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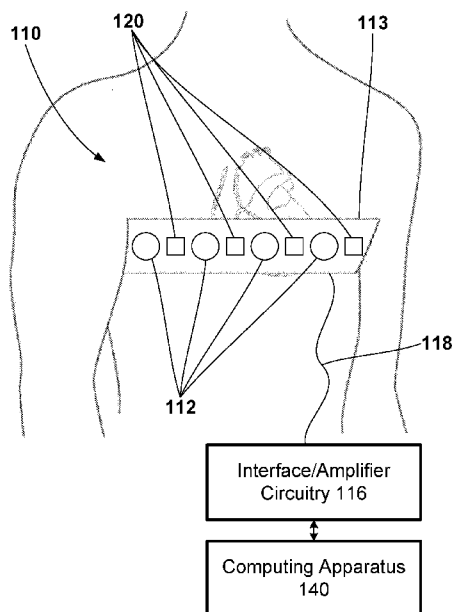


FIG. 2

(57) Abstract: Systems and methods are described herein for evaluation and adjustment of a left ventricular assist device (LVAD). The systems and methods may utilize at least a plurality of external electrodes to monitor cardiac electrical activity before and during LVAD therapy. The cardiac electrical activity as well as other information such as cardiac sound information may be used to determine and adjust one or more LVAD output parameters such as pump speed.

LEFT VENTRICULAR ASSIST DEVICE ADJUSTMENT
AND EVALUATION

- [01] This application claims the benefit of U.S. Patent Application No. 62/649,929, filed March 29, 2018, which is incorporated herein by reference in its entirety.
- [02] The disclosure herein relates to systems and methods for use in the adjustment and evaluation of cardiac therapy provided by a left ventricular assist device (LVAD) using external electrode apparatus.
- [03] Cardiac assistance systems provide additional cardiac output in patients who suffer from insufficient cardiac output. One type of cardiac assistance system is called a left ventricular assist device (LVAD). LVADs may be described as auxiliary pouches intended to function as booster pumps to aid the hearts of individuals suffering from chronic congestive heart failure. Chronic congestive heart failure may be frequently due to heart attacks that reduce the pumping capacity of the human heart. By boosting the capacity of such a weakened heart, individuals suffering from this condition may be allowed to again lead relatively normal, effective lives.
- [04] Heart failure patients undergoing surgery may also be provided with an LVAD to acutely unload the ventricle to promote recovery. About 20% to 30% of patients treated with an LVAD may develop right ventricular failure that is refractory to medical treatment. Right ventricular function may decline as a result of changes to right ventricular preload and after load resulting from abnormal pressure imbalances between the left and right ventricle as well as abnormal wall movement observed as septal shifting and free wall asynchronous bulging. Maintaining a greater degree of synchrony between right and left ventricular

pressure development may prevent the demise of right ventricular function in the presence of an LVAD.

[05] Further, implantable medical devices (IMDs), such as implantable pacemakers, cardioverters, defibrillators, or pacemaker-cardioverter-defibrillators, provide therapeutic electrical stimulation to the heart. IMDs may provide pacing to address bradycardia, or pacing or shocks in order to terminate tachyarrhythmia, such as tachycardia or fibrillation. In some cases, the medical device may sense intrinsic depolarizations of the heart, detect arrhythmia based on the intrinsic depolarizations (or absence thereof), and control delivery of electrical stimulation to the heart if arrhythmia is detected based on the intrinsic depolarizations.

[06] IMDs may also provide cardiac resynchronization therapy (CRT), which is a form of pacing. CRT involves the delivery of pacing to the left ventricle, or both the left and right ventricles. The timing and location of the delivery of pacing pulses to the ventricle(s) may be selected to improve the coordination and efficiency of ventricular contraction.

[07] Systems for implanting medical devices may include workstations or other equipment in addition to the implantable medical device itself. In some cases, these other pieces of equipment assist the physician or other technician with placing the intracardiac leads at particular locations on or in the heart. In some cases, the equipment provides information to the physician about the electrical activity of the heart and the location of the intracardiac lead.

SUMMARY

[08] The exemplary systems, apparatus, methods, and interfaces described herein may be configured to assist a user (e.g., a physician) in evaluating a patient and/or evaluating cardiac therapy (e.g., cardiac therapy being performed on a patient by a left ventricular cardiac assist device(LVAD) and/or an implantable cardiac therapy apparatus). In one or more embodiments, the systems, methods, and interfaces may be described as being noninvasive. For example, in some embodiments, the systems, methods, and interfaces may not need, or include, implantable devices such as leads, probes, sensors, catheters, implantable electrodes, etc. to monitor, or acquire, a plurality of cardiac signals from tissue of the patient for use in evaluating the patient and/or cardiac therapy provided by the LVAD and/or an implantable cardiac therapy apparatus. Instead, the systems, methods, and interfaces may use measurements (e.g., electrical, physical, etc.) taken noninvasively using, e.g., a plurality of external sensors and/or electrodes attached to the skin of a patient about the patient's torso.

[09] One exemplary system may include electrode apparatus comprising a plurality of external electrodes to monitor cardiac electrical activity from tissue of a patient and computing apparatus comprising processing circuitry and coupled to the electrode apparatus. The computing apparatus may be configured to monitor cardiac electrical activity using the plurality of external electrodes at least during delivery of cardiac therapy using a left ventricular assist device (LVAD), generate electrical heterogeneity information based on the monitored electrical activity, and determine an output parameter for the LVAD based the generated electrical heterogeneity information.

