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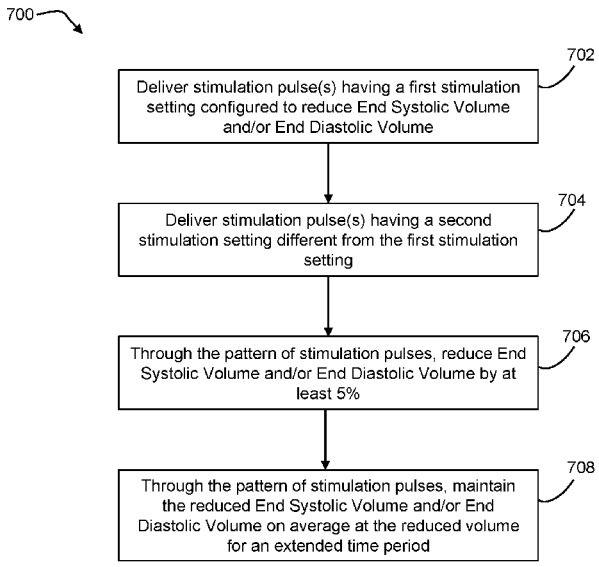

FIG. 7

(57) Abstract: Methods and systems for treating cardiac malfunction are disclosed, which according to an embodiment, may involve delivering a stimulation pattern of stimulation pulses to at least one cardiac chamber of a heart, with at least one of the stimulation pulses having a first stimulation setting configured to reduce at least one of end systolic volume (ESV) and end diastolic volume (EDV) in the heart and at least one of the stimulation pulses having a second stimulation setting different from the first stimulation setting, and with the stimulation pattern being configured to reduce the at least one of end systolic volume (ESV) and end diastolic volume (EDV) by at least 5% and maintain the at least one of end systolic volume (ESV) and end diastolic volume (EDV) on average at such reduced volume for a time period of at least one hour.

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METHODS AND SYSTEMS FOR TREATING CARDIAC MALFUNCTION

[0001] This application claims the benefit of U.S. Provisional Application No. 62/217,299, filed September 11, 2015, which is herein incorporated by reference in its entirety.

BACKGROUND

[0002] The present embodiments relate to the field of treating cardiac malfunction, and more particularly, to methods and systems for stimulating the heart to treat cardiac malfunction, such as congestive heart failure.

SUMMARY

[0003] Methods and systems for treating cardiac malfunction are disclosed.

[0004] In one aspect, a method for treating cardiac malfunction may include delivering a stimulation pattern of stimulation pulses to at least one cardiac chamber of a heart. At least one of the stimulation pulses may have a first stimulation setting configured to reduce at least one of end systolic volume (ESV) and end diastolic volume (EDV) in the heart, and at least one of the stimulation pulses may have a second stimulation setting different from the first stimulation setting. The stimulation pattern may be configured to reduce the at least one of end systolic volume (ESV) and end diastolic volume (EDV) by at least 5% and to maintain the at least one of end systolic volume (ESV) and end diastolic volume (EDV) on average at such reduced volume for a time period of at least one hour.

[0005] In another aspect, a system for treating cardiac malfunction may include a stimulation circuit and at least one controller. The stimulation circuit may be configured to deliver a stimulation pulse to at least one cardiac chamber of a heart of a patient. The at least one controller may be configured to execute delivery of a stimulation pattern of stimulation pulses to the at least one cardiac chamber. At least one of the stimulation pulses may have a first stimulation setting configured to reduce at least one of end systolic volume (ESV) and end diastolic volume (EDV) in the heart, and at least one of the stimulation pulses may have a second stimulation setting different from the first stimulation setting. The stimulation pattern may be configured to reduce

2016319787 02 Oct 2020

the at least one of end systolic volume (ESV) and end diastolic volume (EDV) by at least 5% and maintain the at least one of the end systolic volume (ESV) and end diastolic volume (EDV) on average at such reduced volume for a time period of at least one hour.

[0005A] In particular, the present invention provides a method for treating cardiac malfunction, comprising: delivering over a time period of at least one hour a stimulation pattern of stimulation pulses to at least one cardiac chamber of a heart of a patient, wherein at least one of the stimulation pulses has a first stimulation setting configured to reduce at least one of end systolic volume (ESV) and end diastolic volume (EDV) in the heart of the patient, and at least one of the stimulation pulses has a second stimulation setting different from the first stimulation setting; and wherein the stimulation pattern is configured to: reducing, by delivery of the stimulation pattern over the time period of at least one hour, reduce the at least one of end systolic volume (ESV) and end diastolic volume (EDV) by at least 5%, and maintaining, by delivery of the stimulation pattern over the time period of at least one hour, maintain the at least one of end systolic volume (ESV) and end diastolic volume (EDV) on average at such reduced volume for a the time period of at least one hour, and maintaining, by delivery of the stimulation pattern over maintain, for the time period of at least one hour, blood pressure of the patient within an average pressure of ±10% as compared to a pretreatment blood pressure value for the time period of at least one hour.

[0005B] The present invention also provides a system for treating cardiac malfunction, comprising: a stimulation circuit configured to deliver a stimulation pulse to at least one cardiac chamber of a heart of a patient; and at least one controller configured to execute delivery of a stimulation pattern of stimulation pulses to the at least one cardiac chamber over a time period of at least one hour, wherein at least one of the stimulation pulses has a first stimulation setting configured to reduce at least one of end systolic volume (ESV) and end diastolic volume (EDV) in the heart of the patient, and at least one of the stimulation pulses has a second stimulation setting different from the first stimulation setting, and wherein the stimulation pattern is configured to: reduce, during the time period of at least one hour, the at least one of end systolic volume (ESV) and end diastolic volume (EDV) by at least 5%, maintain, during the time period of at least one hour, the at least one of end systolic volume (ESV) and end diastolic volume

2016319787 02 Oct 2020

(EDV) in the heart of the patient on average at such reduced volume, and maintain, during the time period of at least one hour, blood pressure of the patient within an average pressure of +10% as compared to a pretreatment blood pressure value.

[0005C] There is also provided a method for treating cardiac malfunction, comprising: delivering over a time period of at least one hour a stimulation pattern of stimulation pulses to at least one cardiac chamber of a heart of a patient, wherein at least one of the stimulation pulses has a first stimulation setting that stimulates a ventricle of the heart 40-90 milliseconds after atrial activation and reduces at least one of end systolic volume (ESV) or end diastolic volume (EDV) in the heart of the patient, wherein at least one of the stimulation pulses has a second stimulation setting that stimulates the ventricle 100-180 milliseconds after atrial activation, and wherein the stimulation pattern includes at least 4 consecutive heartbeats having the first stimulation setting for every 1 consecutive heartbeat having the second stimulation setting,such that the stimulation pattern: reduces the at least one of end systolic volume (ESV) or end diastolic volume (EDV) by at least 5%, maintains the at least one of end systolic volume (ESV) or end diastolic volume (EDV) in the heart of the patient on average at such reduced volume for the time period of at least one hour, limits reduction in ejection fraction of the heart to about 2% or less, and maintains, for the time period of at least one hour, blood pressure of the patient within an average pressure of ±10% as compared to a pretreatment blood pressure value

[0006] Other systems, methods, features, and advantages of the present embodiments will be, or will become, apparent to one of ordinary skill in the art upon examination of the following figures and detailed description. It is intended that all such additional systems, methods, features and advantages be included within this description and this summary, be within the scope of the embodiments, and be protected by the following claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0007] The embodiments can be better understood with reference to the following drawings and description. The components in the figures are not necessarily to scale, emphasis instead being placed upon illustrating the principles of the embodiments. Moreover, in the figures, like reference numerals designate corresponding parts throughout the different views.

[0008] FIG. 1 is a plot illustrating change in end systolic volume (ESV) from baseline (BL) as a function of activation time, according to an embodiment;

[0009] FIG. 2 is a plot illustrating change in end diastolic volume (EDV) from baseline (BL) as a function of activation time, according to an embodiment;

[0010] FIG. 3 is a plot illustrating change in ejection fraction (EF) from baseline (BL) as a function of activation time, according to an embodiment;

[0011] FIG. 4 is a plot illustrating change in end systolic volume (ESV) from baseline (BL) as a function of activation time over a longer period (about twenty-four months), according to a second embodiment;

[0012] FIG. 5 a plot illustrating change in end diastolic volume (EDV) from baseline (BL) as a function of activation time over the longer period (about twenty-four months), according to the second embodiment;

[0013] FIG. 6 is a plot illustrating change in ejection fraction (EF) from baseline (BL) as a function of activation time over the longer period (about twenty-four months), according to the second embodiment;

[0014] FIG. 7 is a flow chart illustrating an exemplary method for treating cardiac malfunction, according to an embodiment; and

[0015] FIG. 8 is a schematic drawing illustrating an exemplary system for treating cardiac malfunction, which may perform one or more of the methods described herein, such as the method of FIG. 7.

