjects can also be designed to mimic the physiological impact of both the state of the body during normal exercise (i.e., the active state) and the state of the body post exercise.

A therapeutic regime that includes a stimulation profile directed to mimicking an active state can be titrated. In other words, the maximum impact of a stimulation pattern can be set based upon the level of a physiological marker and/or patient feedback. For example, the correct starting stimulation pattern can be determined using patient feedback, monitoring to ensure that there is no significant (e.g., greater than 20%) rise in rennin, angiotensin II or NPY, monitoring glucose, and or glucagon, monitoring for a 10-20% rise in BP or HR, and/or by monitoring one or more of the cardiovascular metrics described above.

Stimulation patterns designed to mimic an active state can improve the cardiovascular health of an exercise compromised subject by using variations in ON times. For example, at the initiation of a therapeutic regime stimulation doses that last for less than 10 minutes can be used. These 10 minute doses can be delivered two or more times in the first day of therapy. In some instances, it may be desirable to maintain a patient on a stimulation pattern having such relatively short doses. In other instances, upon improvement (measured by patient comfort and/or physiological markers) the duration of the ON time can be increased to, for example, less than 15 minutes, less than 20 minutes, less than 25 minutes or less than 30, 40, 45, 50, or 60 minutes. These ON times can be separated by various OFF

times having certain durations. Generally, such therapeutic regimes are intended to bring a subject up to a certain level of cardiovascular fitness that can be established by improvements in one or more of the cardiovascular metrics described. When such level of fitness is achieved, the duration of the final ON time in the final dose is termed the TARGET. If it is desired, a subject can be maintained at the TARGET through further stimulation.

Stimulation patterns designed to mimic an active state can also be classified as mimicking mild, moderate or intense active states. For example, a stimulation pattern can cause direct and/or indirect modulation of muscles and arterial baroflex gain by putting the body into various exercise states: mild, moderate or intense exercise. It is believed that the benefits observed relating to cardiovascular metrics after dosed therapy may be due, in part, to this mechanism.

In other examples, the stimulation pattern designed to mimic an active exercise state can include a total dose-time designed to accelerate gluconeogenesis and shift the liver from a lactate-producing to a lactate-consuming state. One of ordinary skill in the art will appreciate that when gluconeogenesis is used to titrate a stimulation pattern lactate and/or glucose can be measured.

As mentioned above, a post exercise state can also be triggered through a stimulation pattern. For example, a 1 hour low intensity dose can be included after the active state has been induced. This post exercise stimulation mimics the normal physiological mobilization of free fatty acids and glycerol. A dose at 3 mA or less has been observed to mobilize free fatty acids, glycerol, glucagon and ghrelin (results not shown). In some examples, a dose having a current of 1-2.5 mA, a PW of from about 100 to about 600 microseconds, a frequency of from about 1-10 Hz and lasting from about 30-60 minutes can be delivered to approximate post exercise.

Examples that are more specific are described in the following Examples section. These examples are provided to further support the overall description and they are not intended to limit the scope of the description.

Examples

Example 1.

This example shows the benefits of using frequency and current ramping to control acute blood pressure during stimulation.

Initial studies indicate that at the onset of stimulation there can be an acute rise in blood pressure (BP). Such acute rises can be mitigated through selection of stimulation intensity parameters, however, as described herein they can also be mitigated using current ramping. See FIG. 7A which compares the BP changes that occur without current ramping to those that occur with a ramped dose. As is evident from FIG. 7A, the peak BP level from the ramped dose is less than that observed with static stimulation and the subsequent depression in BP is also mitigated. Thus, ramping can serve to reduce the overall BP changes compared to those created during static stimulation.

Dogs were implanted with IPGs and baseline heart rate (HR) and BP measurements were taken. These dogs were then subjected to static stimulation (i.e., at the onset of stimulation maximum frequency and current were used and held without dosing). Dogs were also subjected to a dynamic stimulation pattern involving doses having 80 minutes ON and 160 minutes OFF and a 60/60 duty cycle with a leading current dose ramp of 30 minutes and an ending ramp of 10 minutes. Six of these doses were given in a day. BP and HR were measured and the baseline measurements were compared to static stimulation and dose ramping (see, FIG. 7B). The results show that dose ramping decreased mean arterial blood pressure changes compared to static stimulation and moreover, the dose ramping MAP was below baseline MAP.

Additional studies were done with frequency based dose ramping to 5 mA. Similar to above, the frequency based dose ramping results were compared to static stimulation, as well as current dose ramping. The results are shown in FIG. 8. Similar to current dose ramping, frequency dose ramping mitigated the high BP level seen with dose onset.

In conclusion, dosing and dose ramping (e.g., current dose ramping and/or frequency dose ramping) can be used to mitigate acute changes in BP due to stimulation onset, without the need to alter the maximum stimulation intensity achieved in a dose. For example, see FIG. 8. Additionally, the results indicate that over a longer period of time dosing can provide improvements in cardiovascular metrics.

Example 2.

This example describes using dose ramping stimulation patterns to reduce blood pressure to below baseline blood pressure.

Leptos Biomedical, Fridley, MN implantable pulse generators (IPG)–Model 300/301 with firmware (FW) version 2.7 were implanted in 4 mature female beagles. The leads used were the Cyberonics (Cyberonics Company in Houston, Tex) Model 302. Blood pressure was monitored using the implantable Data Science International invasive pressure monitors for large animals (PCT-D70). The beagles were allowed to rest for one week after surgery and stimulation then followed for 7 weeks. Throughout the study, the animals were feed ad libitum.

Baseline blood pressure and other data were collected for no less than 1 week. The animals were then stimulated for 7 weeks with the profile described in FIGS. 9 and 10. FIGS. 9 and 10 show the programming interface that was established to deliver the dosed profile in which stimulation was active for 30 minutes, then inactive for 60 minutes. The 90 minute pattern was repeated 15 times over the course of each day. The daily current was adjusted between 50% and 100% of the maximum current during the course of each week. Therefore, on a day to day basis the doses were ramped. This weekly escalation in current reoccurred each week of stimulation to avoid habituation.

The maximum current was set at MTC + 2.0 mA, as clear acute blood pressure cycling (20 mm Hg) was seen with stimulation at this current intensity during the first week of stimulation. Each animals weight was recorded 3x per week prior to feeding. On a daily basis, the animal's food intake was recorded for the previous 24 hours. Continuous monitoring of the blood pressure was done at 10 sec average pressures using the Data Science International devices described above. One fasting blood draw was taken during the study (≥5 mL plasma).

The battery in the device in one dog ran out so that data from three dogs was collected.

The results indicated that at the end of stimulation MAP for two dogs (08D63 and 09D16) were below baseline and one dog was at baseline (09D15). Thus showing a downward trend as compared to baseline. See FIG. 11.

Example 3.

This example describes the use of sympathetic nerve stimulation to improve cardiovascular health.

Fourteen (14) mature, obese female beagles (ex-breeders, Marshall Farms) were stratified into four cohorts. Cohorts 1-2 were treatment groups. Cohorts 3 and 4 were control groups not exposed to an electrical stimulation protocol. **Table 1** below shows the breakdown of the cohorts. Each animal was implanted with a pulse generator and lead (either Leptos M6 Lead or CYBX Lead). The M6 leads were positioned on the right greater splanchnic nerves (RGSN), while the CYBX leads stimulated the left greater splanchnic nerves (LGSN).

Table 1: Cohort Layout

Cohort	Animal ID
Tx 1 - M6/RGSN	08D22
	08D24
	08D30
	08D36
Tx 2 – CYBX/LGSN	08D63
	08D66
	08D69
	08D71
C 1 - M6	08D23
	08D25
	08D26
	08D35
C 2 - CYBX	08D64
	08D68

Animals were housed singly in pens. All animals were given food and water *ad libitum*. Data were collected for safety and efficacy of the treatment.

Baseline Phase:

The Baseline Phase constituted a 2-week period wherein baseline data was collected on all animals. Daily food intake and behavioral notations were taken on all animals, along with continuous cardiovascular readings on select dogs. Body weight was measured three times per week for all dogs (M-W-F). On the last day, blood samples were collected for all dogs, along with additional blood for HbA1c. Lead impedances and muscle twitch tests were also performed that day, excepting the Control dogs that only had impedance readings taken.

1. Treatment Phase:

The Treatment Phase began with programming the dogs for unilateral stimulation. Cohort 1's treatment target was the RGSN, while Cohort 2's target was the LGSN. Cohort 2 dogs repeated the first stimulation pattern for an additional two weeks and then completed the remaining patterns, thus finishing two weeks later. Four stimulation programs were used for Cohorts 1 and 2. **Table 3** below, and corresponding FIGS. 12 and 13, show the stimulation algorithms used. For all of the algorithms, the current was ramped to 5 mA over 1 hour at the beginning of stimulation every day. Each pulse train delivered in the algorithms has a 2 second ramp up to the pulse train current amplitude and a 2 second ramp down at the end of the pulse train. There is also a frequency ramp of about 1 minute.

Each dog was stimulated with one of the stimulation algorithms for 2 weeks, and then moved on to the next algorithm. Each animal was stimulated with each algorithm in a different order from the other dogs in the same cohort.

Table 3: Tx1/Tx2 Stimulation Algorithms

Algorithm ID*	Description
A	Reduced Duty Cycle - Std = 50% (60s ON / 60s OFF), Algo A = ~17% (20s ON / 100s OFF)
B	Short Doses - Doses of 6 min each delivered 80 times/day with ~12 min OFF time between dose
D	Long Doses - Doses of 80 min each delivered 6 times/day with ~160 min OFF time between dos
D	Days Off - One day of Stim ON (24 hrs at 50% Duty Cycle) and Two days OFF

* All algorithms for Tx1/Tx2 represent doses approximately 33% (# of pulses/time) of the standard continuous (24/7) stimulation at 50% duty cycle. Constants across all algorithms (5 mA, 20 Hz, 519 microseconds).

Blood pressure and heart rate were measured continuously on select dogs in the Tx 1 and Tx 2 cohorts. Blood samples were collected bi-weekly at the end of each stimulation algorithm. Impedance and body twitch data were collected periodically. After 8 weeks (and having completed all 4 stimulation algorithms), the animals were turned off and moved to the Recovery Phase.