[10] A method may include monitoring electrical activity from tissue of a patient using a plurality of electrodes at least during delivery of cardiac therapy using a left ventricular assist device (LVAD), generating electrical heterogeneity information based on the monitored electrical activity, and determining an output parameter for the LVAD based the generated electrical heterogeneity information.

[11] The exemplary systems, apparatus, and methods disclosed herein may be described as a general-purpose tool for titrating pacing parameters for maximizing cardiac electrical synchronization during cardiac resynchronization therapy (CRT). More specifically, the exemplary systems, apparatus, and methods may use a plurality of external electrodes to measure and monitor global cardiac activation patterns during the use of cardiac therapy using a left ventricular assist device (LVAD) for use in, e.g., LVAD therapy evaluation, follow-up/programming for titrating LVAD therapy including speed of the pump and concomitant of pacing therapy. The exemplary systems, apparatus, and methods disclosed herein may be further described as providing an instant, non-invasive means of titrating LVAD therapies for optimal patient outcomes.

[12] In one or more embodiments, the exemplary systems, apparatus, and methods may be outfitted with, or include, one or more additional sensors to aid with the LVAD device and patient management. For example, an array of acoustic sensors could be incorporated into electrode apparatus, which includes the plurality of external electrodes, and the acoustic signals may be used to infer mechanical activation of heart (e.g., valve openings and closings) as well as detection of acoustic signatures corresponding to thrombus buildup inside the pump of an LVAD or other mechanical issues with the LVAD.

[13] Further, in one or more embodiments, the exemplary systems, apparatus, and methods including, for example, signal amplifiers, the electrode array, analysis processes or algorithms may be described as being integrated with an LVAD controller or LVAD monitor of an LVAD system. The exemplary systems, apparatus, and methods may further contain, or utilize, algorithms for automatically titrating parameters for best response (e.g., lowest right ventricular (RV) dyssynchrony, shortest RV activation time, etc.) and least chance of a patient to develop RV failure.

[14] In one or more embodiments, the exemplary systems, apparatus, and methods may be configured to titrate either LVAD pump speed alone or LVAD

pump speed with a pacing device pacing parameters (either automatically or manually). Further, the exemplary systems, apparatus, and methods may also include, or have, other cutaneous sensors and associated signal processing integrated (such as acoustics) to provide input on mechanical function of the heart (e.g., valve openings and closings) as well as diagnostics related to the pump function itself (e.g., “build up” of thrombus inside the pump, etc.).

- [15] The above summary is not intended to describe each embodiment or every implementation of the present disclosure. A more complete understanding will become apparent and appreciated by referring to the following detailed description and claims taken in conjunction with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

- [16] FIG. 1 is a diagram of an exemplary system including electrode apparatus, a left ventricular assist device (LVAD) apparatus, display apparatus, and computing apparatus.
- [17] FIGS. 2-3 are diagrams of exemplary external electrode apparatus for measuring torso-surface potentials.
- [18] FIG. 4 is a block diagram of an exemplary method for determining an LVAD output parameter.
- [19] FIG. 5 is a block diagram of an exemplary method for adjusting one or both of a LVAD output parameter and a pacing parameter.
- [20] FIG. 6 is a block diagram of an exemplary method for adjusting a LVAD based on one or both of electrical heterogeneity information and cardiac sounds.
- [21] FIG. 7 is a diagram of an exemplary system including an exemplary implantable medical device (IMD).

- [22] FIG. 8 is a diagram of an exemplary system including an exemplary LVAD apparatus and the IMD of FIG. 7.
- [23] FIG. 9A is a diagram of the exemplary IMD of FIG. 7.
- [24] FIG. 9B is a diagram of an enlarged view of a distal end of the electrical lead disposed in the left ventricle of FIG. 9A.
- [25] FIG. 10A is a block diagram of an exemplary IMD, e.g., the systems of FIGS. 7-9.
- [26] FIG. 10B is another block diagram of an exemplary IMD (e.g., an implantable pulse generator) circuitry and associated leads employed in the systems of FIGS. 7-9.

DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS

- [27] In the following detailed description of illustrative embodiments, reference is made to the accompanying figures of the drawing which form a part hereof, and in which are shown, by way of illustration, specific embodiments which may be practiced. It is to be understood that other embodiments may be utilized and structural changes may be made without departing from (e.g., still falling within) the scope of the disclosure presented hereby.
- [28] Exemplary systems and methods shall be described with reference to Figures 1-10. It will be apparent to one skilled in the art that elements or processes from one embodiment may be used in combination with elements or processes of the other embodiments, and that the possible embodiments of such methods and systems using combinations of features set forth herein is not limited to the specific embodiments shown in the Figures and/or described herein. Further, it will be recognized that the embodiments described herein may include many elements that are not necessarily shown to scale. Still further, it will be recognized that timing of the processes and the size and shape of various elements

herein may be modified but still fall within the scope of the present disclosure, although certain timings, one or more shapes and/or sizes, or types of elements, may be advantageous over others.