DETAILED DESCRIPTION

[0016] A healthy cardiac contraction cycle includes two phases: a systole and a diastole. The systole is a period of cardiac contraction, commencing with ventricular contraction. The systole causes blood to be ejected from the heart and into the vascular system. At the end of this contraction, cardiac muscles relax. This period of relaxation is the diastole. During diastole, the heart passively fills with blood from the vascular system and at the end of diastole the atria contract and provide additional filling to the ventricle. Accordingly, at the end of the diastole and just before the heart begins to contract, cardiac blood volume peaks. This peak volume is the end diastolic volume (EDV). At the end of the systole, when contraction ends and cardiac filling is about to commence, cardiac blood volume reaches a minimal value. This minimal volume is the end systolic volume (ESV). The amount of blood ejected in a heartbeat is known as the stroke volume (SV) and equals the difference between end diastolic volume (EDV) and end systolic volume (ESV). The ejection fraction (EF) is the fraction of blood that is ejected by the heart (i.e., SV divided by EDV).

[0017] Cardiac remodeling is a phenomenon that results from cardiac load or injury, and is an accepted determinant of the clinical course of heart failure (HF). It manifests clinically as changes in size, shape, and function of the heart.

[0018] As a result of damage to the heart, abnormal strain patterns are manifested in the heart, and the cells that experience a high strain undergo hypertrophy and some loss of function. This affects cardiac function and blood pressure parameters, and as a consequence, neuronal and/or hormonal pathways are activated in an attempt to compensate for cardiac damage. For example, poor contraction results in high end systolic volume (ESV) and thus a reduction in stroke volume (SV). This may lead to increase in end diastolic volume (EDV) as well. As cardiac volumes increase, so does the wall tension in the heart, as known from Laplace's Law. According to the law, a dilated ventricle requires more tension in the wall to generate the same pressure as would a smaller ventricle. This increase in tension increases sympathetic stimulation and vasopressin (antidiuretic hormone or ADH) secretion. Vasopressin is known to constrict blood vessels and increase heart rate, which causes an increase in blood pressure and an increase in oxygen consumption by the heart muscle cells. However,

this also causes an additional increase in cardiac strain, since the heart beats faster and in every systole needs to eject blood against a system showing an increased resistance. This increased strain may cause additional hypertrophy and further loss of function. Thus, a vicious cycle comes into play where the cardiovascular system's attempts at reducing the effect of the damaged tissue cause additional reduction in cardiac performance.

[0019] Many attempts have been made to develop devices and methods to treat heart failure, including, for example, devices intended to mechanically control cardiac volumes:

U.S. Patent No. 7,651,461 to Alferness et al., entitled "Cardiac Support with Metallic Structure," which is herein incorporated by reference in its entirety, describes a jacket "configured to surround the myocardium" which "provides reduced expansion of the heart wall during diastole by applying constraining surfaces at least at diametrically opposing aspects of the heart;" and

U.S. Patent No. 7,618,364 to Walsh et al., entitled "Cardiac Wall Tension Relief Device and Method," which is herein incorporated by reference in its entirety, states that "[i]t is believed that such resistance decreases wall tension on the heart and permits a diseased heart to beneficially remodel."

[0020] Interfering with cardiac filling may reduce blood pressure in hypertensive patients. One option for interfering with cardiac filling to reduce blood pressure may be to reduce or even eliminate atrial kick. Atrial kick may provide a relatively small boost to ventricle filling (10-30%) that is caused by atrial contraction before an atrioventricular (AV) valve between the atrium and the ventricle is closed. Once the ventricle begins to contract, pressure builds up in the ventricle and causes the AV valve to passively close. The inventors also found that when effecting treatment that reduces or even eliminates atrial kick, the cardiovascular system acts to adapt to the change and return performance values to those that occurred before treatment commenced. International Publications Nos. WO2015/094401 and WO2014/100429, both to Mika et al., and both herein incorporated by reference in their entirety, describe, inter alia, methods and systems providing pacing patterns of stimulation pulses that comprise pulses configured to reduce or prevent atrial kick and also reduce or even eliminate the cardiovascular system's adaptation to the reduction in blood pressure. The

reduction in adaptation may be achieved by reducing neurohormonal response to changes in generated pressure and stretch using specific patterns.

[0021] Heart failure patients, on the other hand, typically (although not exclusively) have blood pressure values that are not significantly elevated. Accordingly, in some cases, it may be preferred to reduce cardiac volumes (e.g., at least one of end diastolic volume and end systolic volume) and/or reduce cardiac strain without significantly affecting blood pressure.

[0022] The inventors have developed methods and systems of applying cardiac stimulations that yield surprising results in meeting the needs of heart failure patients. Embodiments provide methods and system that may reduce the strain sensed by cardiac muscles by applying cardiac stimulations that reduce at least one of end systolic volume (ESV) and end diastolic volume (EDV) without significantly affecting the ejection fraction (EF) of the heart, and optionally also without significantly affecting blood pressure. A reduction of such strain may be useful in reversing cardiac remodeling or at least in slowing down or even stopping the remodeling process. In some embodiments, a stimulation pattern may be configured to reduce a neurohormonal response to changes in strain without significantly affecting blood pressure.

[0023] Optionally, when a patient is provided with a cardiac stimulation device, a stimulation pattern is selected based on sensing of one or more of: at least one blood-pressure-related parameter (e.g., an indication of pretreatment and/or treatment blood pressure) and at least one cardiac-strain and/or volume-related parameter (e.g., a pressure measurement within a chamber and/or echocardiogram-derived information). These parameters can be used to adjust one or more of the properties of one or more (or two or more) pulses in a pulse pattern and/or the proportion between pulses having different settings and/or the order of the pulses in the pattern. Optionally, reducing at least one of end diastolic volume (EDV) and end systolic volume (ESV) suppresses sympathetic stimulation, for example, by at least one of reducing wall strain and hence reducing or eliminating the activation of sympathetic pathways involved with adaptation of the cardiovascular system to changes.

[0024] Optionally, a device is configured to receive feedback information regarding one or more of the at least one blood-pressure-related parameter and at least

one cardiac strain/volume related parameter. This may be performed periodically (e.g., in a periodic measurement such as a periodic checkup) and/or ongoing (e.g., with an associated or integral sensor). The information may be received, for example, via communication with a user through an input interface and/or by communication with implanted and/or external devices. Further details of suitable devices are described below in reference to Figure 8.

[0025] A stimulation setting means one or more parameters of one or more stimulation pulses delivered in a single cardiac cycle. For example, these parameters may include one or more of: a time interval between electrical pulses that are included in a single stimulation pulse (e.g., AV delay), a period of delivery with respect to the natural rhythm of the heart, the length of a stimulation pulse or a portion thereof, and the site of delivery between two or more chambers. In some embodiments, a pulse setting includes applying an excitatory pulse to a ventricle, timed in synchronization to the natural activity of an atrium of the heart. In some embodiments, a pulse setting includes applying an excitatory pulse to an atrium timed in synchronization to the natural activity of a ventricle of the heart. In some embodiments, a pulse setting includes applying an excitatory pulse to each of a ventricle and an atrium.

[0026] A stimulation pattern may include a series of pulses having identical stimulation settings or a stimulation pattern may include multiple pulses each having different stimulation settings. For example, a stimulation pattern may have one or more pulses having a first setting and one or more pulses having a second setting that is different from the first setting. When stating that a stimulation pattern has a setting, it is understood that this means a stimulation pattern may include at least one stimulation pulse having that setting. It is also understood that, in some embodiments a stimulation pattern may include one or more cardiac cycles where no stimulation pulse is delivered, in which case the pulse(s) may be viewed as being delivered at zero power. A stimulation pattern may include a plurality of identical pulses or a sequence of pulses including two or more different settings. Two stimulation sequences in a pattern may differ in the order of pulses provided within a setting. Two or more stimulation sequences may optionally differ in their lengths (in time and/or number of heartbeats). In some embodiments, a stimulation pattern may include pulses having blood pressure

reduction (BPR) settings. In some embodiments, a stimulation pattern may include pulses that do not have BPR settings.

[0027] **Experimental Results**

[0028] In an experiment according to a first embodiment, a plurality of patients' hearts were paced at the ventricle and atrium using a pacing pattern that included 9 to 10 pulses having a first stimulation setting (according to which the ventricle was stimulated 40-90 milliseconds after atrial activation) and 1 to 2 pulses having a second stimulation setting (according to which the ventricle was stimulated 100-180 milliseconds after atrial activation). Pulses having the first stimulation setting reduced atrial kick, while pulses having the second stimulation setting did not do so. The pacing pattern was applied continuously for a period of up to about six months. Changes in end systolic volume (ESV), end diastolic volume (EDV), and ejection fraction (EF) were derived from echocardiogram data.

[0029] Before treatment, end systolic volume (ESV) and end diastolic volume (EDV) were measured and ejection fraction (EF) was calculated to provide baseline (BL) values for each patient. Thereafter, the same values were obtained approximately one, two, three, and six months after treatment commenced, and the change from baseline (BL) for each patient was calculated. Each of Figures 1-3 depicts results obtained for a plurality of patients (N), as indicated on the plots. The numbers (N) of patients includes only data for which a core lab analysis determined that the echocardiogram was suitable for measurement. The baseline values were approximately 110 ml for diastolic volume, approximately 45 ml for systolic volume, and approximately 62% for ejection fraction.