2. Recovery Phase:

The Recovery Phase began when stimulation was terminated in the treatment animals. Monitoring of animals and data collection continued, allowing the animals to re-establish baseline parameters, for at least 4 weeks.

The results showed that MAP and HR decreased over the course of the study for all cohorts. FIG. 14 is a graph reflecting the overall algorithm blood pressure changes from baseline. Table 4, below, provides additional MAP information.

Table 4

Overall Algorithm Blood Pressure Changes (Combined Cohort Data)

Algorithm	Change from Baseline	SEM
Algorithm A (static, not dosed)	5.14	4.10
Algorithm B (dosed)	-3.96	2.86
Algorithm C (dosed)	-3.11	2.48
Algorithm D (not dosing, but with days off)	-2.10	0.52

The dosing algorithms were successful in reducing the overall blood pressure, while the static algorithm (Algorithm A), increased the blood pressure values. The difference between Algorithm A and the other cohorts is significant (P-value = 0.015).

As mentioned two of the dosing algorithms also decreased HR. FIG. 15 is a graph showing the data. In total, the changes in baseline (and associated standard error), are summarized in **Table 7** below.

Table 7

Overall Algorithm Heart Rate Changes

Algorithm	Change from Baseline	SEM
Algorithm A	-3.29	4.35
Algorithm B	+3.10	3.41
Algorithm C	-4.63	3.76
Algorithm D	-5.14	3.74

All of the algorithms except Algorithm B lowered the overall heart rate over time. The greatest decrease was seen in Algorithm D (-5.1 bpm change). Comparing Algorithm B with the other algorithms, the P-values range from 0.017 to 0.038, showing that the difference between Algorithm B's results are significant from the other algorithm's values.

The results also showed that the BP and HR benefits achieved during stimulation were maintained after stimulation stopped (i.e., post stimulation). As shown in FIGS. 16 and 17, the decrease in MAP and HR, respectively, that were achieved during stimulation (see, FIG. 16 "Stim 4") were maintained one week post stimulation (Post-Stim 1) and continued to remain below baseline, and even decrease during the second week post stimulation (Post-Stim 2).

Overall, these results indicate that dose ramping with a soft transition can be used to mitigate changes in HR and BP during sympathetic stimulation. The benefits achieved from the use of dose ramping can also allow for the control of HR and BP post stimulation. Therefore, such stimulation patterns can be used to both optimize stimulation patterns that are useful, among other things, for treating weight-loss, diabetes, fatty liver disease as well as other abnormalities that can be mitigated through stimulation of the sympathetic nervous system.

Example 4.

This example describes the use of sympathetic nerve stimulation for the treatment of hypertension.

Subjects having hypertension are chosen (e.g., greater than 140 mmHg systolic or greater than 90 mmHg diastolic) and implanted with the device described in Example 2, above. A one month rest period is allowed for recovery from surgery. Each subject is stimulated with either algorithm SR, A, B, C, or D as shown in FIG. 12. The dose within of each of the respective algorithms is shown in FIG. 13. The subjects are stimulated for 3 months and BP and HR are measured and compared to baseline. It is expected that BP and HR will be less than baseline blood pressure post stimulation. It is also expected that BP and HR will remain below baseline for at least one week after stimulation is terminated.

While certain aspects and embodiments of the invention have been described, these have been presented by way of example only, and are not intended to limit the scope of the invention. Indeed, the

825 novel methods and systems described herein can be embodied in a variety of other forms without departing from the spirit thereof. The accompanying claims and their equivalents are intended to cover such forms or modifications as would fall within the scope and spirit of the invention.

What is claimed is:

1. A method of lowering blood pressure in a subject comprising:

establishing a baseline blood pressure;

electrically stimulating a sympathetic nerve with at least one stimulation pattern comprising more than one dose comprising at least one soft transition, at least one dose ramp or combinations thereof, wherein the electrical stimulation with the at least one stimulation pattern occurs for at least one week;

establishing a post stimulation blood pressure, wherein the post stimulation blood pressure is lower than the baseline blood pressure.

2. A method of treating a subject having hypertension comprising:

selecting a subject having hypertension; and

electrically stimulating a sympathetic nerve with at least one stimulation pattern comprising more than one dose comprising at least one soft transition, at least one dose ramp or combinations thereof, wherein the electrical stimulation with the at least one stimulation pattern occurs for at least one week, wherein the hypertensive state of the patient is improved.

3. A method of improving the cardiovascular health of a subject comprising:

selecting a subject that is exercise compromised;

measuring an at least one cardiovascular metric;

electrically stimulating a sympathetic nerve with at least one stimulation pattern comprising more than one dose comprising at least one soft transition, at least one dose ramp or combinations thereof, wherein the electrical stimulation with the at least one stimulation pattern occurs for at least one week; and

measuring the at least one cardiovascular metric, wherein the cardiovascular metric is improved.

4. The method of any one of claims 1-3, wherein the at least one stimulation pattern comprises at least one frequency, at least one pulse width and at least one current.

5. The method of claim 4, wherein the at least one frequency is less than 20 Hz.

6. The method of claim 4, wherein the at least one frequency is less than 2 Hz.

7. The method of claim 4, wherein the current is less than 1 mA.

8. The method of claim 4, wherein the current is less than 5 mA.

9. The method of claim 4, wherein the current is less than 2 mA.

10. The method of claim 4, wherein the pulse width is less than 600 microseconds.

11. The method of claim 4, wherein the pulse width is less than 300 microseconds.

12. The method of any one of claims 1-3, wherein the subject is a human.

13. The method of any one of claims 1-3, wherein the soft transition comprising a leading soft transition and an ending soft transition.

14. The method of claim 13 wherein the leading soft transition is less than 10 seconds and the ending soft transition is less than 10 seconds.

15. The method of any one of claims 1-3, wherein the soft transition is less than 20 seconds.

16. The method of any one of claims 1-3, wherein the soft transition rate is from about 0.1 mA/second to about 1 mA/second.

17. The method of any one of claims 1-3, wherein the more than one doses occur within 24 hours.

18. The method of any one of claims 1-3, wherein the dose ramping comprises an initial signal intensity and a MAX signal intensity and the dose ramping is selected from; ramping from the initial signal intensity to the MAX signal intensity in less than 1 hours, ramping from the MAX signal intensity to the initial signal intensity in less than 1 hours, or combinations thereof.

19. The method of any one of claims 1-3, wherein the dose ramping comprises an initial signal intensity and a MAX signal intensity and the dose ramping is selected from; ramping from the initial signal intensity to the MAX signal intensity in less than 30 minutes, ramping from the MAX signal intensity to the initial signal intensity in less than 30 minutes, or combinations thereof.

20. The method of claim 2, wherein the hypertensive subject is selected based upon blood pressure.

21. The method of claim 3, wherein the cardiovascular metric is blood pressure.

22. The method of any one of claims 1, 20 or 21, wherein the post stimulation blood pressure is at least 0.1% lower than the baseline blood pressure.

23. The method of any one of claims 1, 20 or 21, wherein the post stimulation blood pressure is at least 0.5% lower than the baseline blood pressure.

24. The method of any one of claims 1, 20 or 21, wherein the post stimulation blood pressure remains lower than the baseline blood pressure for at least one week post stimulation.

25. The method of any one of claims 1-3, wherein there is no significant difference between the weight of the subject before electrical stimulation and after electrical stimulation.

26. The method of claim 2, wherein the subject having hypertension has a systolic pressure of greater than 120 mmHg.

27. The method of claim 2, wherein the subject having hypertension has a systolic pressure of greater than 140.

28. The method of claim 2, wherein the subject having hypertension has a diastolic pressure of greater than 80 mmHg.

29. The method of claim 2, wherein the subject having hypertension has a diastolic pressure of greater than 90 mmHg.

30. The method according to claim 3, wherein the exercise compromised subject's movement is impaired.

31. The method according to any one of claims 1-3, further comprising titrating the stimulation pattern to a physiological marker.

32. The method according to claim 3, wherein the exercise compromised subject is unconscious.

33. The method according to any one of claims 1-31, or 34-43, wherein the electrical stimulation comprises electrically stimulating at least one splanchnic nerve or a celiac ganglia.

34. The method according to claim 3, wherein the stimulation pattern has at least one ON time and wherein the at least one ON time is lengthened until it reaches a TARGET time.

35. The method of any one of claims 1, 20 or 21, wherein the electrical stimulation is titrated to blood pressure changes.

36. The method of any one of claims 1, 20 or 21, wherein the blood pressure remains below baseline for at least two weeks post stimulation.

37. The method according to any one of claims 1-3, wherein the subject displays a disorder selected from obesity, metabolic syndrome and diabetes.

38. The method according to any one of claims 1-3, further comprising administering a blood pressure modulating pharmaceutical.

39. The method according to claim 39, wherein the blood pressure controlling pharmaceutical is selected from diuretics, ACE inhibitors and calcium channel blockers.

40. The method of any one of claims 1-3, wherein the more than one dose comprises an inter dose ramp.

41. The method according to any one of claims 1-3, further comprising a sensor, wherein the sensor triggers titration of the stimulation pattern based upon a physiological marker.

42. The method according to any one of claims 1, 20 or 21, wherein the blood pressure is maintained within safe limits.

43. The method according to any one of claims 1-3, further comprising titrating the electrical stimulation to a subject's tolerability threshold.