[29] A plurality of electrocardiogram (ECG) recordings or signals may be measured, or monitored, using a plurality of external electrodes positioned about the surface, or skin, of a patient. The ECG signals may be used to evaluate and configured cardiac therapy such as, e.g., cardiac therapy provide by an LVAD or CRT. As described herein, the ECG signals may be gathered or obtained noninvasively since, e.g., implantable electrodes may not be used to measure the ECG signals. Further, the ECG signals may be used to determine cardiac electrical activation times, which may be used to generate various metrics (e.g., electrical heterogeneity information) that may be used by a user (e.g., physician) to optimize one or more settings, or parameters, of cardiac therapy provided by an LVAD or pacing therapy such as CRT.

[30] Various exemplary systems and methods may be configured to use electrode apparatus including external electrodes, display apparatus, and computing apparatus to noninvasively assist a user (e.g., a physician) in the evaluation of cardiac health and/or the configuration (e.g., optimization) of cardiac therapy. An exemplary system 100 including electrode apparatus 110, computing apparatus 140, LVAD apparatus 151, and a remote computing device 160 is depicted in FIG. 1.

[31] The exemplary LVAD apparatus 151 may be generally described as including a LVAD 150, which operably coupled to the patient's heart to perform left ventricular assist cardiac therapy, and a LVAD controller 152 operably coupled to the LVAD 150 to control and provide power to the LVAD 150. The LVAD 150 may be operatively coupled to the LVAD controller 152 (e.g., through one or wired electrical connections, wirelessly, etc.). As shown, the LVAD 150 is operably coupled, or connected, to the LVAD controller 152 through the use of wired connection or wire. The exemplary LVAD apparatus 151 may be further

described herein with reference to FIG. 8. It is to be understood that the LVAD apparatus 151 may include lower output flow, partial cardiac assistance systems may be useful for a broader range of HF patients including those that are less symptomatic and those with preserved ejection fraction (HFpEF) where high cardiac filling pressures may cause HF symptoms. Implantation methods for these lower output pumps may be performed with minimally invasive techniques and may include various placements such as left atrium to aorta circulatory support. For purposes of this disclosure, all such full and partial cardiac assistance systems including those that treat HF with preserved ejection fraction will be referred to as LVADs.

[32] The electrode apparatus 110 as shown includes a plurality of electrodes incorporated, or included, within a band wrapped around the chest, or torso, of a patient 14. The electrode apparatus 110 is operatively coupled to the computing apparatus 140 (e.g., through one or wired electrical connections, wirelessly, etc.) to provide electrical signals from each of the electrodes to the computing apparatus 140 for analysis, evaluation, etc. Exemplary electrode apparatus may be described in U.S. Patent No. 9,320,446 entitled “Bioelectric Sensor Device and Methods” filed March 27, 2014 and issued on March 26, 2016, which is incorporated herein by reference in its entirety. Further, exemplary electrode apparatus 110 will be described in more detail in reference to FIGS. 2-3.

[33] Although not described herein, the exemplary system 100 may further include imaging apparatus. The imaging apparatus may be any type of imaging apparatus configured to image, or provide images of, at least a portion of the patient in a noninvasive manner. For example, the imaging apparatus may not use any components or parts that may be located within the patient to provide images of the patient except noninvasive tools such as contrast solution. It is to be understood that the exemplary systems and methods described herein may further use imaging apparatus to provide noninvasive assistance to a user (e.g., a physician) to locate, or place, the LVAD 150 (or one or more portions thereof) or

one or more pacing electrodes proximate the patient's heart in conjunction with the configuration of cardiac therapy.

[34] For example, the exemplary systems and methods may provide image guided navigation that may be used to navigate one or more portions of a LVAD 150, leads including electrodes, leadless electrodes, wireless electrodes, catheters, etc., within the patient's body while also providing noninvasive cardiac therapy configuration including determining an effective, or optimal, LVAD parameters A-V interval, etc. Exemplary systems and methods that use imaging apparatus and/or electrode apparatus may be described in U.S. Pat. App. Pub. No. 2014/0371832 to Ghosh published on December 18, 2014, U.S. Pat. App. Pub. No. 2014/0371833 to Ghosh et al. published on December 18, 2014, U.S. Pat. App. Pub. No. 2014/0323892 to Ghosh et al. published on October 30, 2014, U.S. Pat. App. Pub. No. 2014/0323882 to Ghosh et al. published on October 20, 2014, each of which is incorporated herein by reference in its entirety.

[35] Exemplary imaging apparatus may be configured to capture x-ray images and/or any other alternative imaging modality. For example, the imaging apparatus may be configured to capture images, or image data, using isocentric fluoroscopy, bi-plane fluoroscopy, ultrasound, computed tomography (CT), multi-slice computed tomography (MSCT), magnetic resonance imaging (MRI), high frequency ultrasound (HIFU), optical coherence tomography (OCT), intra-vascular ultrasound (IVUS), two dimensional (2D) ultrasound, three dimensional (3D) ultrasound, four dimensional (4D) ultrasound, intraoperative CT, intraoperative MRI, etc. Further, it is to be understood that the imaging apparatus may be configured to capture a plurality of consecutive images (e.g., continuously) to provide video frame data. In other words, a plurality of images taken over time using the imaging apparatus may provide video frame, or motion picture, data. Additionally, the images may also be obtained and displayed in two, three, or four dimensions. In more advanced forms, four-dimensional surface rendering of the heart or other regions of the body may also be achieved by incorporating heart data or other soft tissue data from a map or from pre-operative

image data captured by MRI, CT, or echocardiography modalities. Image datasets from hybrid modalities, such as positron emission tomography (PET) combined with CT, or single photon emission computer tomography (SPECT) combined with CT, could also provide functional image data superimposed onto anatomical data, e.g., to be used to navigate implantable apparatus to target locations within the heart or other areas of interest.