[0030] As shown in Figures 1-3, for a period of up to about six months, end systolic volume (ESV) decreased by approximately 7 ml (about 15%), end diastolic volume (EDV) decreased by approximately 20 ml (about 17%), and ejection fraction (EF) decreased slightly (about a 2% decrease). This means that muscle strain was reduced (due to the lower volume of blood in the chambers), while the heart's efficiency (as shown by the ejection fraction (EF)) remained almost unchanged. A reduction of strain works against the vicious cycle of the heart in which cardiac strain plays a significant role, especially when ejection fraction (EF) is not significantly reduced, and thus remodeling is prevented or at least its progress rate is reduced. Experimental

observations suggest that beneficial effects may be obtained over a shorter period, for example, reducing at least one of end systolic volume (ESV) and end diastolic volume (EDV) by at least 5% and maintaining the at least one of end systolic volume (ESV) and end diastolic volume (EDV) on average at such reduced volume for a time period of at least one hour. In particular, according to Laplace's Law, pressure (P) is directly proportional to wall tension (T) and inversely proportional to radius (R), such that $P \propto T/R$. This means that, as long as pressure (P) is maintained essentially constant, wall tension (T) is a direct function of radius (R). Cardiac volume (V) in turn is a function of R^3, so T is a direct function of $V^{1/3}$. Therefore, when V decreases by approximately 20%, R decreases by approximately 7%, and so does T. In other words, a 20% decrease in V is (0.8 × V), and $(0.8)^{1/3}$ equals 0.93, yielding (0.93 × R), or a 0.07 (or 7%) decrease in R. Extending this analysis to the at least 5% reduction suggested by the experimental observations, when V decreases by approximately 5%, R decreases by approximately 2%, and so does T.

[0031] Figures 4-6 illustrate a second set of experimental results according to a second embodiment, over a longer period of activation time (about twenty-four months), and including a greater number of patients. Similar to the first embodiment, in the experiment of the second embodiment, a plurality of patients' hearts were paced at the ventricle and atrium using a pacing pattern that included 9 to 10 pulses having a first stimulation setting (according to which the ventricle was stimulated 40-90 milliseconds after atrial activation) and 1 to 2 pulses having a second stimulation setting (according to which the ventricle was stimulated 100-180 milliseconds after atrial activation). Pulses having the first stimulation setting reduced atrial kick, while pulses having the second stimulation setting did not do so. The pacing pattern was applied continuously for a period of up to about twenty-four months. Changes in end systolic volume (ESV), end diastolic volume (EDV), and ejection fraction (EF) were derived from echocardiogram data.

[0032] Before treatment, end systolic volume (ESV) and end diastolic volume (EDV) were measured and ejection fraction (EF) was calculated to provide baseline (BL) values for each patient. Thereafter, the same values were obtained eight times after treatment commenced, and the change from baseline (BL) for each patient was calculated. The eight times were at approximately the following months after treatment

commenced: one, two, three, six, twelve, eighteen, and twenty-four. Each of Figures 4-6 depicts results obtained for a plurality of patients (N), as indicated on the plots. The numbers (N) of patients includes only data for which a core lab analysis determined that the echocardiogram was suitable for measurement. The baseline values were approximately 115 ml for diastolic volume and approximately 40 ml for systolic volume.

[0033] As shown in Figures 4-6, for a period of up to about twenty-four months, end systolic volume (ESV) and end diastolic volume (EDV) remained at reduced levels, with values at the twenty-four month decreased by about 9% and 8%, respectively, while ejection fraction (EF) initially decreased slightly and insignificantly, and later increased steadily (to about a 2% increase at twenty-four months). This means that muscle strain was reduced (due to the lower volume of blood in the chambers), while the heart's efficiency (as shown by the ejection fraction (EF)) improved slightly. A reduction of strain works against the vicious cycle of the heart in which cardiac strain plays a significant role, especially when ejection fraction (EF) improves, and thus remodeling is prevented or at least its progress rate is reduced. The longer term data of Figures 4-6 therefore demonstrates a slight increase in ejection fraction (~60%) with normal global cardiac function over a period of twenty-four months, which suggests a trend toward continuing improvement of cardiac function beyond that longer term. Thus, in embodiments, a stimulation pattern may be configured to reduce the at least one of end systolic volume (ESV) and end diastolic volume (EDV) by at least 5% and maintain the at least one of end systolic volume (ESV) and end diastolic volume (EDV) on average at such reduced volume for a time period of at least one hour, including as long as three months, twenty-four months, or even longer.

[0034] In light of the experimental results, embodiments provide methods and systems for treating cardiac malfunction. In a first aspect, a method for treating cardiac malfunction may include delivering a stimulation pattern of stimulation pulses to at least one cardiac chamber of a heart. At least one of the stimulation pulses may have a first stimulation setting configured to reduce at least one of end systolic volume (ESV) and end diastolic volume (EDV) in the heart and at least one of the stimulation pulses may have a second stimulation setting different from the first stimulation setting. The stimulation pattern may be configured to reduce the at least one of end systolic volume (ESV) and end diastolic volume (EDV) by at least 5% and maintain the at least one of

end systolic volume (ESV) and end diastolic volume (EDV) on average at such reduced volume for a time period of at least one hour.

[0035] Figure 7 illustrates an embodiment of the first aspect, providing a method 700 for treating cardiac malfunction that includes delivering a stimulation pattern of stimulation pulses to at least one cardiac chamber of a heart. As shown, in step 702, the method may begin by delivering at least one stimulation pulse having a first stimulation setting configured to reduce at least one of end systolic volume (ESV) and end diastolic volume (EDV) in the heart. In step 704, the method may continue by delivering at least one stimulation pulse having a second stimulation setting different from the first stimulation setting. Through the delivery of the stimulation pattern of stimulation pulses of steps 702 and 704, the method in step 706 reduces end systolic volume (ESV) and/or end diastolic volume (EDV) by at least 5% and in step 708 maintains the reduced end systolic volume (ESV) and/or end diastolic volume (EDV) on average at such reduced volume for an extended time period (e.g., at least one hour).

[0036] In a second aspect, the time period may be at least three months.

[0037] In a third aspect, the method of the first or second aspect may include a stimulation pattern configured to reduce cardiac strain by at least 2% and maintain the cardiac strain on average at such reduced strain for the time period.

[0038] In the method of the invention, the stimulation pattern is configured to maintain blood pressure within an average pressure of ±10% as compared to a pretreatment blood pressure value for the time period.

[0039] In a fifth aspect, the method of any of the preceding aspects may include a stimulation pattern configured to prevent cardiac remodeling in the patient.

[0040] In a sixth aspect, the method of any of the preceding aspects may provide that the first stimulation setting is configured to reduce or prevent atrial kick in at least one ventricle and at least one of the stimulation pulses has a second stimulation setting different from the first stimulation setting.

[0041] In a seventh aspect, the method of any of the preceding aspects may provide that the first stimulation setting is configured to reduce the at least one of end systolic volume (ESV) and end diastolic volume (EDV) by at least 5% and the second stimulation setting is configured to reduce a baroreflex response or adaptation to the

reduction in the at least one of end systolic volume (ESV) and end diastolic volume (EDV). In some embodiments, the stimulation pattern is configured not to activate a baroreceptor of the patient.

[0042] In an eighth aspect, the method of any of the preceding aspects may provide that the stimulation pattern is configured to reduce a baroreflex response or adaptation to the reduction in the at least one of end systolic volume (ESV) and end diastolic volume (EDV).

[0043] In a ninth aspect, the method of any of the preceding aspects may provide that the first stimulation setting is configured to reduce the at least one of end systolic volume (ESV) and end diastolic volume (EDV) by at least 5% and the second stimulation setting is configured to reduce a neuronal response or adaptation to the reduction in the at least one of end systolic volume (ESV) and end diastolic volume (EDV).

[0044] In a tenth aspect, the method of any of the preceding aspects may provide that the stimulation pattern is configured to reduce a neuronal response or adaptation to the reduction in the at least one of end systolic volume (ESV) and end diastolic volume (EDV).

[0045] In an eleventh aspect, the method of any of the preceding aspects may provide that the first stimulation setting is configured to reduce the at least one of end systolic volume (ESV) and end diastolic volume (EDV) by at least 5% and the second stimulation setting is configured to increase hormonal secretion.

[0046] In a twelfth aspect, the method of any of the preceding aspects may provide that the stimulation pattern is configured to increase hormonal secretion.

[0047] In a thirteenth aspect, the method of any of the preceding aspects may provide that the first stimulation setting comprises stimulating a ventricle of the heart 40-90 milliseconds after atrial activation.

[0048] In a fourteenth aspect, the method of the thirteenth aspect may provide that the second stimulation setting comprises stimulating an atrium of the heart to thereby produce atrial stimulation.

[0049] In a fifteenth aspect, the method of any of the preceding aspects may provide that the second stimulation setting comprises stimulating a ventricle of the heart 100-180 milliseconds after atrial activation.

[0050] In a sixteenth aspect, the method of any of the first aspect through fourteenth aspect may provide that the second stimulation setting comprises allowing a natural AV delay to occur.

[0051] In a seventeenth aspect, the method of any of the preceding aspects may provide that the stimulation pattern includes at least 4 consecutive heartbeats having the first stimulation setting for every 1 consecutive heartbeat having the second stimulation setting.

[0052] In an eighteenth aspect, the method of the seventeenth aspect may provide that the stimulation pattern includes at least 8 consecutive heartbeats having the first stimulation setting for every 1 consecutive heartbeat having the second stimulation setting.

[0053] In a nineteenth aspect, the method of any of the preceding aspects may provide that the stimulation pattern comprises at least one stimulation pulse having a third stimulation setting different from the first and second stimulation settings.