44. A device programmed to include a stimulation pattern described in any one of claims 1-43.

FIG. 1

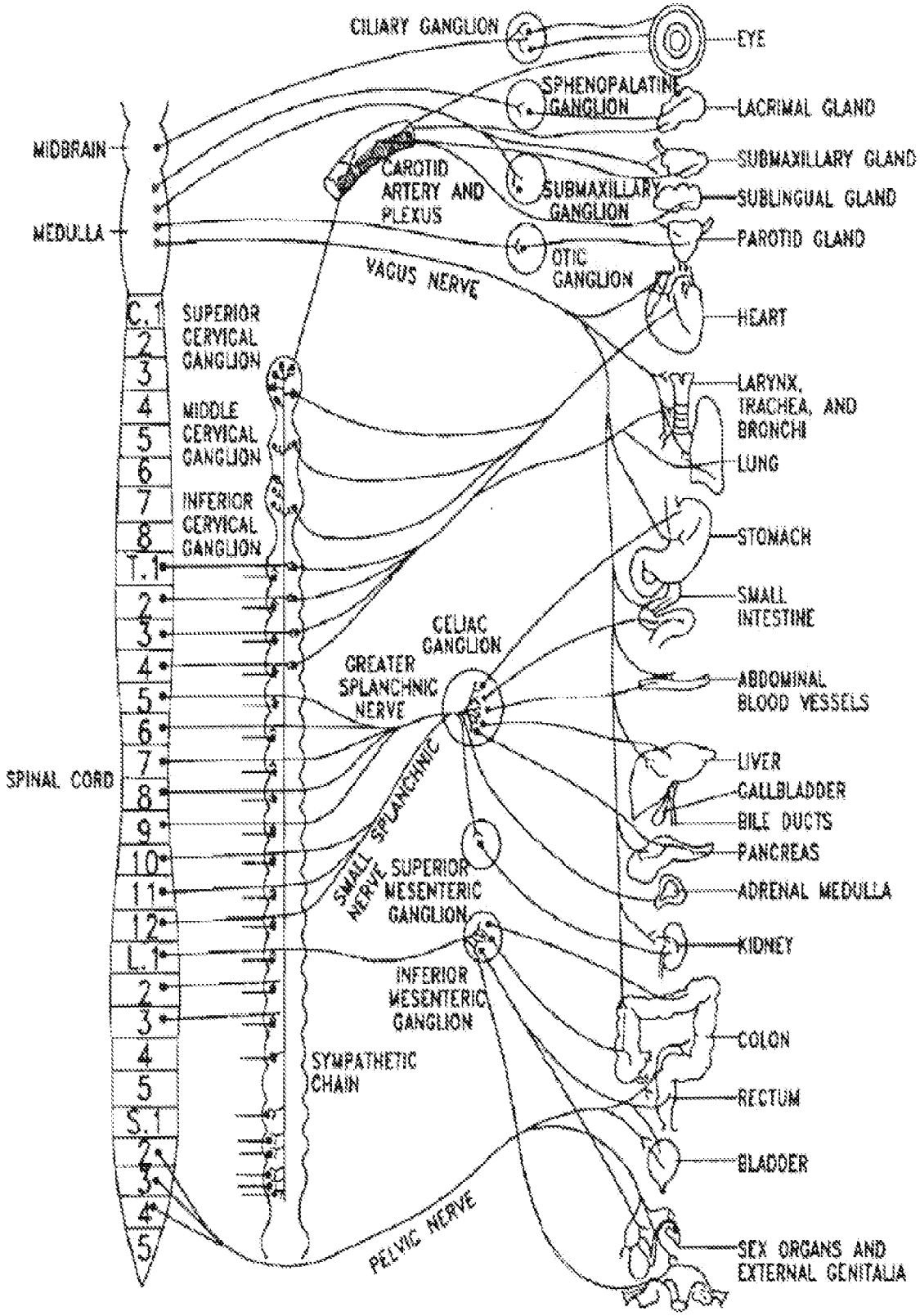
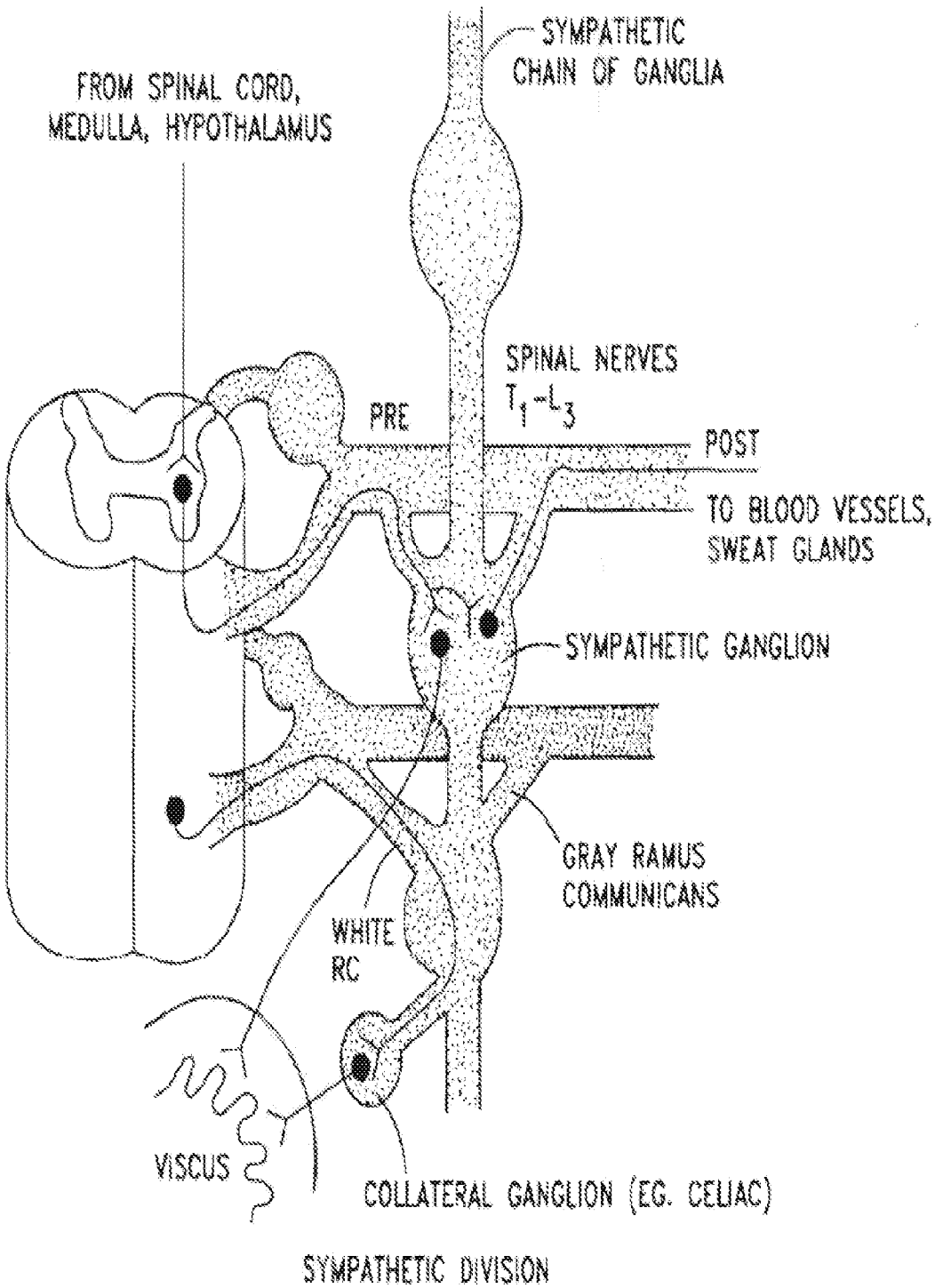

CILIARY GANGLION
EYE
SPHENOPALATINE GANGLION
LACRIMAL GLAND
MIDBRAIN
CAROTID ARTERY AND PLEXUS
SUBMAXILLARY GLAND
SUBMAXILLARY GANGLION
SUBLINGUAL GLAND
MEDULLA
PAROTID GLAND
OTIC GANGLION
VAGUS NERVE
HEART
C 1
2
3
SUPERIOR CERVICAL GANGLION
4
MIDDLE CERVICAL GANGLION
5
6
7
INFERIOR CERVICAL GANGLION
8
T 1
LARYNX, TRACHEA, AND BRONCHI
LUNG
2
3
4
5
6
7
8
9
10
11
12
L 1
2
3
4
5
S 1
2
3
4
5
STOMACH
SMALL INTESTINE
CELIAC GANGLION
GREATER SPLANCHNIC NERVE
ABDOMINAL BLOOD VESSELS
SPINAL CORD
LIVER
GALLBLADDER
BILE DUCTS
PANCREAS
SMALL SPLANCHNIC NERVE
SUPERIOR MESENTERIC GANGLION
ADRENAL MEDULLA
KIDNEY
INFERIOR MESENTERIC GANGLION
COLON
SYMPATHETIC CHAIN
RECTUM
BLADDER
PELVIC NERVE
SEX ORGANS AND EXTERNAL GENITALIA

FIG.2


SYMPATHETIC
CHAIN OF GANGLIA
FROM SPINAL CORD,
MEDULLA, HYPOTHALAMUS
SPINAL NERVES
T_1-L_3
PRE
POST
TO BLOOD VESSELS,
SWEAT GLANDS
SYMPATHETIC GANGLION
GRAY RAMUS
COMMUNICANS
WHITE
RC
VISCUS
COLLATERAL GANGLION (EG. CELIAC)
SYMPATHETIC DIVISION