- [36] Systems and/or imaging apparatus that may be used in conjunction with the exemplary systems and method described herein are described in U.S. Pat. App. Pub. No. 2005/0008210 to Evron et al. published on January 13, 2005, U.S. Pat. App. Pub. No. 2006/0074285 to Zarkh et al. published on April 6, 2006, U.S. Pat. No. 8,731,642 to Zarkh et al. issued on May 20, 2014, U.S. Pat. No. 8,861,830 to Brada et al. issued on October 14, 2014, U.S. Pat. No. 6,980,675 to Evron et al. issued on December 27, 2005, U.S. Pat. No. 7,286,866 to Okerlund et al. issued on October 23, 2007, U.S. Pat. No. 7,308,297 to Reddy et al. issued on December 11, 2011, U.S. Pat. No. 7,308,299 to Burrell et al. issued on December 11, 2011, U.S. Pat. No. 7,321,677 to Evron et al. issued on January 22, 2008, U.S. Pat. No. 7,346,381 to Okerlund et al. issued on March 18, 2008, U.S. Pat. No. 7,454,248 to Burrell et al. issued on November 18, 2008, U.S. Pat. No. 7,499,743 to Vass et al. issued on March 3, 2009, U.S. Pat. No. 7,565,190 to Okerlund et al. issued on July 21, 2009, U.S. Pat. No. 7,587,074 to Zarkh et al. issued on September 8, 2009, U.S. Pat. No. 7,599,730 to Hunter et al. issued on October 6, 2009, U.S. Pat. No. 7,613,500 to Vass et al. issued on November 3, 2009, U.S. Pat. No. 7,742,629 to Zarkh et al. issued on June 22, 2010, U.S. Pat. No. 7,747,047 to Okerlund et al. issued on June 29, 2010, U.S. Pat. No. 7,778,685 to Evron et al. issued on August 17, 2010, U.S. Pat. No. 7,778,686 to Vass et al. issued on August 17, 2010, U.S. Pat. No. 7,813,785 to Okerlund et al. issued on October 12, 2010, U.S. Pat. No. 7,996,063 to Vass et al. issued on August 9, 2011, U.S. Pat. No. 8,060,185 to Hunter et al. issued on November 15, 2011, and U.S. Pat. No. 8,401,616 to Verard et al. issued on March 19, 2013, each of which is incorporated herein by reference in its entirety.

[37] The computing apparatus 140 and the remote computing device 160 may each include display apparatus 130, 160, respectively, that may be configured to display and analyze data such as, e.g., electrical signals (e.g., electrocardiogram data), electrical activation times, electrical heterogeneity information, etc. For example, one cardiac cycle, or one heartbeat, of a plurality of cardiac cycles, or heartbeats, represented by the electrical signals collected or monitored by the electrode apparatus 110 may be analyzed and evaluated for one or more metrics including activation times and electrical heterogeneity information that may be pertinent to the therapeutic nature of one or more parameters related to cardiac therapy such as, e.g., LVAD pump speed, LVAD pump power/current (e.g., current delivered to pump to affect pump speed and/or other pump parameters), LVAD pump throughput, other LVAD operating parameters, pacing parameters, lead location, etc. More specifically, for example, the QRS complex of a single cardiac cycle may be evaluated for one or more metrics such as, e.g., QRS onset, QRS offset, QRS peak, electrical heterogeneity information, electrical activation times, left ventricular or thoracic standard deviation of electrical activation times (LVED), standard deviation of activation-times (SDAT), average left ventricular or thoracic surrogate electrical activation times (LVAT), referenced to earliest activation time, QRS duration (e.g., interval between QRS onset to QRS offset), difference between average left surrogate and average right surrogate activation times, relative or absolute QRS morphology, difference between a higher percentile and a lower percentile of activation times (higher percentile may be 90%, 80%, 75%, 70%, etc. and lower percentile may be 10%, 15%, 20%, 25% and 30%, etc.), other statistical measures of central tendency (e.g. median or mode), dispersion (e.g. mean deviation, standard deviation, variance, interquartile deviations, range) applied to all activation times or right or left surrogate activation times, etc.

[38] In at least one embodiment, one or both of the computing apparatus 140 and the remote computing device 160 may be a server, a personal computer, or a tablet computer. The computing apparatus 140 may be configured to receive input from input apparatus 142 (e.g., a keyboard) and transmit output to the display apparatus