[0054] In a twentieth aspect, the method of any of the preceding aspects may provide that the cardiac malfunction is associated with an increase in at least one of end systolic volume (ESV) and end diastolic volume (EDV).

[0055] In a twenty-first aspect, the method of any of the preceding aspects may provide that the cardiac malfunction is congestive heart failure.

[0056] In a twenty-second aspect, the method of any of the preceding aspects may further include applying the stimulation pattern at a stimulation pattern configuration for a first period, sensing at least one parameter indicative of at least one of end systolic volume (ESV), end diastolic volume (EDV), cardiac strain, and blood pressure for the first period, and adjusting the stimulation pattern configuration according to the sensing.

[0057] In a twenty-third aspect, the method of the twenty-second aspect may provide that adjusting the stimulation pattern includes adjusting at least one of the first stimulation setting and the second stimulation setting.

[0058] In a twenty-fourth aspect, the method of either the twenty-second or twenty-third aspect may provide that adjusting the stimulation pattern configuration includes adjusting at least one of the number and proportion of at least one of

stimulation pulses having the first stimulation setting and stimulation pulses having the second stimulation setting within the stimulation pattern.

[0059] Another aspect provides a system for treating cardiac malfunction. The system may include a stimulation circuit configured to deliver a stimulation pulse to at least one cardiac chamber of a heart of a patient, and at least one controller configured to execute delivery of a stimulation pattern of stimulation pulses to the at least one cardiac chamber. At least one of the stimulation pulses may have a first stimulation setting configured to reduce at least one of end systolic volume (ESV) and end diastolic volume (EDV) in the heart and at least one of the stimulation pulses may have a second stimulation setting different from the first stimulation setting. The stimulation pattern may be configured to reduce the at least one of end systolic volume (ESV) and end diastolic volume (EDV) by at least 5% and maintain the at least one of end systolic volume (ESV) and end diastolic volume (EDV) on average at such reduced volume for a time period of at least one hour.

[0060] In a further aspect of the system, the at least one controller may be configured to receive input data relating to at least one sensed parameter indicative of at least one of end systolic volume (ESV), end diastolic volume (EDV), cardiac strain, and blood pressure for the time period and to adjust the stimulation pattern configuration according to the at least one sensed parameter.

[0061] In a further aspect of the system, the system may further comprise at least one sensor configured to sense the at least one sensed parameter and to communicate the input data to the at least one controller.

[0062] In a further aspect of the system, the at least one controller, the stimulation circuit, and the at least one sensor may be combined in a single device.

[0063] Figure 8 illustrates an embodiment of a system 800 for treating cardiac malfunction, which includes a stimulation circuit and at least one controller as described above. System 800 may be constructed and have components similar to a cardiac pacemaker essentially as known in the art with some modifications as discussed herein. Optionally, the system, or device, is implantable. Optionally, the system comprises components that may provide additional and/or alternative electrical treatments of the heart (e.g., defibrillation). System 800 may be configured for implantation in the body of

a patient essentially as is known in the art for implantable pacemakers, optionally with some modifications as discussed herein.

[0064] System 800 may include a biocompatible body 51, one or more controllers 52, a power source 53, and a telemetry unit 56. Body 51 may comprise a housing for encasing a plurality of components of the system. Controller(s) 52 may be configured to control the operation of the system, and may implement any of the embodiments and methods disclosed herein. For example, controller(s) 52 may control the delivery of stimulation pulses. In some embodiments, power source 53 may include a battery. For example, power source 53 may include a rechargeable battery. In some embodiments, power source 53 may include a battery that is rechargeable by induction. In some embodiments, telemetry unit 56 may be configured to communicate with one or more other units and/or components. For example, telemetry unit 56 may be configured to communicate with an external programmer and/or a receiving unit for receiving data recorded on system 800 during operation.

[0065] In some embodiments, system 800 may include one or more electrodes and/or sensors. The electrodes and/or sensors may be integrated in system 800, attached thereto, and/or connectable therewith. In some embodiments, the electrodes may include ventricular electrode(s) 561 configured to pace at least one ventricle. Additionally or alternatively, the system may be connected, optionally via wires or wirelessly, to at least one implanted artificial valve 562. Additionally, system 800 may comprise one or more atrial electrode(s) 57 for pacing one or more atria, and/or one or more atrial sensors 58 for sensing the onset of atrial excitation, and/or one or more sensors 59 for providing other feedback parameters (e.g., a blood-pressure-related parameter and a cardiac strain/volume related parameter).

[0066] In some embodiments, sensor(s) 59 may comprise one or more pressure sensors, electrical sensors (e.g., ECG monitoring), flow sensors, heart rate sensors, activity sensors, and/or volume sensors. Sensor(s) 59 may include mechanical sensors and/or electronic sensors (e.g., ultrasound sensors, electrodes, and/or RF transceivers). In some embodiments, sensor(s) 59 may communicate with system 800 via telemetry.

[0067] In some embodiments, ventricular electrode(s) 561 and/or atrial electrode(s) 57 may be standard pacing electrodes. Ventricular electrode(s) 561 may be

positioned relative to the heart at positions as known in the art for ventricular pacing. For example, ventricular electrode(s) may be placed in and/or near one or more of the ventricles. In some embodiments, atrial electrode(s) 57 may be placed in and/or near one or more of the atria. In some embodiments, atrial electrode(s) 57 may be attached to the one or more atria at one or more positions selected to provide early detection of atrial excitation or depolarization. For example, in some embodiments, atrial electrode(s) 57 may be attached to the right atrium near the site of the sinoatrial (SA) node.

[0068] One position of ventricular electrode(s) 561 may be such that pacing may reduce or minimize the prolongation of QRS when the heart is paced, to reduce or even minimize dyssynchrony. In some embodiments, this position is on the ventricular septum near the Bundle of His. Ventricular electrode(s) 561 may additionally or alternatively be placed on the epicardium of the heart or in coronary veins. More than one electrode can be placed on the ventricles to provide biventricular pacing, optionally to reduce dyssynchrony.

[0069] System 800 may include a pulse generator, or stimulation circuit, configured to deliver a stimulation pulse to at least one cardiac chamber. The pulse generator, or stimulation circuit, may include some or all standard capabilities of a conventional pacemaker. Controller 52 may be configured to control the pulse generator, or stimulation circuit. Atrial sensor(s) 58 (and optionally other electrode sensors configured to sense other heart chambers) may be connected to system 800 via specific circuits that amplify the electrical activity of the heart and allow sampling and detection of the activation of the specific chamber. Other circuits may be configured to deliver stimulation to a specific electrode to pace the heart, creating propagating electrical activation.

[0070] In some embodiments, one or more additional sensors 59 may be placed in and/or on one or more of the atria and/or in and/or on one or more of the ventricles and/or in and/or on one or more other locations that might optionally be adjacent the heart. For example, one or more sensors may be placed on and/or in vena cava and/or on one or more arteries and/or within one or more cardiac chambers. These sensors may measure pressure, or other indicators, such as, for example, impedance and/or flow.

[0071] In some embodiments, controller 52 may comprise or be a microprocessor powered by power source 53. In some embodiments, system 800 may comprise a clock 54, for example, generated by a crystal. System 800 may comprise an internal memory 55 and/or be connected to external memory. For example, device may connect to an external memory via telemetry unit 56. In some embodiments, telemetry unit 56 may be configured to allow communication with external devices such as a programmer and/or one or more of sensors 59. Any and all feedback information and/or a log of device operation may be stored in internal memory 55 and/or relayed by telemetry unit 56 to an external memory unit.

[0072] In some embodiments, controller 52 may operate in accordance with at least one embodiment of a method described herein.

[0073] In some embodiments, system 800 may comprise one or more sensors for sensing one or more feedback parameters to control the application of the AV delay and/or its magnitude.

[0074] According to further embodiments, additional systems and devices suitable for implementing the methods presented herein are described in U.S. Patent No. 9,370,662 to Mika et al., issued June 21, 2016, for example, in reference to Figures 9 and 14 of that patent. The entirety of U.S. Patent No. 9,370,662 is herein incorporated by reference.

[0075] The foregoing disclosure has been presented for purposes of illustration and description. It is not intended to be exhaustive or to limit the embodiments to the precise forms disclosed. Many variations and modifications of the embodiments described herein will be apparent to one of ordinary skill in the art in light of the above disclosure.

[0076] While various embodiments have been described, the description is intended to be exemplary, rather than limiting and it will be apparent to those of ordinary skill in the art that many more embodiments and implementations are possible that are within the scope of the embodiments. Any feature of any embodiment may be used in combination with or substituted for any other feature or element in any other embodiment unless specifically restricted. Accordingly, the embodiments are not to be restricted except in light of the attached claims and their equivalents. Also, various modifications and changes may be made within the scope of the attached claims.

2016319787 02 Oct 2020

[0077] Further, in describing representative embodiments, the specification may have presented a method and/or process as a particular sequence of steps. However, to the extent that the method or process does not rely on the particular order of steps set forth herein, the method or process should not be limited to the particular sequence of steps described. As one of ordinary skill in the art would appreciate, other sequences of steps may be possible. Therefore, the particular order of the steps set forth in the specification should not be construed as limitations on the claims. In addition, the claims directed to the method and/or process should not be limited to the performance of their steps in the order written, and one skilled in the art can readily appreciate that the sequences may be varied and still remain within the spirit and scope of the present embodiments.