FIGs. 3A-3C

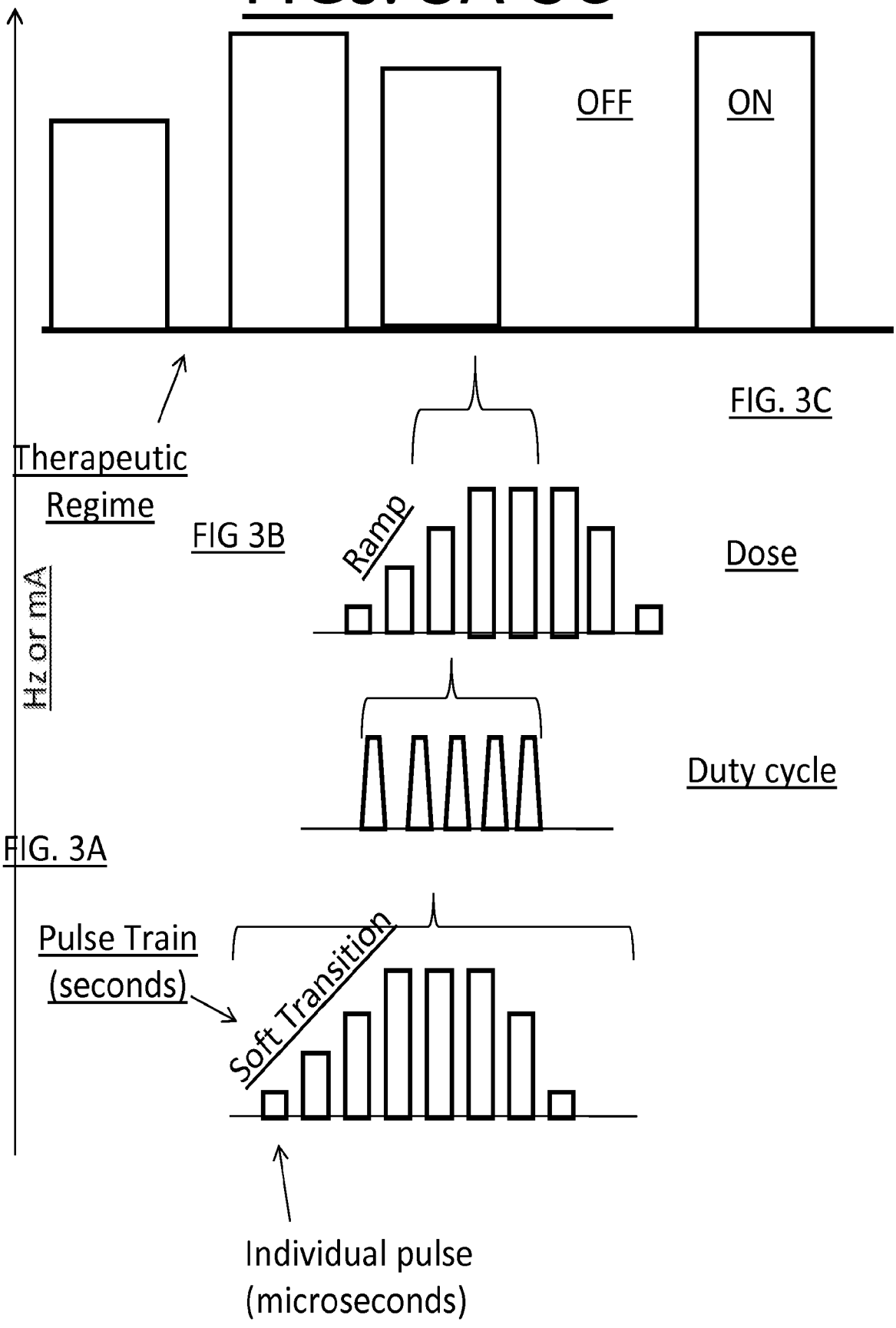

OFF
ON
FIG. 3C
Therapeutic Regime
FIG 3B
Ramp
Dose
Hz or mA
Duty cycle
FIG. 3A
Pulse Train (seconds)
Soft Transition
Individual pulse (microseconds)

FIG.4

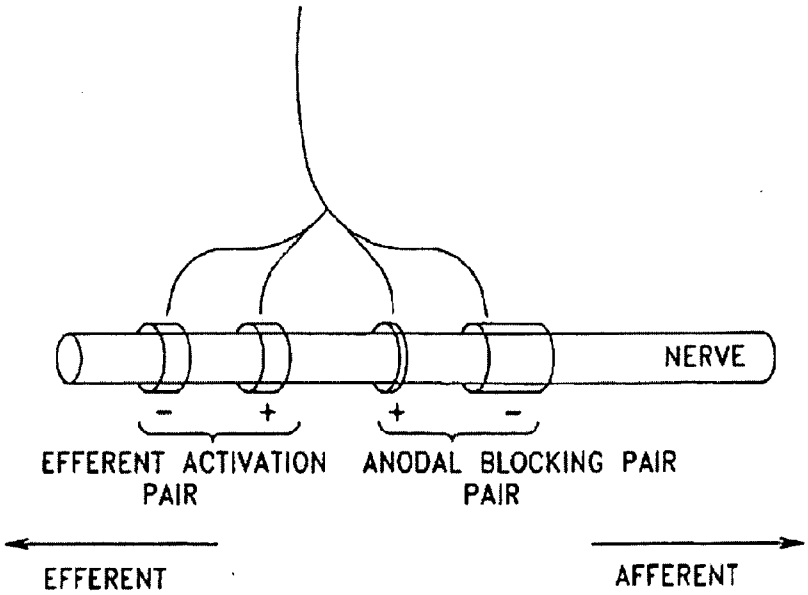


FIGURE Y-QUADRAPOLAR BLOCKING ELECTRODE

FIG.5

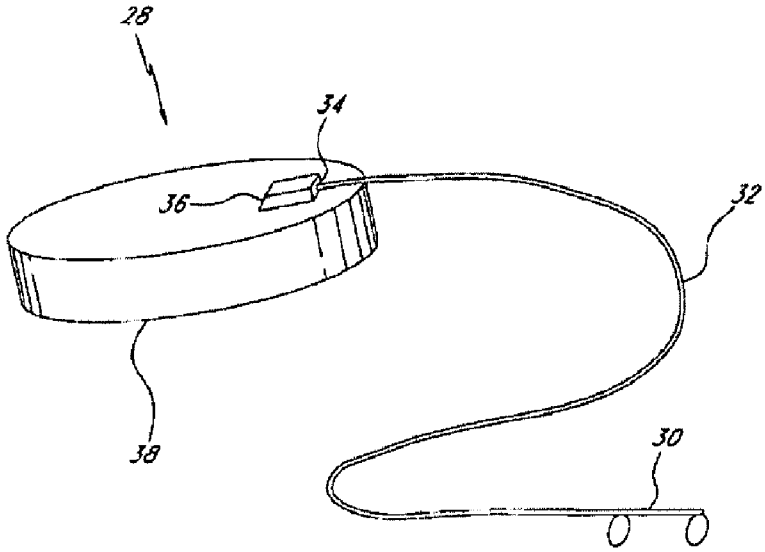
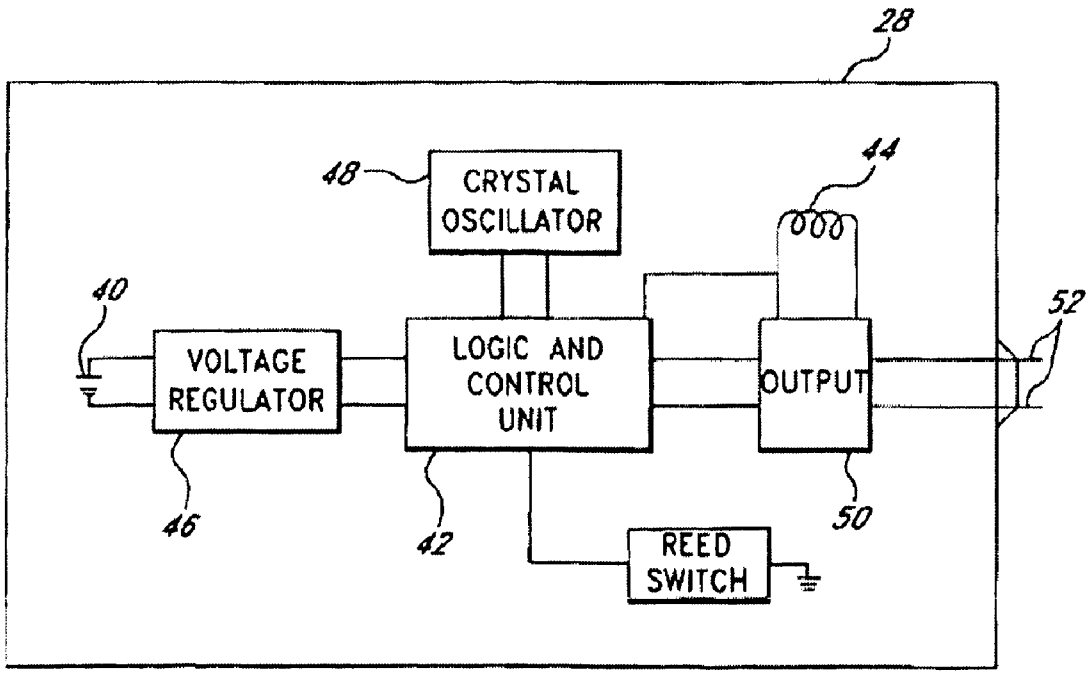