130, and the remote computing device 160 may be configured to receive input from input apparatus 162 (e.g., a touchscreen) and transmit output to the display apparatus 170. Both of the computing apparatus 140 and the remote computing device 160 may include data storage that may allow for access to processing programs or routines and/or one or more other types of data, e.g., for analyzing a plurality of electrical signals captured by the electrode apparatus 110, for determining QRS onsets, QRS offsets, medians, modes, averages, peaks or maximum values, valleys or minimum values, for determining electrical activation times, for driving a graphical user interface configured to noninvasively assist a user in configuring one or more LVAD operating parameters, or settings, such as LVAD pump speed, LVAD pump throughput, LVAD pump power, LVAD pump current, pump inflow gimbal angle, automatic algorithmic responses to events such as pump suction, patient activity level changes, and physiologic parameter inputs, enabling/disabling periodic pump speed modulation features such as the Lavare cycle, for driving a graphical user interface configured to noninvasively assist a user in configuring one or more pacing parameters, or settings, such as, e.g., pacing rate, ventricular pacing rate, A-V interval, V-V interval, pacing pulse width, pacing vector, multipoint pacing vector (e.g., left ventricular vector quad lead), pacing voltage, pacing configuration (e.g., biventricular pacing, right ventricle only pacing, left ventricle only pacing, etc.), and arrhythmia detection and treatment, rate adaptive settings and performance, etc.

- [39] The computing apparatus 140 may be operatively coupled to the input apparatus 142 and the display apparatus 130 to, e.g., transmit data to and from each of the input apparatus 142 and the display apparatus 130, and the remote computing device 160 may be operatively coupled to the input apparatus 162 and the display apparatus 170 to, e.g., transmit data to and from each of the input apparatus 162 and the display apparatus 170. For example, the computing apparatus 140 and the remote computing device 160 may be electrically coupled to the input apparatus 142, 162 and the display apparatus 130, 170 using, e.g., analog electrical connections, digital electrical connections, wireless connections, bus-based connections, network-based connections, internet-based connections,

etc. As described further herein, a user may provide input to the input apparatus 142, 162 to view and/or select one or more pieces of configuration information related to the cardiac therapy delivered by one or both of the LVAD apparatus 151 and an implantable medical device.

[40] Although as depicted the input apparatus 142 is a keyboard and the input apparatus 162 is a touchscreen, it is to be understood that the input apparatus 142 may include any apparatus capable of providing input to the computing apparatus 140 to perform the functionality, methods, and/or logic described herein. For example, the input apparatus 142, 162 may include a keyboard, a mouse, a trackball, a touchscreen (e.g., capacitive touchscreen, a resistive touchscreen, a multi-touch touchscreen, etc.), etc. Likewise, the display apparatus 130, 170 may include any apparatus capable of displaying information to a user, such as a graphical user interface 132, 172 including one or more heartbeats, QRS complexes, LVAD operating parameters, LVAD metrics of operation, pacing parameters, electrical heterogeneity information, textual instructions, graphical depictions of electrical activation information, graphical depictions of anatomy of a human heart, images or graphical depictions of the patient's heart, graphical depictions of locations of one or more electrodes, graphical depictions of a human torso, images or graphical depictions of the patient's torso, graphical depictions or actual images of implanted electrodes and/or leads, etc. Further, the display apparatus 130, 170 may include a liquid crystal display, an organic light-emitting diode screen, a touchscreen, a cathode ray tube display, etc.

[41] The processing programs or routines stored and/or executed by the computing apparatus 140 and the remote computing device 160 may include programs or routines for computational mathematics, matrix mathematics, decomposition algorithms, compression algorithms (e.g., data compression algorithms), calibration algorithms, image construction algorithms, signal processing algorithms (e.g., various filtering algorithms, Fourier transforms, fast Fourier transforms, etc.), standardization algorithms, comparison algorithms, vector mathematics, or any other processing required to implement one or more

exemplary methods and/or processes described herein. Data stored and/or used by the computing apparatus 140 and the remote computing device 160 may include, for example, electrical signal/waveform data from the electrode apparatus 110 (e.g., a plurality of QRS complexes), electrical activation times from the electrode apparatus 110, cardiac sound/signal/waveform data from the acoustic sensors 120, graphics (e.g., graphical elements, icons, buttons, windows, dialogs, pull-down menus, graphic areas, graphic regions, 3D graphics, etc.), graphical user interfaces, results from one or more processing programs or routines employed according to the disclosure herein (e.g., electrical signals, electrical heterogeneity information, etc.), or any other data that may be necessary for carrying out the one and/or more processes or methods described herein.

[42] In one or more embodiments, the exemplary systems and methods may be implemented using one or more computer programs executed on programmable computers, such as computers that include, for example, processing capabilities, data storage (e.g., volatile or non-volatile memory and/or storage elements), input devices, and output devices. Program code and/or logic described herein may be applied to input data to perform functionality described herein and generate desired output information. The output information may be applied as input to one or more other devices and/or methods as described herein or as would be applied in a known fashion.

[43] The one or more programs used to implement the systems, apparatus, methods, and/or interfaces described herein may be provided using any programmable language, e.g., a high-level procedural and/or object orientated programming language that is suitable for communicating with a computer system. Any such programs may, for example, be stored on any suitable device, e.g., a storage media, that is readable by a general or special purpose program running on a computer system (e.g., including processing apparatus) for configuring and operating the computer system when the suitable device is read for performing the procedures described herein. In other words, at least in one embodiment, the exemplary systems and methods interfaces may be implemented

using a computer readable storage medium, configured with a computer program, where the storage medium so configured causes the computer to operate in a specific and predefined manner to perform functions described herein. Further, in at least one embodiment, the exemplary systems, apparatus, methods, and interfaces may be described as being implemented by logic (e.g., object code) encoded in one or more non-transitory media that includes code for execution and, when executed by a processor, is operable to perform operations such as the methods, processes, and/or functionality described herein.