[0078] The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

[0079] Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

2016319787 07 May 2021

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method for treating cardiac malfunction, comprising:

delivering over a time period of at least one hour a stimulation pattern of stimulation pulses to at least one cardiac chamber of a heart of a patient,

wherein at least one of the stimulation pulses has a first stimulation setting configured to reduce at least one of end systolic volume (ESV) and end diastolic volume (EDV) in the heart of the patient, and at least one of the stimulation pulses has a second stimulation setting different from the first stimulation setting;

reducing, by delivery of the stimulation pattern over the time period of at least one hour, the at least one of end systolic volume (ESV) and end diastolic volume (EDV) by at least 5%,

maintaining, by delivery of the stimulation pattern over the time period of at least one hour, the at least one of end systolic volume (ESV) and end diastolic volume (EDV) on average at such reduced volume for the time period of at least one hour, and

maintaining, by delivery of the stimulation pattern over the time period of at least one hour, blood pressure of the patient within an average pressure of ±10% as compared to a pretreatment blood pressure value for the time period of at least one hour.

2. The method of claim 1, wherein the time period is at least three months.

3. The method of claim 1, wherein the stimulation pattern is configured to reduce cardiac strain, as measured by wall tension, by at least 2% and maintain the cardiac strain on average at such reduced strain for the time period.

4. The method of claim 1, wherein the stimulation pattern is configured to limit reduction in ejection fraction of the heart to a maximum of 6% reduction and a time average of 2% reduction.

5. The method of claim 1, wherein the stimulation pattern is configured to prevent cardiac remodeling in the patient.

2016319787 07 May 2021

6. The method of claim 1, further comprising:

applying the stimulation pattern at a stimulation pattern configuration for a first period;

sensing cardiac strain for the first period; and

adjusting the stimulation pattern configuration according to the sensing.

7. The method of claim 1, wherein the first stimulation setting is configured to reduce the at least one of end systolic volume (ESV) and end diastolic volume (EDV) by at least 5% and the second stimulation setting is configured to reduce a baroreflex response or adaptation to the reduction in the at least one of end systolic volume (ESV) and end diastolic volume (EDV).

8. The method of claim 1, wherein the stimulation pattern is configured to reduce a baroreflex response or adaptation to the reduction in the at least one of end systolic volume (ESV) and end diastolic volume (EDV).

9. The method of claim 1, wherein the first stimulation setting is configured to reduce the at least one of end systolic volume (ESV) and end diastolic volume (EDV) by at least 5% and the second stimulation setting is configured to reduce a neuronal response or adaptation to the reduction in the at least one of end systolic volume (ESV) and end diastolic volume (EDV).

10. The method of claim 1, wherein the first stimulation setting is configured to reduce the at least one of end systolic volume (ESV) and end diastolic volume (EDV) by at least 5% and the second stimulation setting is configured to increase hormonal secretion.

11. The method of claim 1, wherein the cardiac malfunction is associated with an increase in at least one of end systolic volume (ESV) and end diastolic volume (EDV).

12. The method of claim 1, wherein the cardiac malfunction is congestive heart failure.

13. The method of claim 1, further comprising:

applying the stimulation pattern at a stimulation pattern configuration for a first period;

sensing at least one parameter indicative of at least one of end systolic volume (ESV), end diastolic volume (EDV), cardiac strain, and blood pressure for the first period; and

adjusting the stimulation pattern configuration according to the sensing.

14. The method of claim 13, wherein adjusting the stimulation pattern configuration includes adjusting at least one of the number and proportion of at least one of stimulation pulses having the first stimulation setting and stimulation pulses having the second stimulation setting within the stimulation pattern.

15. A system for treating cardiac malfunction, comprising:

a stimulation circuit configured to deliver a stimulation pulse to at least one cardiac chamber of a heart of a patient; and

at least one controller configured to execute delivery of a stimulation pattern of stimulation pulses to the at least one cardiac chamber over a time period of at least one hour,

wherein at least one of the stimulation pulses has a first stimulation setting configured to reduce at least one of end systolic volume (ESV) and end diastolic volume (EDV) in the heart of the patient, and at least one of the stimulation pulses has a second stimulation setting different from the first stimulation setting, and

wherein the stimulation pattern is configured to:

reduce, during the time period of at least one hour, the at least one of end systolic volume (ESV) and end diastolic volume (EDV) by at least 5%,

maintain, during the time period of at least one hour, the at least one of end systolic volume (ESV) and end diastolic volume (EDV) in the heart of the patient on average at such reduced volume, and

maintain, during the time period of at least one hour, blood pressure of the patient within an average pressure of +10% as compared to a pretreatment blood pressure value.

2016319787 07 May 2021

16. The system of claim 15, wherein the at least one controller is configured to receive input data relating to at least one sensed parameter indicative of cardiac strain for the time period and to adjust the stimulation pattern configuration according to the at least one sensed parameter.

17. The system of claim 16, further comprising at least one sensor configured to sense the at least one sensed parameter and to communicate the input data to the at least one controller.

18. The system of claim 17, wherein the at least one controller, the stimulation circuit, and the at least one sensor are combined in a single device.

19. A method for treating cardiac malfunction, comprising:

delivering over a time period of at least one hour a stimulation pattern of stimulation pulses to at least one cardiac chamber of a heart of a patient,

wherein at least one of the stimulation pulses has a first stimulation setting that stimulates a ventricle of the heart 40-90 milliseconds after atrial activation and reduces at least one of end systolic volume (ESV) or end diastolic volume (EDV) in the heart of the patient,

wherein at least one of the stimulation pulses has a second stimulation setting that stimulates the ventricle 100-180 milliseconds after atrial activation, and

wherein the stimulation pattern includes at least 4 consecutive heartbeats having the first stimulation setting for every 1 consecutive heartbeat having the second stimulation setting,

such that the stimulation pattern:

reduces the at least one of end systolic volume (ESV) or end diastolic volume (EDV) by at least 5%,

maintains the at least one of end systolic volume (ESV) or end diastolic volume (EDV) in the heart of the patient on average at such reduced volume for the time period of at least one hour,

limits reduction in ejection fraction of the heart to about 2% or less, and

maintains, for the time period of at least one hour, blood pressure of the patient

2016319787 07 May 2021

within an average pressure of ±10% as compared to a pretreatment blood pressure value.

20. The method of claim 1, wherein the stimulation pattern is configured to limit, for the time period of at least one hour, reduction in the average pressure of the blood pressure of the patient to less than 4% of the pretreatment blood pressure value.

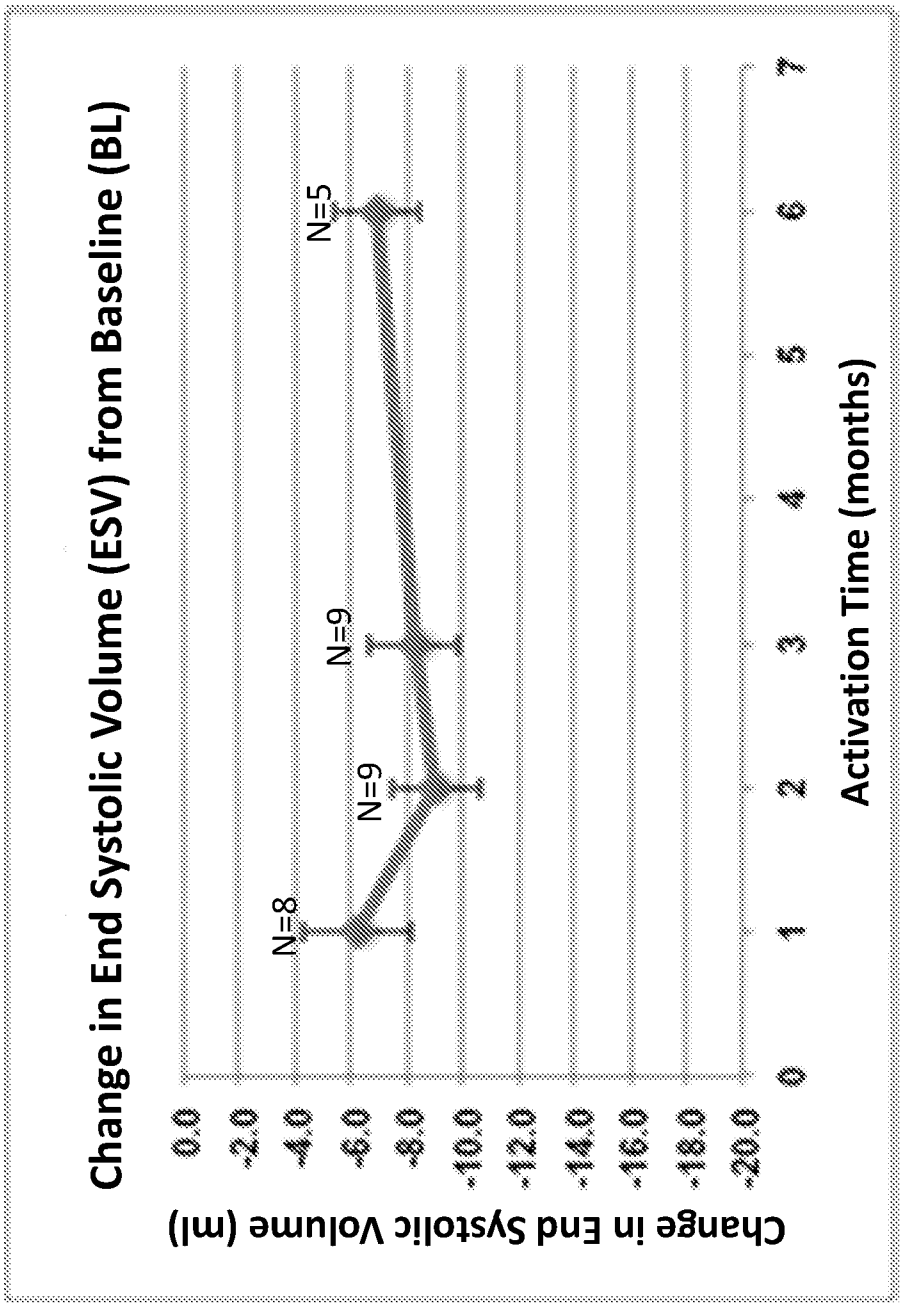
Change in End Systolic Volume (ESV) from Baseline (BL)
Change in End Systolic Volume (ml)
0.0
-2.0
-4.0
-6.0
-8.0
-10.0
-12.0
-14.0
-16.0
-18.0
-20.0
0
1
2
3
4
5
6
7
Activation Time (months)
N=8
N=9
N=9
N=5