28
34
36
32
38
30

FIG.6


28
48
CRYSTAL OSCILLATOR
44
40
VOLTAGE REGULATOR
LOGIC AND CONTROL UNIT
OUTPUT
52
46
42
50
REED SWITCH

FIGS. 7A and 7B

FIG. 7A

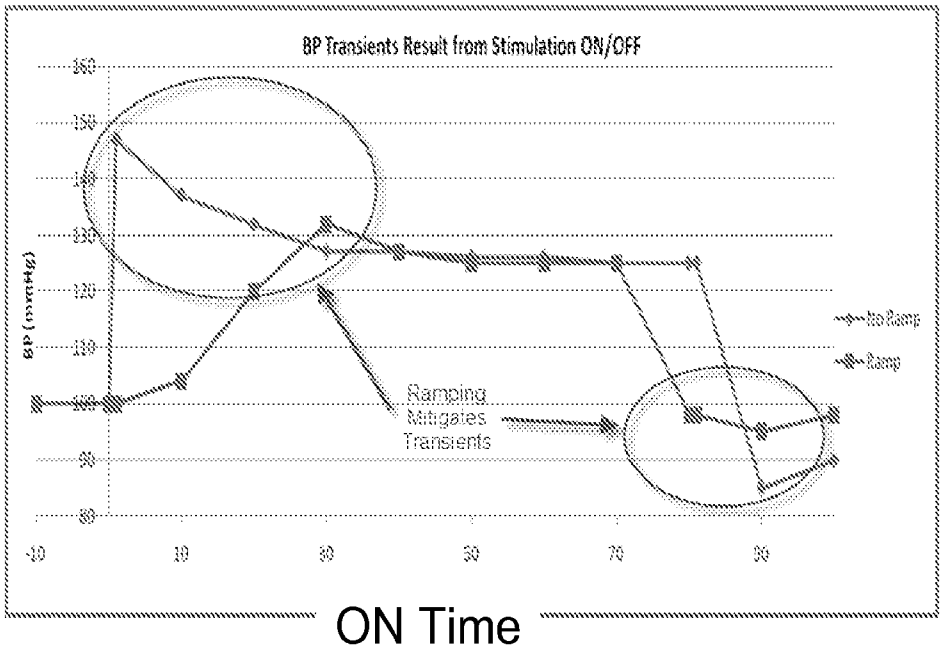


FIG. 7B

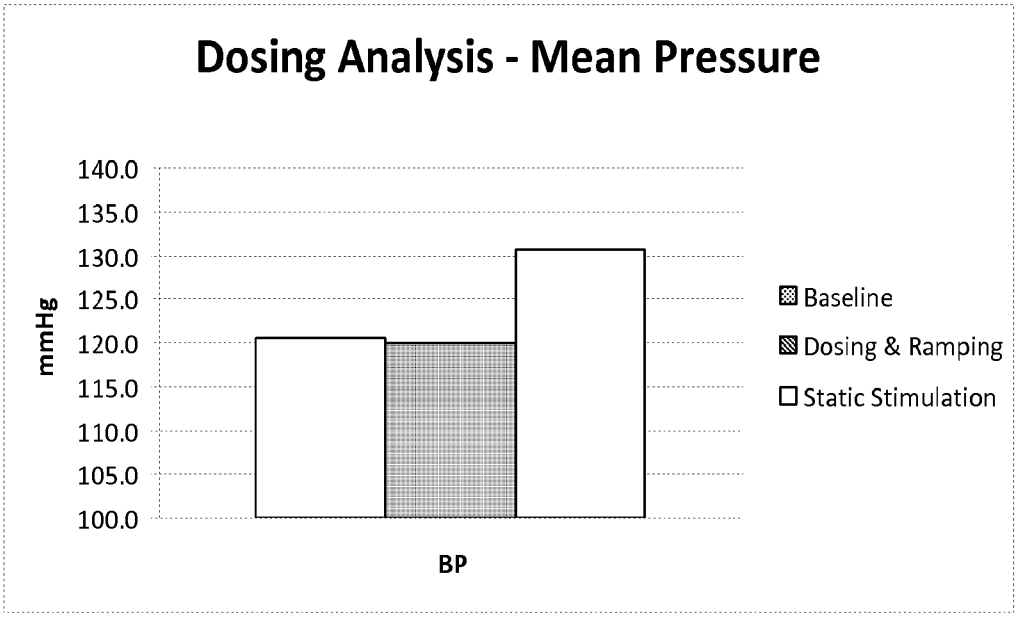


FIG. 8

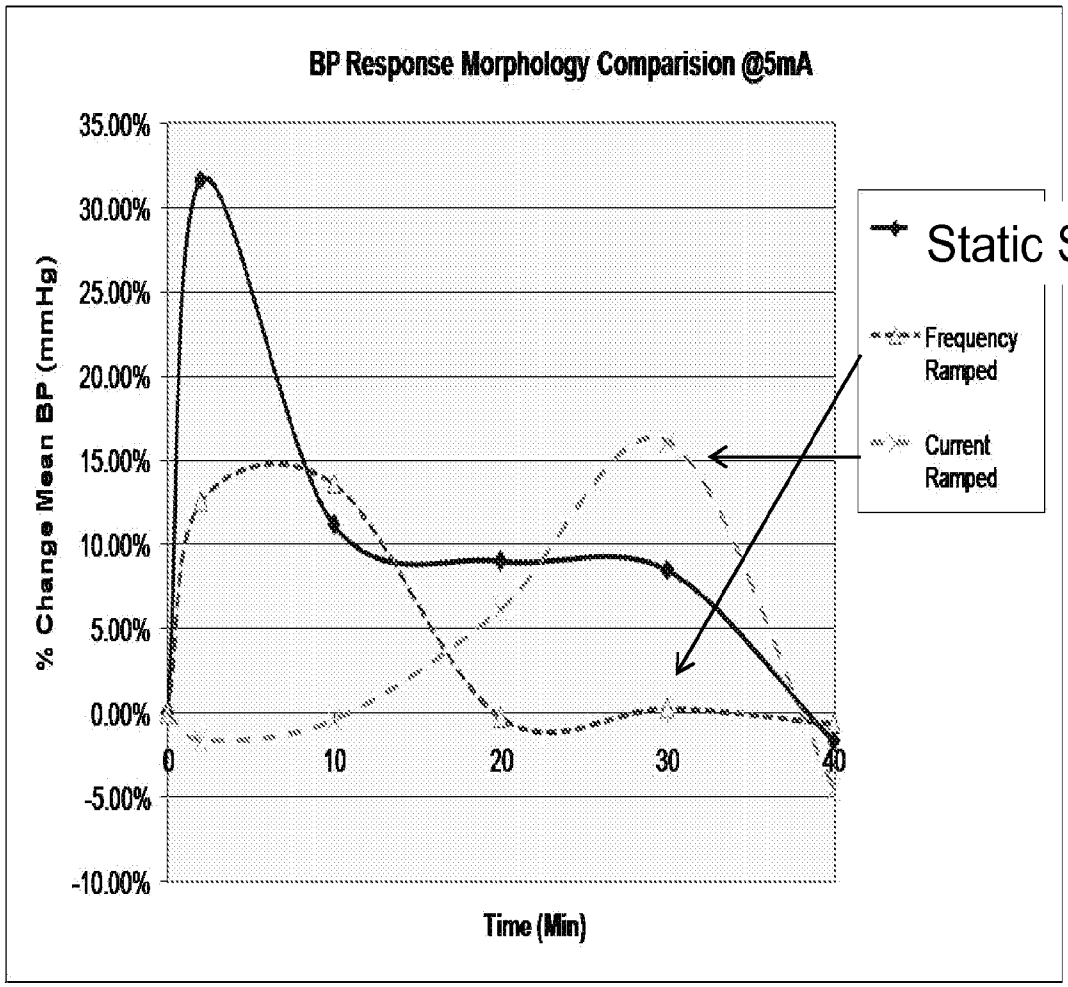

BP Response Morphology Comparision @5mA
% Change Mean BP (mmHg)
35.00%
30.00%
25.00%
20.00%
15.00%
10.00%
5.00%
0.00%
-5.00%
-10.00%
0
10
20
30
40
Time (Min)
Static Stim
Frequency Ramped
Current Ramped

FIG. 9

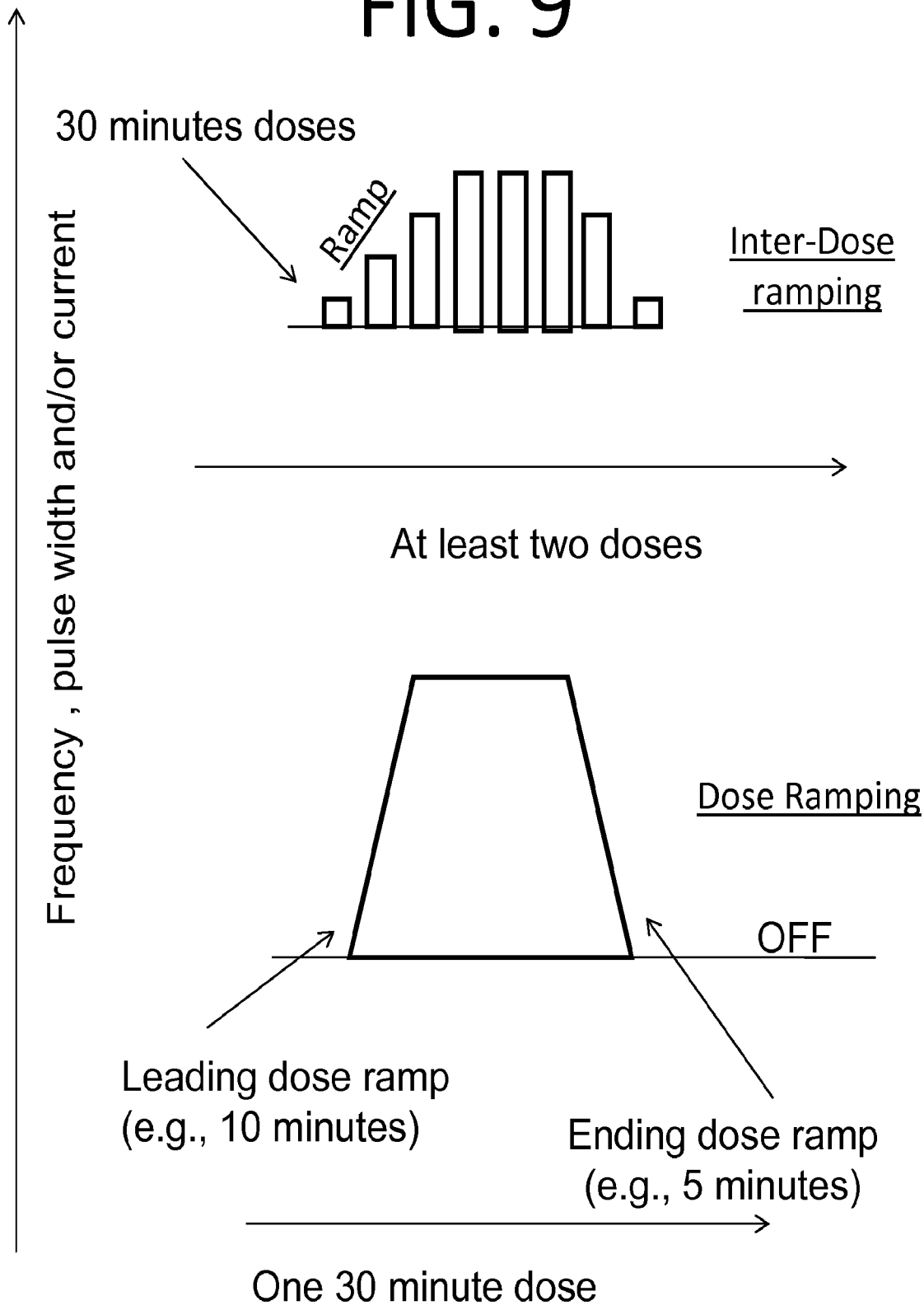

30 minutes doses
Ramp
Inter-Dose ramping
Frequency , pulse width and/or current
At least two doses
Dose Ramping
OFF
Leading dose ramp (e.g., 10 minutes)
Ending dose ramp (e.g., 5 minutes)
One 30 minute dose