[44] The computing apparatus 140 and the remote computing device 160 may be, for example, any fixed or mobile computer system (e.g., a controller, a microcontroller, a personal computer, minicomputer, tablet computer, etc.). The exact configurations of the computing apparatus 140 and the remote computing device 160 are not limiting, and essentially any device capable of providing suitable computing capabilities and control capabilities (e.g., signal analysis, mathematical functions such as medians, modes, averages, maximum value determination, minimum value determination, slope determination, minimum slope determination, maximum slope determination, graphics processing, etc.) may be used. As described herein, a digital file may be any medium (e.g., volatile or non-volatile memory, a CD-ROM, a punch card, magnetic recordable tape, etc.) containing digital bits (e.g., encoded in binary, trinary, etc.) that may be readable and/or writable by the computing apparatus 140 and the remote computing device 160 described herein. Also, as described herein, a file in user-readable format may be any representation of data (e.g., ASCII text, binary numbers, hexadecimal numbers, decimal numbers, graphically, etc.) presentable on any medium (e.g., paper, a display, etc.) readable and/or understandable by a user.

[45] In view of the above, it will be readily apparent that the functionality as described in one or more embodiments according to the present disclosure may be implemented in any manner as would be known to one skilled in the art. As such, the computer language, the computer system, or any other software/hardware which is to be used to implement the processes described herein shall not be

limiting on the scope of the systems, processes, or programs (e.g., the functionality provided by such systems, processes, or programs) described herein.

[46] The exemplary electrode apparatus 110 may be configured to measure body-surface potentials of a patient 14 and, more particularly, torso-surface potentials of a patient 14. As shown in FIG. 2, the exemplary electrode apparatus 110 may include a set, or array, of electrodes 112, a strap 113, and interface/amplifier circuitry 116. The electrodes 112 may be attached, or coupled, to the strap 113 and the strap 113 may be configured to be wrapped around the torso of a patient 14 such that the electrodes 112 surround the patient's heart. As further illustrated, the electrodes 112 may be positioned around the circumference of a patient 14, including the posterior, lateral, posterolateral, anterolateral, and anterior locations of the torso of a patient 14.

[47] The exemplary electrode apparatus 110 may be further configured to measure, or monitor, sounds from at least one or both the patient 14 and one or more devices located within or operably coupled to the patient 14 such as the LVAD 150. As shown in FIG. 2, the exemplary electrode apparatus 110 may include a set, or array, of acoustic sensors 120 attached, or coupled, to the strap 113. The strap 113 may be configured to be wrapped around the torso of a patient 14 such that the acoustic sensors 120 surround the patient's heart. As further illustrated, the acoustic sensors 120 may be positioned around the circumference of a patient 14, including the posterior, lateral, posterolateral, anterolateral, and anterior locations of the torso of a patient 14.

[48] Further, the electrodes 112 and the acoustic sensors 120 may be electrically connected to interface/amplifier circuitry 116 via wired connection 118. The interface/amplifier circuitry 116 may be configured to amplify the signals from the electrodes 112 and the acoustic sensors 120 and provide the signals to one or both of the computing apparatus 140 and the remote computing device 160. Other exemplary systems may use a wireless connection to transmit the signals sensed by electrodes 112 to the interface/amplifier circuitry 116 and, in turn, to one or

both of the computing apparatus 140 and the remote computing device 160, e.g., as channels of data. In one or more embodiments, the interface/amplifier circuitry 116 may be electrically coupled to the computing apparatus 140 using, e.g., analog electrical connections, digital electrical connections, wireless connections, bus-based connections, network-based connections, internet-based connections, etc.

[49] Although in the example of FIG. 2 the electrode apparatus 110 includes a strap 113, in other examples any of a variety of mechanisms, e.g., tape or adhesives, may be employed to aid in the spacing and placement of electrodes 112 and the acoustic sensors 120. In some examples, the strap 113 may include an elastic band, strip of tape, or cloth. Further, in some examples, the strap 113 may be part of, or integrated with, a piece of clothing such as, e.g., a t-shirt. In other examples, the electrodes 112 and the acoustic sensors 120 may be placed individually on the torso of a patient 14. Further, in other examples, the electrodes 112 (e.g., arranged in an array) and the acoustic sensors 120 (e.g., also arranged in an array) may be part of, or located within, patches, vests, and/or other manners of securing the electrodes 112 and the acoustic sensors 120 to the torso of the patient 14. Still further, in other examples, the electrodes 112 and the acoustic sensors 120 may be part of, or located within, two sections of material or two “patches.” One of the two sections or patches may be located on the anterior side of the torso of the patient 14 (to, e.g., monitor electrical signals representative of the anterior side of the patient’s heart, measure surrogate cardiac electrical activation times representative of the anterior side of the patient’s heart, monitor or measure sounds of the anterior side of the patient, etc.) and the other section or patch may be located on the posterior side of the torso of the patient 14 (to, e.g., monitor electrical signals representative of the posterior side of the patient’s heart, measure surrogate cardiac electrical activation times representative of the posterior side of the patient’s heart, monitor or measure sounds of the posterior side of the patient, etc.). And still further, in other examples, the electrodes 112 and the acoustic sensors 120 may be arranged in a top row and bottom row that extend from the anterior side of the patient 14 across the left side of the patient 14 to the anterior

side of the patient 14. Yet still further, in other examples, the electrodes 112 and the acoustic sensors 120 may be arranged in a curve around the armpit area and may have an electrode/sensor-density that less dense on the right thorax than the other remaining areas.