FIG. 1

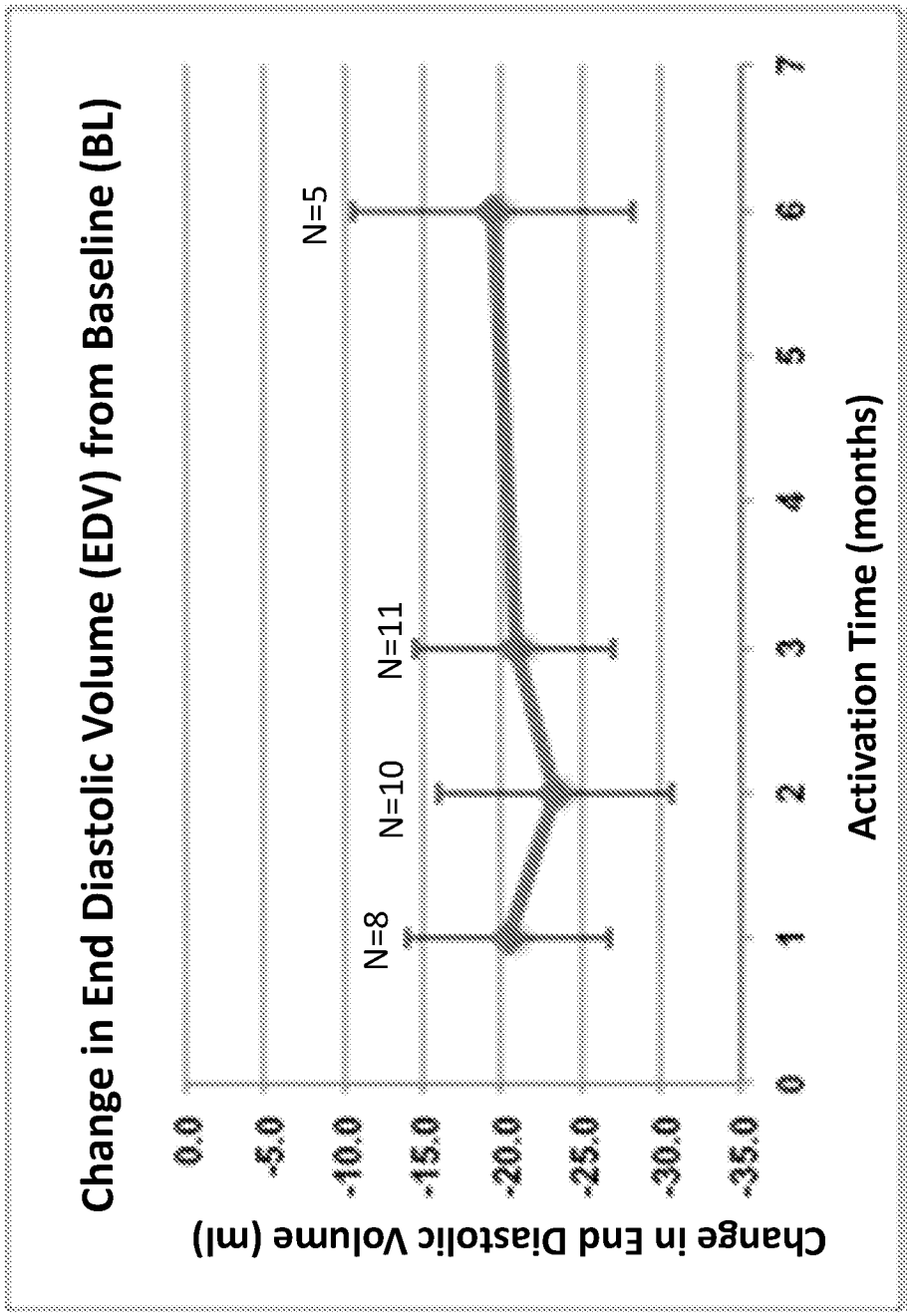
Change in End Diastolic Volume (EDV) from Baseline (BL)
Change in End Diastolic Volume (ml)
0.0
-5.0
-10.0
-15.0
-20.0
-25.0
-30.0
-35.0
0
1
2
3
4
5
6
7
Activation Time (months)
N=8
N=10
N=11
N=5

FIG. 2

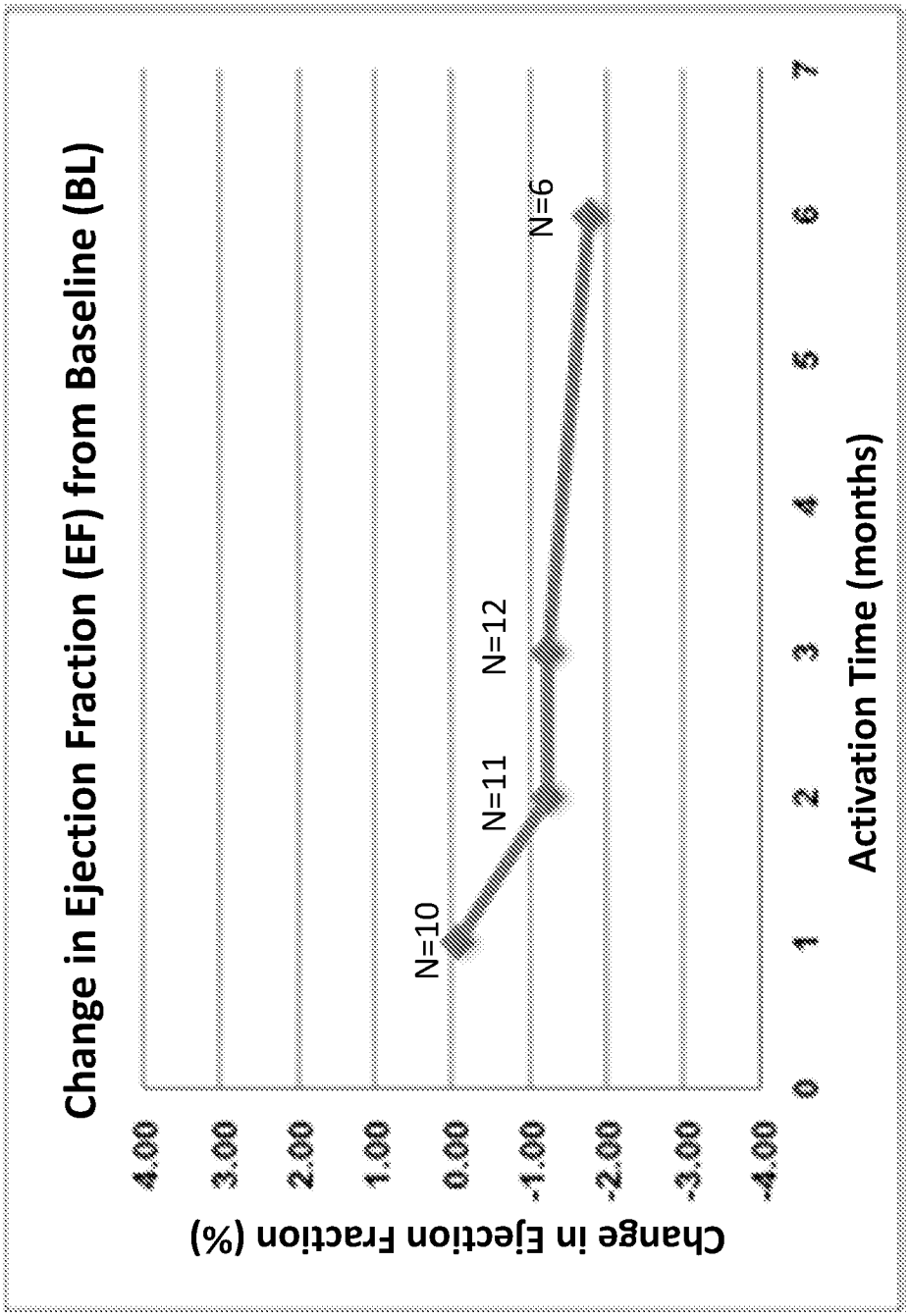
Change in Ejection Fraction (EF) from Baseline (BL)
Change in Ejection Fraction (%)
4.00
3.00
2.00
1.00
0.00
-1.00
-2.00
-3.00
-4.00
0
1
2
3
4
5
6
7
Activation Time (months)
N=10
N=11
N=12
N=6