FIG. 10

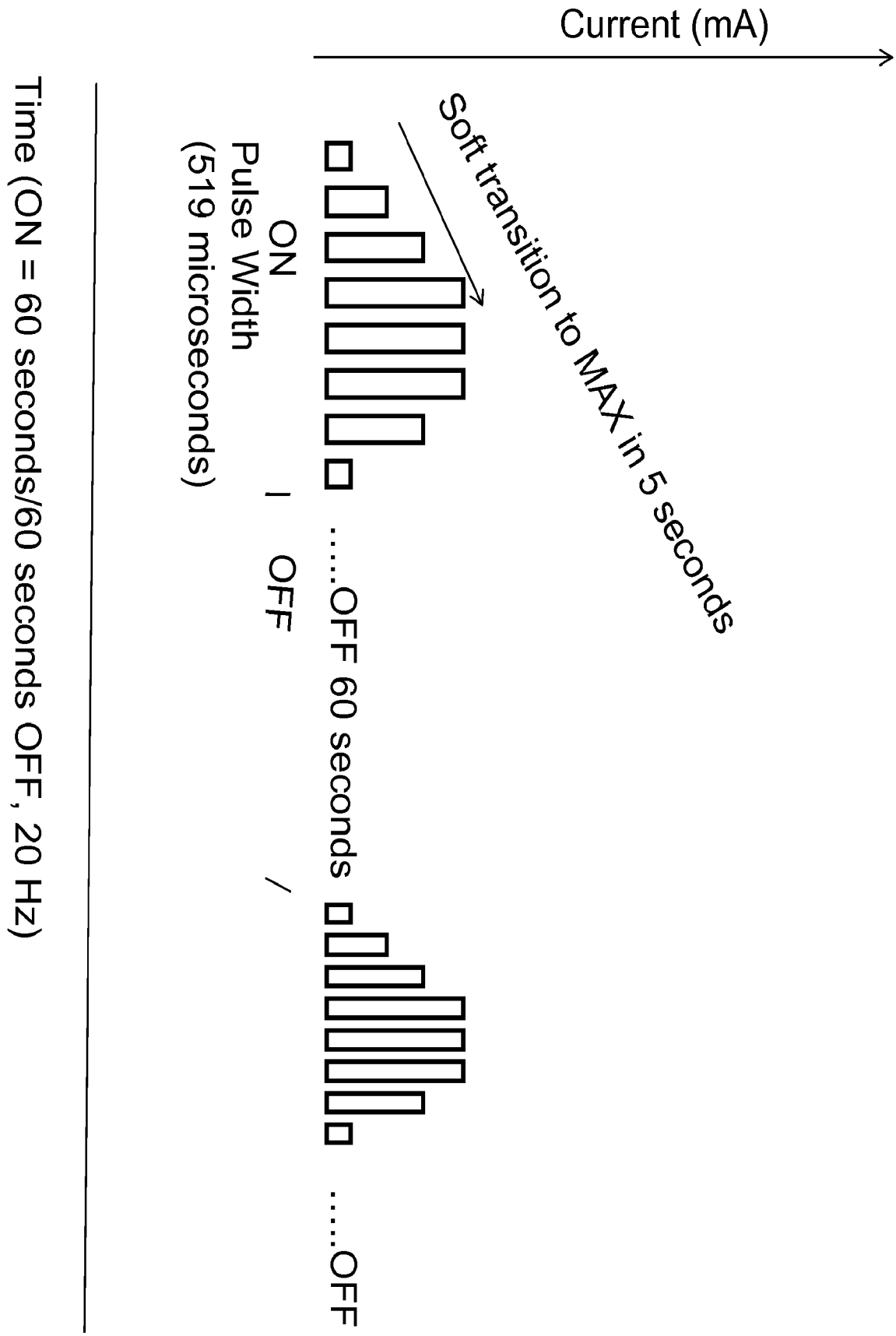

Current (mA)
Soft transition to MAX in 5 seconds
ON
Pulse Width
(519 microseconds)
OFF
.....OFF 60 seconds
.....OFF
Time (ON = 60 seconds/60 seconds OFF, 20 Hz)

FIG. 11

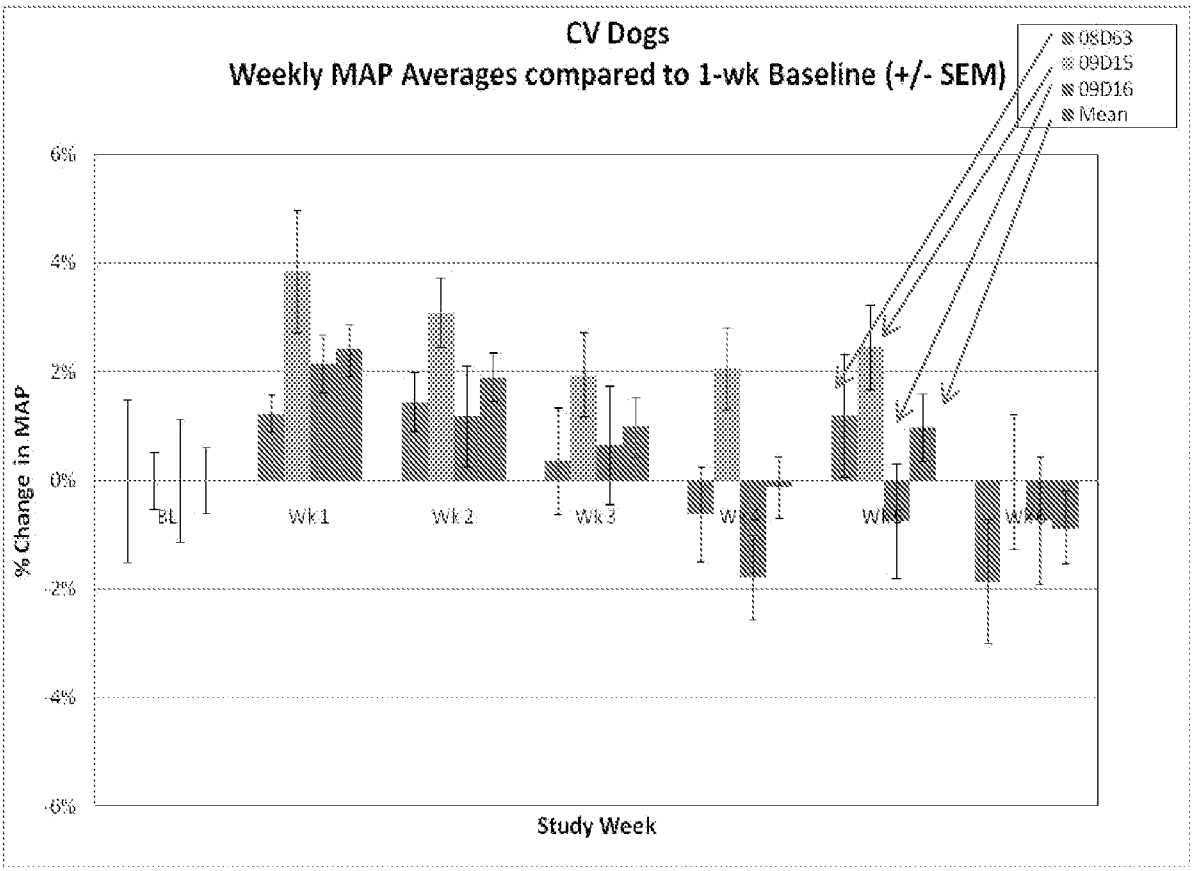

CV Dogs
Weekly MAP Averages compared to 1-wk Baseline (+/- SEM)
08D63
09D15
09D16
Mean
6%
4%
2%
0%
-2%
-4%
-6%
% Change in MAP
BL
Wk 1
Wk 2
Wk 3
Study Week