[50] The electrodes 112 may be configured to surround the heart of the patient 14 and record, or monitor, the electrical signals associated with the depolarization and repolarization of the heart after the signals have propagated through the torso of a patient 14. Each of the electrodes 112 may be used in a unipolar configuration to sense the torso-surface potentials that reflect the cardiac signals. The interface/amplifier circuitry 116 may also be coupled to a return or indifferent electrode (not shown) that may be used in combination with each electrode 112 for unipolar sensing.

[51] In some examples, there may be about 12 to about 50 electrodes 112 and about 12 to about 50 acoustic sensors 120 spatially distributed around the torso of a patient. Other configurations may have more or fewer electrodes 112 and more or fewer acoustic sensors 120. It is to be understood that the electrodes 112 and acoustic sensors 120 may not be arranged or distributed in an array extending all the way around or completely around the patient 14. Instead, the electrodes 112 and acoustic sensors 120 may be arranged in an array that extends only part of the way or partially around the patient 14. For example, the electrodes 112 and acoustic sensors 120 may be distributed on the anterior, posterior, and left sides of the patient with less or no electrodes and acoustic sensors proximate the right side (including posterior and anterior regions of the right side).

[52] The computing apparatus 140 may record and analyze the torso-surface potential signals sensed by electrodes 112 and the acoustic sensors 120 and amplified/conditioned by the interface/amplifier circuitry 116. The computing apparatus 140 may be configured to analyze the electrical signals from the electrodes 112 to provide electrocardiogram (ECG) signals, information, or data from the patient's heart as will be further described herein. The computing

apparatus 140 may be configured to analyze the electrical signals from the acoustic sensors 120 to provide sound signals, information, or data from the patient's body and/or devices implanted therein (such as the LVAD 150) as will be further described herein.

[53] Additionally, the computing apparatus 140 and the remote computing device 160 may be configured to provide graphical user interfaces 132, 172 depicting the ECGs including QRS complexes obtained using the electrode apparatus 110 and depicting the sound data including sound waves obtained using the acoustic sensors 120 as well as other information related thereto. Exemplary systems and methods may noninvasively use the electrical information collected using the electrode apparatus 110 and the sound information collected using the acoustic sensors 120 to evaluate a patient's cardiac health, evaluate and configure cardiac therapy being delivered to the patient, and evaluate the mechanical functionality of implanted devices such as the LVAD 150.

[54] Further, the electrode apparatus 110 may further include reference electrodes and/or drive electrodes to be, e.g. positioned about the lower torso of the patient 14, that may be further used by the system 100. For example, the electrode apparatus 110 may include three reference electrodes, and the signals from the three reference electrodes may be combined to provide a reference signal. Further, the electrode apparatus 110 may use of three caudal reference electrodes (e.g., instead of standard references used in Wilson Central Terminal) to get a "true" unipolar signal with lesser noise from averaging three caudally located reference signals.

[55] FIG. 3 illustrates another exemplary electrode apparatus 110 that includes a plurality of electrodes 112 configured to surround the heart of the patient 14 and record, or monitor, the electrical signals associated with the depolarization and repolarization of the heart after the signals have propagated through the torso of the patient 14 and a plurality of acoustic sensors 120 configured to surround the heart of the patient 14 and record, or monitor, the sound signals associated with

the heart and/or an implanted device such as the LVAD 150 after the signals have propagated through the torso of the patient 14. The electrode apparatus 110 may include a vest 114 upon which the plurality of electrodes 112 and the plurality of acoustic sensors 120 may be attached, or to which the electrodes 112 and the acoustic sensors 120 may be coupled. In at least one embodiment, the plurality, or array, of electrodes 112 may be used to collect electrical information such as, e.g., surrogate electrical activation times. Similar to the electrode apparatus 110 of FIG. 2, the electrode apparatus 110 of FIG. 3 may include interface/amplifier circuitry 116 electrically coupled to each of the electrodes 112 and the acoustic sensors 120 through a wired connection 118 and be configured to transmit signals from the electrodes 112 and the acoustic sensors 120 to computing apparatus 140. As illustrated, the electrodes 112 and the acoustic sensors 120 may be distributed over the torso of a patient 14, including, for example, the posterior, lateral, posterolateral, anterolateral, and anterior locations of the torso of a patient 14.

[56] The vest 114 may be formed of fabric with the electrodes 112 and the acoustic sensors 120 attached to the fabric. The vest 114 may be configured to maintain the position and spacing of electrodes 112 and the acoustic sensors 120 on the torso of the patient 14. Further, the vest 114 may be marked to assist in determining the location of the electrodes 112 and the acoustic sensors 120 on the surface of the torso of the patient 14. In some examples, there may be about 25 to about 256 electrodes 112 and about 25 to about 256 acoustic sensors 120 distributed around the torso of the patient 14, though other configurations may have more or fewer electrodes 112 and more or fewer acoustic sensors 120.