FIG. 3

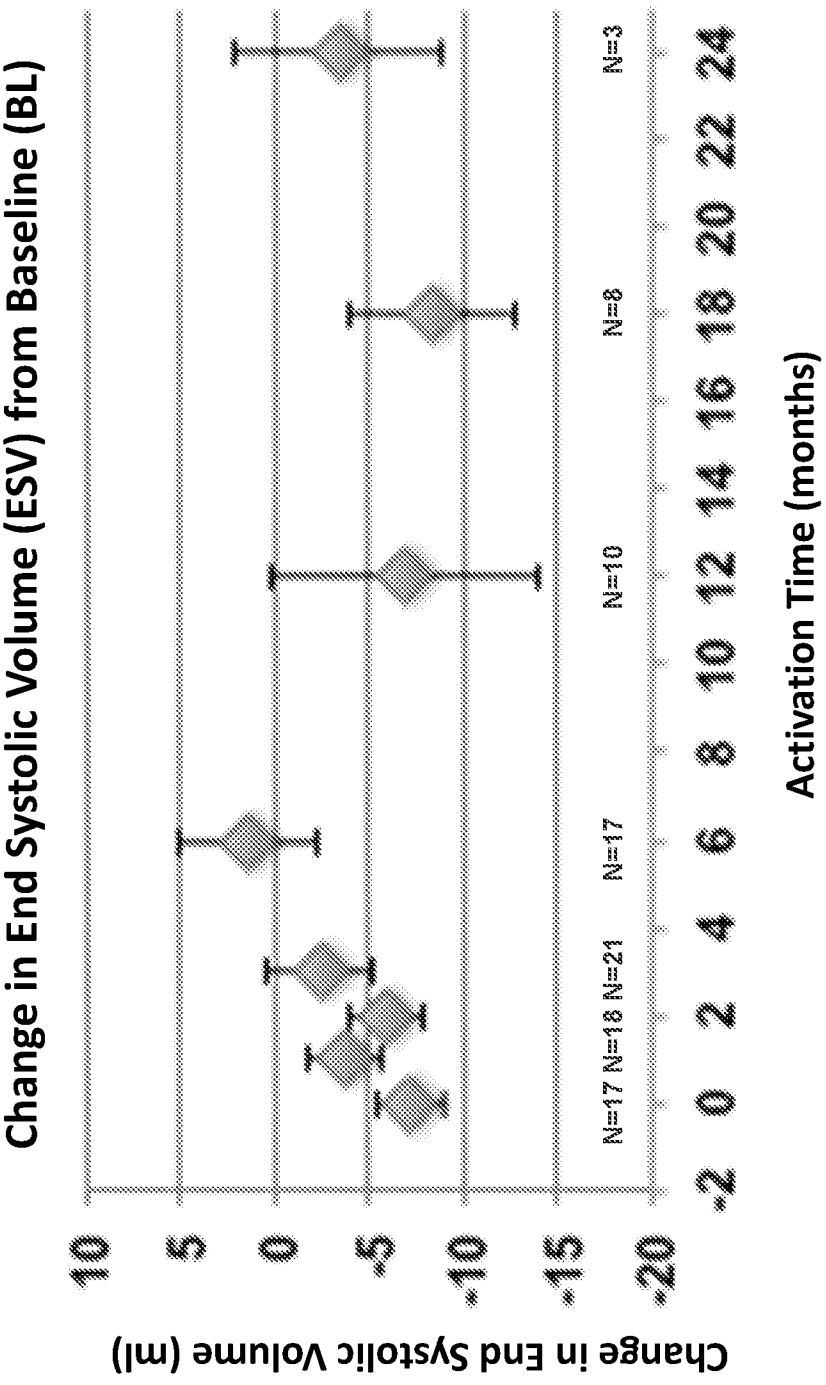
Change in End Systolic Volume (ESV) from Baseline (BL)
Change in End Systolic Volume (ml)
10
5
0
-5
-10
-15
-20
-2 0 2 4 6 8 10 12 14 16 18 20 22 24
Activation Time (months)
N=17 N=18 N=21 N=17 N=10 N=8 N=3

FIG. 4

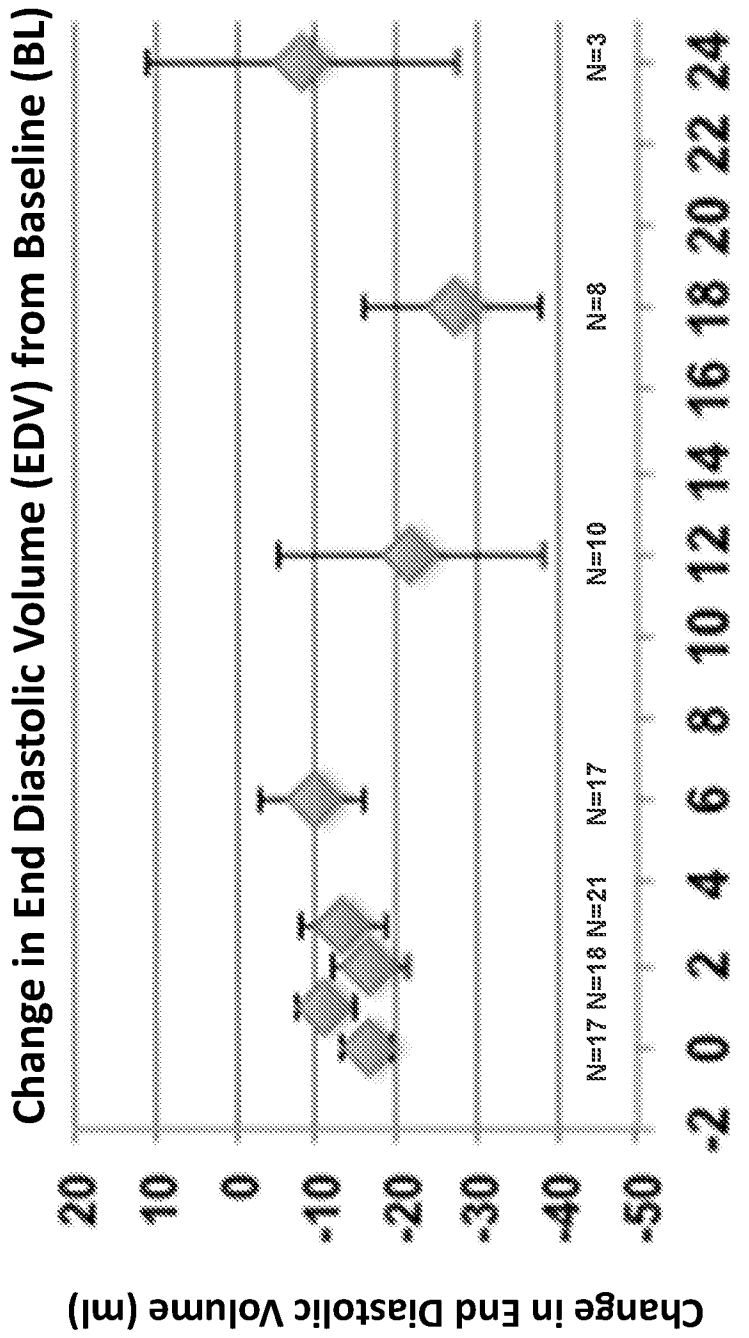
Change in End Diastolic Volume (EDV) from Baseline (BL)
Change in End Diastolic Volume (ml)
20
10
0
-10
-20
-30
-40
-50
-2 0 2 4 6 8 10 12 14 16 18 20 22 24
Activation Time (months)
N=17 N=18 N=21 N=17 N=10 N=8 N=3