FIG. 12

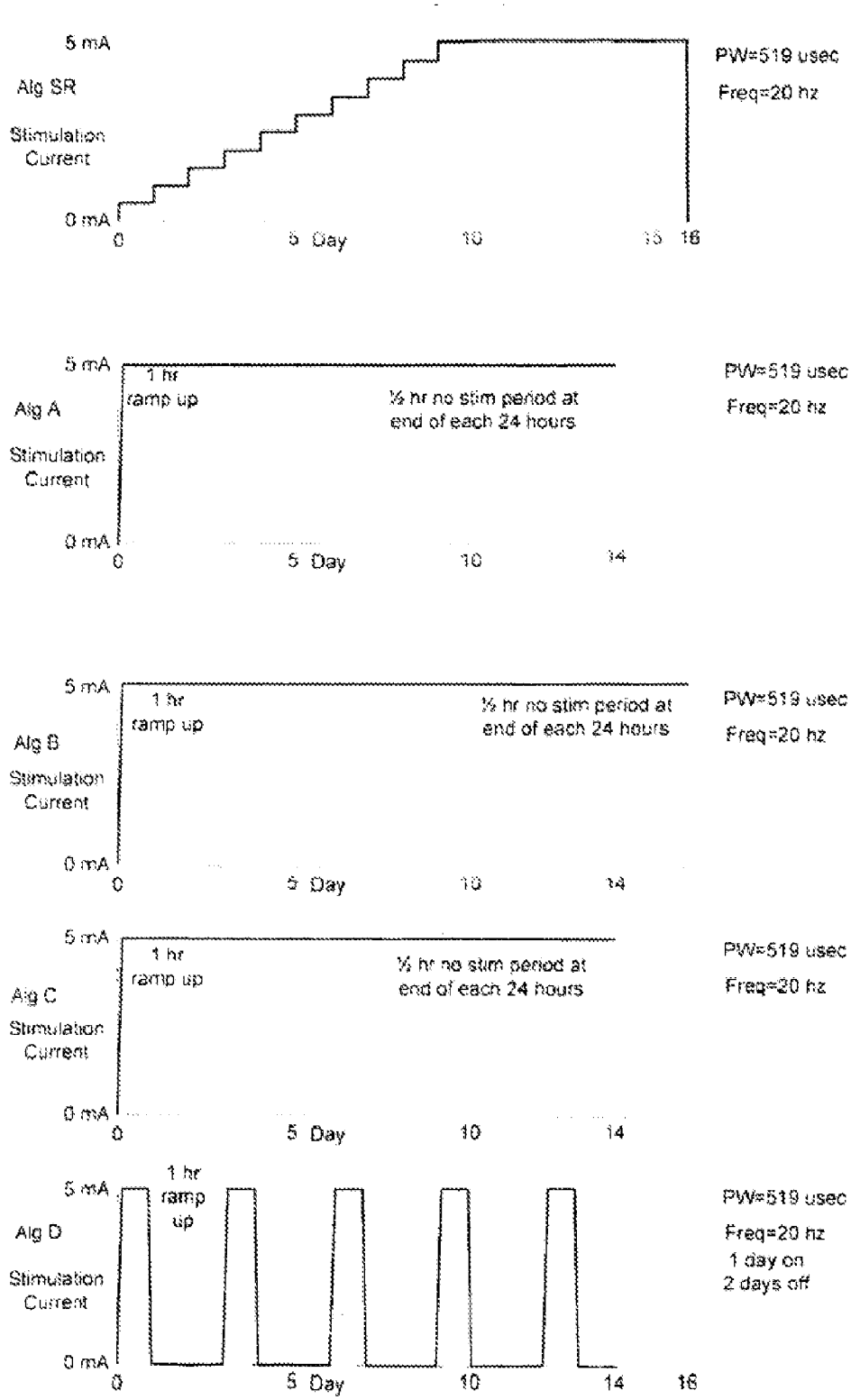

5 mA
Alg SR
Stimulation Current
0 mA
0
5 Day
10
15
16
PW=519 usec
Freq=20 hz
5 mA
Alg A
Stimulation Current
0 mA
1 hr ramp up
½ hr no stim period at end of each 24 hours
0
5 Day
10
14
PW=519 usec
Freq=20 hz
5 mA
Alg B
Stimulation Current
0 mA
1 hr ramp up
½ hr no stim period at end of each 24 hours
0
5 Day
10
14
PW=519 usec
Freq=20 hz
5 mA
Alg C
Stimulation Current
0 mA
1 hr ramp up
½ hr no stim period at end of each 24 hours
0
5 Day
10
14
PW=519 usec
Freq=20 hz
5 mA
Alg D
Stimulation Current
0 mA
1 hr ramp up
0
5 Day
10
14
16
PW=519 usec
Freq=20 hz
1 day on
2 days off

FIG. 13

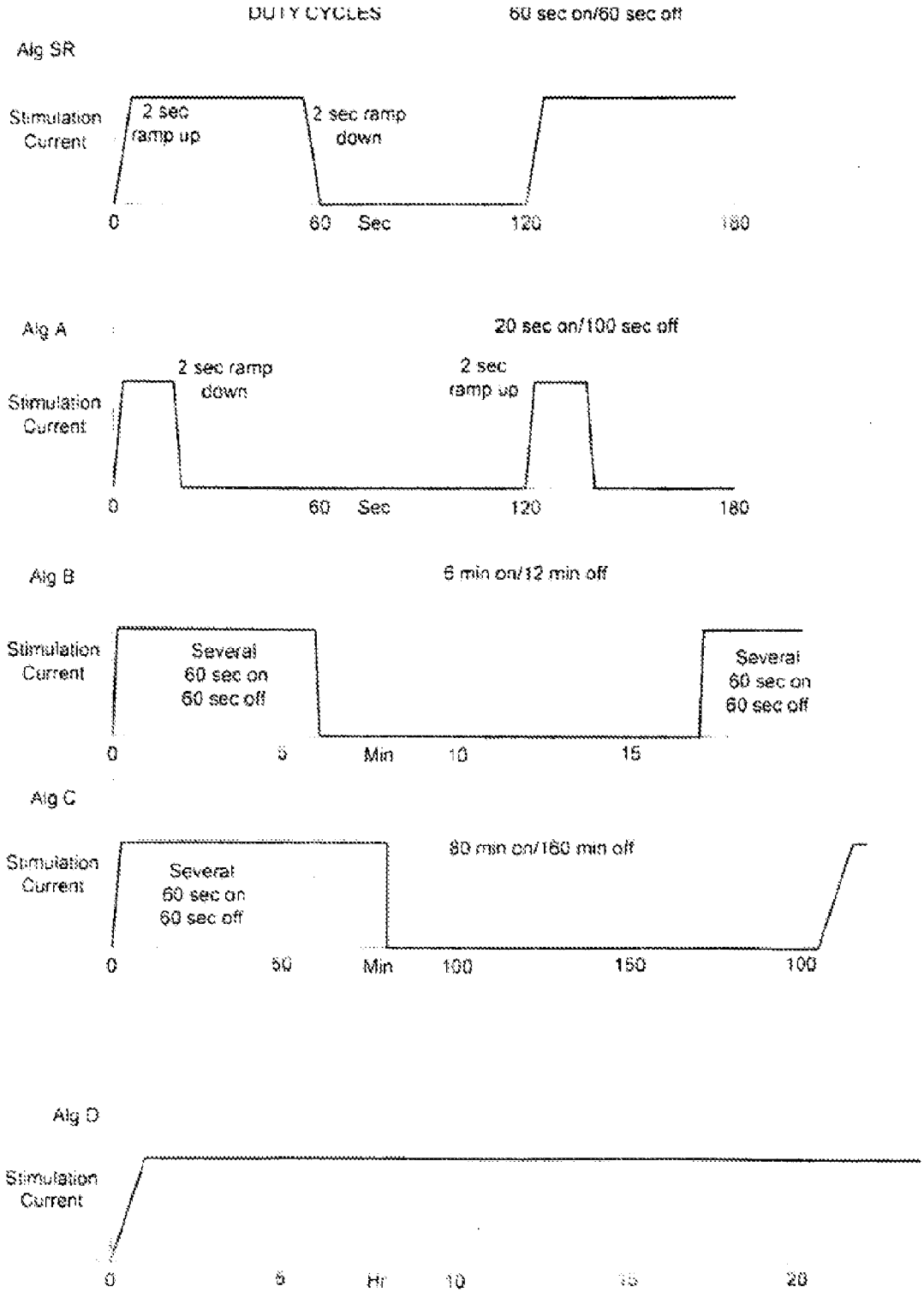

DUTY CYCLES
60 sec on/60 sec off
Alg SR
Stimulation Current
2 sec ramp up
2 sec ramp down
0
60
Sec
120
180
Alg A
20 sec on/100 sec off
2 sec ramp down
2 sec ramp up
Stimulation Current
0
60
Sec
120
180
Alg B
6 min on/12 min off
Stimulation Current
Several 60 sec on 60 sec off
Several 60 sec on 60 sec off
0
5
Min
10
15
Alg C
Stimulation Current
Several 60 sec on 60 sec off
80 min on/180 min off
0
50
Min
100
150
100
Alg D
Stimulation Current
0
5
Hr
10
15
20

FIG. 14

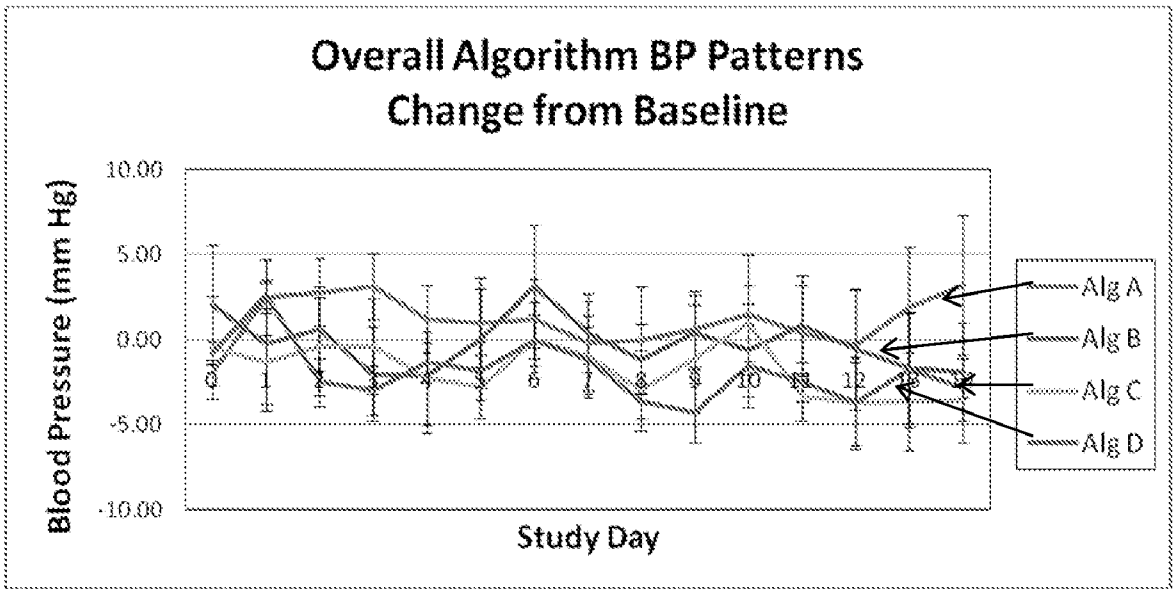

Overall Algorithm BP Patterns
Change from Baseline
Blood Pressure (mm Hg)
10.00
5.00
0.00
-5.00
-10.00
Study Day
Alg A
Alg B
Alg C
Alg D