FIG. 5

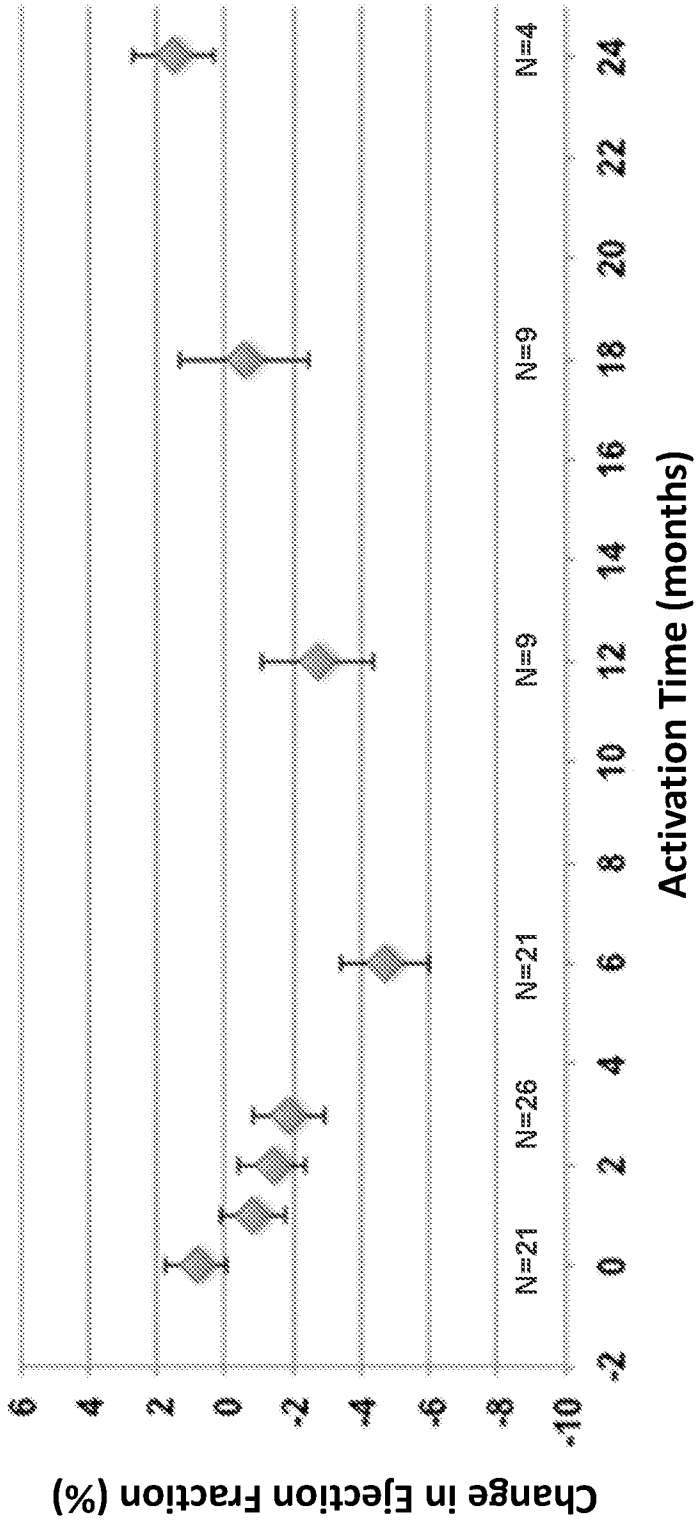
Change in Ejection Fraction (EF) from Baseline (BL)
Change in Ejection Fraction (%)
6
4
2
0
-2
-4
-6
-8
-10
-2
0
2
4
6
8
10
12
14
16
18
20
22
24
Activation Time (months)
N=21
N=26
N=21
N=9
N=9
N=4

FIG. 6

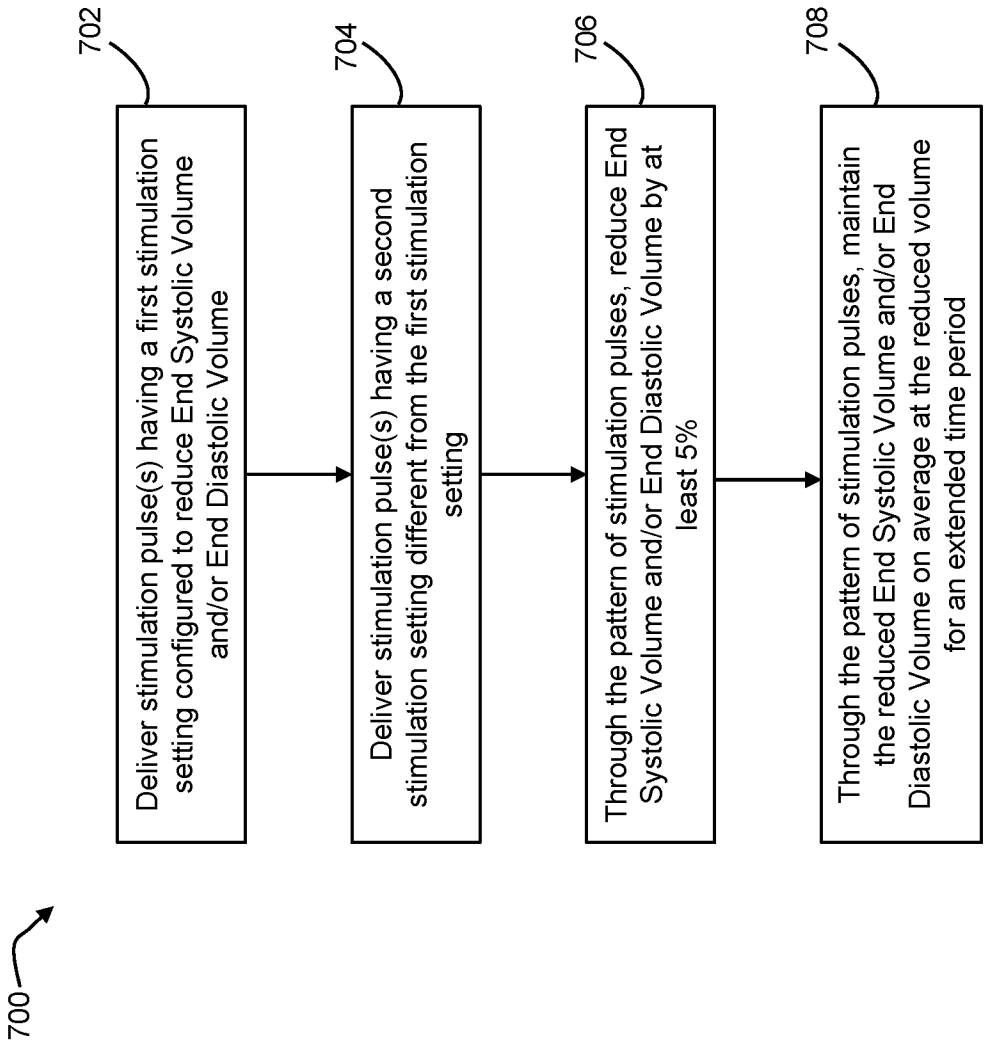
700
702
Deliver stimulation pulse(s) having a first stimulation setting configured to reduce End Systolic Volume and/or End Diastolic Volume
704
Deliver stimulation pulse(s) having a second stimulation setting different from the first stimulation setting
706
Through the pattern of stimulation pulses, reduce End Systolic Volume and/or End Diastolic Volume by at least 5%
708
Through the pattern of stimulation pulses, maintain the reduced End Systolic Volume and/or End Diastolic Volume on average at the reduced volume for an extended time period

FIG. 7

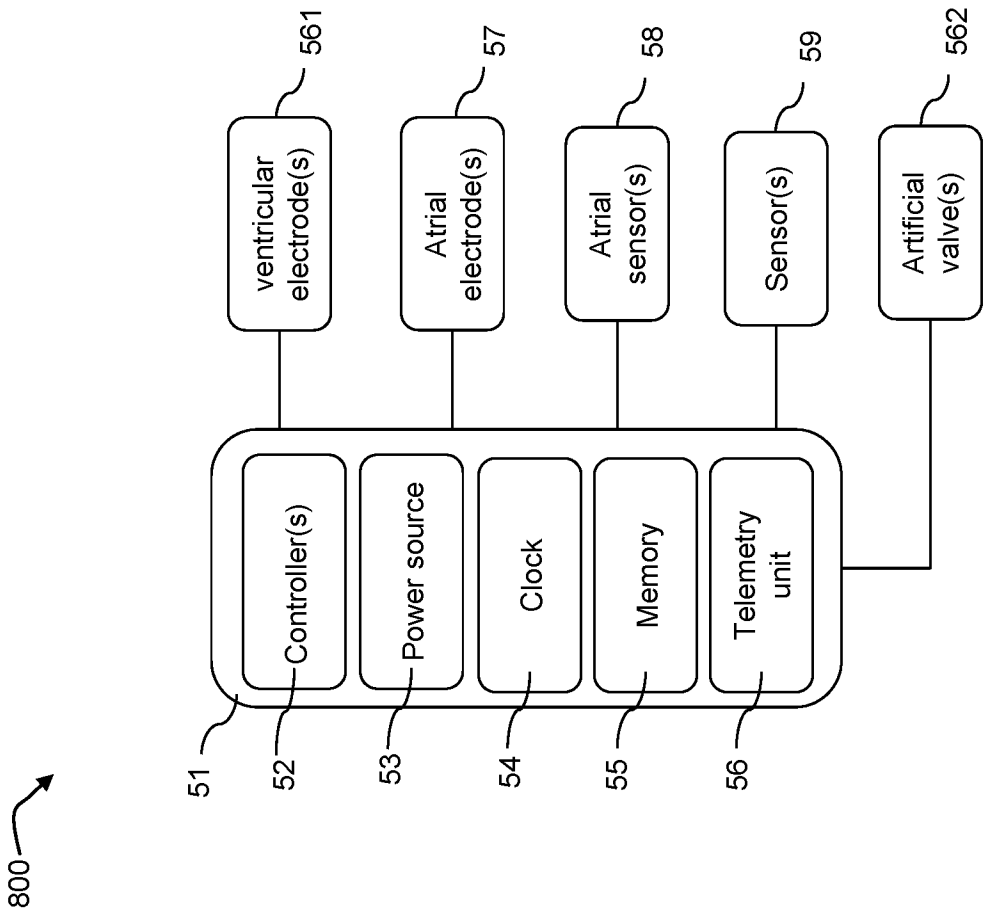
800
51
Controller(s)
52
Power source
53
Clock
54
Memory
55
Telemetry unit
56
ventricular electrode(s)
561
Atrial electrode(s)
57
Atrial sensor(s)
58
Sensor(s)
59
Artificial valve(s)
562

FIG. 8