FIG. 15

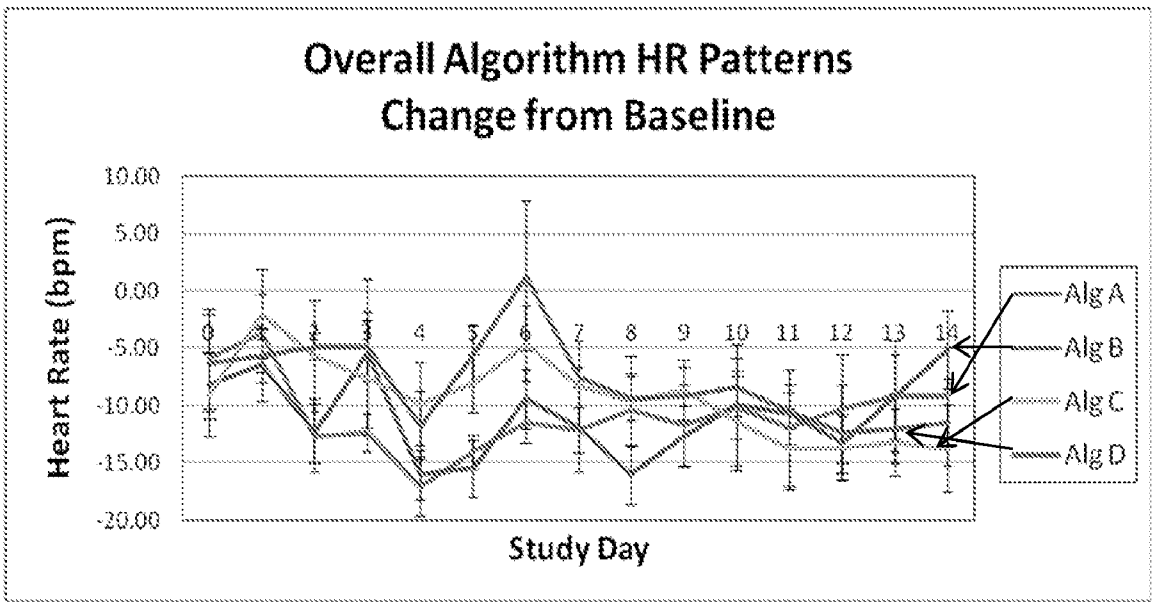

Overall Algorithm HR Patterns
Change from Baseline
Heart Rate (bpm)
10.00
5.00
0.00
-5.00
-10.00
-15.00
-20.00
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
Study Day
Alg A
Alg B
Alg C
Alg D

FIG. 16

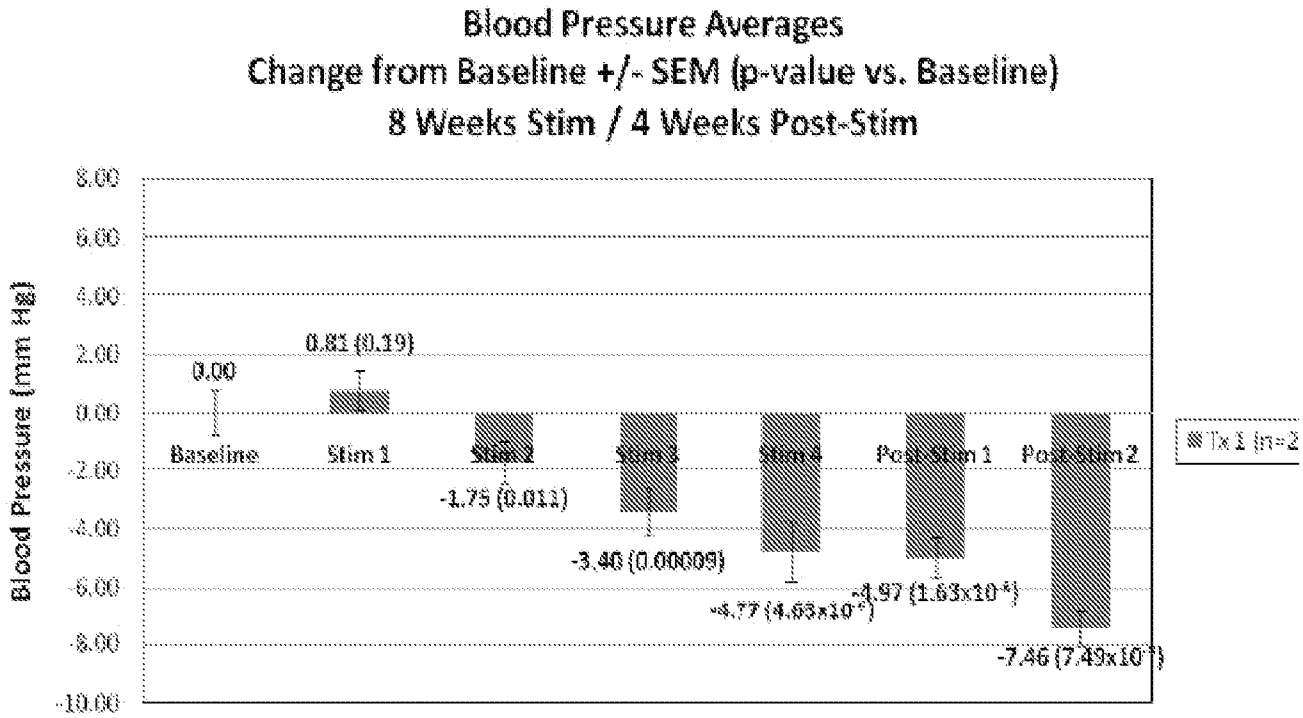
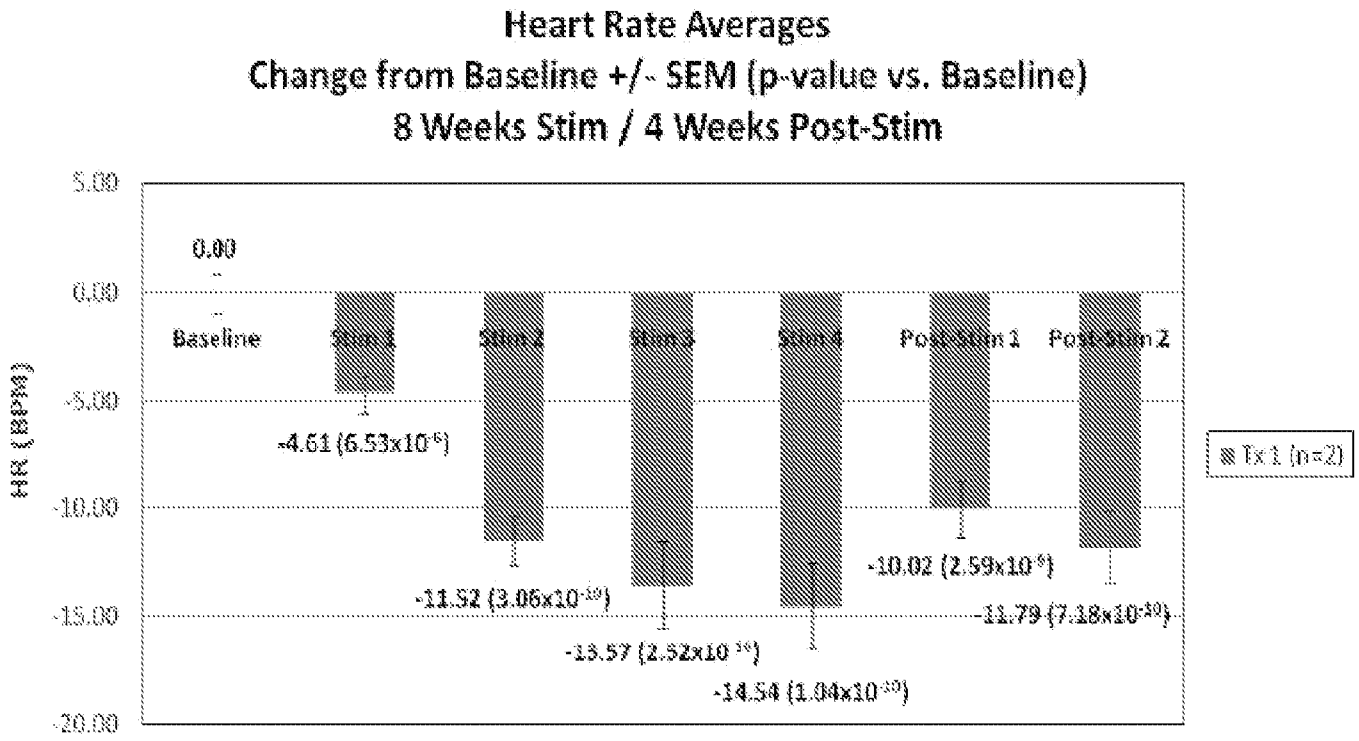

Blood Pressure Averages
Change from Baseline +/- SEM (p-value vs. Baseline)
8 Weeks Stim / 4 Weeks Post-Stim
Blood Pressure (mm Hg)
8.00
6.00
4.00
2.00
0.00
-2.00
-4.00
-6.00
-8.00
-10.00
0.00
0.81 (0.19)
-1.75 (0.011)
-3.40 (0.00009)
-4.77 (4.63x10⁻⁶)
-4.97 (1.63x10⁻⁶)
-7.46 (7.49x10⁻⁹)
Baseline
Stim 1
Stim 2
Stim 3
Stim 4
Post-Stim 1
Post-Stim2
※Tx 1 (n=2

FIG. 17


Heart Rate Averages
Change from Baseline +/- SEM (p-value vs. Baseline)
8 Weeks Stim / 4 Weeks Post-Stim
HR (BPM)
5.00
0.00
-5.00
-10.00
-15.00
-20.00
0.00
Baseline
Stim 1
Stim 2
Stim 3
Stim 4
Post-Stim 1
Post-Stim 2
-4.61 (6.53x10-6)
-11.52 (3.06x10-10)
-13.57 (2.52x10-14)
-14.54 (1.04x10-20)
-10.02 (2.59x10-6)
-11.79 (7.18x10-20)
Tx 1 (n=2)