[57] The exemplary systems and methods may be used to provide noninvasive assistance to a user in the evaluation of a patient's cardiac health and/or evaluation and configuration of cardiac therapy being presently-delivered to the patient (e.g., by a LVAD, by an implantable medical device, etc.). For example, the exemplary systems and methods may be used to assist a user in the configuration and/or adjustment of one or more cardiac therapy settings for left ventricular assist cardiac therapy being delivered to a patient by the LVAD 150. Further, for

example, the exemplary systems and methods may provide optimization of the A-V interval, or delay, of pacing therapy (e.g., left univentricular pacing therapy). Still further, for example, the exemplary systems and methods may be used to assist a user in the configuration and/or adjustment of one or more cardiac therapy settings for both LVAD-delivered cardiac therapy and pacing therapy using, e.g., an implantable medical device.

[58] Further, it is to be understood that the computing apparatus 140, the remote computing device 160, and the LVAD controller 152 may be operatively coupled to each other in a plurality of different ways so as to perform, or execute, the functionality described herein. For example, in the embodiment depicted, the computing device 140 may be wireless operably coupled to the remote computing device 160 and the LVAD controller 152 as depicted by the wireless signal lines emanating therebetween. Further, for example, in the embodiment depicted, the remote computing device 160 may be wireless operably coupled to the computing apparatus 140 and the LVAD controller 152 as depicted by the wireless signal lines emanating therebetween. Further, for example, as opposed to wireless connections, one or more of the computing apparatus 140, the remote computing device 160, and the LVAD controller 152 may be operably coupled through one or wired electrical connections.

[59] An exemplary method 200 of determining an LVAD output parameter is depicted in FIG. 4 using, e.g., the systems and apparatus depicted in FIGS. 1-3 and 7-10. As shown, the method 200 includes monitoring electrical activity 202 of the patient using a plurality of external electrodes such as, e.g., the electrode apparatus 110 described herein with reference to FIG. 1-3. The electrical activity 202 may be monitored for a plurality of cardiac cycles or heartbeats. Further, the electrical activity 202 may be monitored for a selected period of time such as, e.g., five seconds. The electrical activity can be monitored 202 by a plurality of electrodes in the absence of LVAD therapy or during LVAD therapy.

[60] The method 200 may further include generating electrical heterogeneity information 204 from the monitored electrical activity 202. The electrical heterogeneity information can be generated using metrics of electrical heterogeneity. The metrics of electrical heterogeneity information can include a metric of right ventricular activation time (RVAT) of electrodes on the right side of the torso of the patient. A metric of RVAT may be determined from electrodes on both the anterior and posterior surfaces. Further, the RVAT may be mean, median, or another statistical composite value based on, or computed from, the electrical signals from a right set of electrodes on the right side of the torso of the patient (e.g., right torso of the patient). Also, the metrics of electrical heterogeneity information can include septal electrical heterogeneity information indicative of septal dyssynchrony generated using electrical activity monitored by a central set of external electrodes of the plurality of external electrodes positioned proximate the sternum or spine of the patient. More specifically, septal dyssynchrony may be ascertained by looking at a subset of electrodes near the sternum and spine, and septal timing relative to right-sided activation (or left-sided activation) may be helpful for titrating LVAD pump speed to avoid suction, right ventricular failure, etc.

[61] Further, the metrics of electrical heterogeneity can include a metric of standard deviation of activation times (SDAT) of electrodes on a left side of a torso of the patient and/or a metric of mean left ventricular activation time (LVAT) of electrodes on the left side of the torso of the patient. A metric of LVAT may be determined from electrodes on both the anterior and posterior surfaces. The metrics of electrical heterogeneity can include a metric of mean total activation time (mTAT) taken from a plurality of electrode signals from both sides of the torso of the patient, or it may include other metrics (e.g., standard deviation, interquartile deviations, a difference between a latest activation time and earliest activation time) reflecting a range or dispersion of activation times on a plurality of electrodes located on the right side of the patient torso or left side of the patient torso, or combining both right and left sides of the patient torso.

- [62] Additionally, spatial repolarization indices may also be used to titration-opportunity for good diastole or uniformity, and further may be useful to minimize RV activation time (measure by activation time from the right-side thorax electrodes). Further, it may be described that right ventricular or left ventricular remodeling may be monitored using the systems and methods described herein by, e.g., measures of right ventricular and left ventricular activation times and patterns.
- [63] As described herein, electrical activity can be monitored 202 by a plurality of electrodes in the absence of LVAD therapy or during LVAD therapy. If the electrical activity is monitored 202 in the absence of LVAD therapy, the electrical heterogeneity information generated 204 therefrom may be representative of a baseline cardiac health value. If the electrical activity is monitored 202 during LVAD therapy, the electrical heterogeneity information generated 204 therefrom may be representative of a cardiac health value during the delivery of the LVAD therapy at one or more LVAD output parameters, which may be configurable, or adjustable, using the exemplary systems, apparatus, devices, and methods described herein.
- [64] The exemplary method 200 may further include determining an LVAD output parameter 206 based on the generated electrical heterogeneity information 204. For example, to determine an LVAD output parameter 206, the septal central electrical heterogeneity information may be compared to other electrical heterogeneity information generated from a set of external electrodes to the right or left of the sternum or spine of the patient. Specifically, if the septal central electrical heterogeneity information when compared to other electrical heterogeneity information from a set of external electrodes to the right or left of the sternum or spine of the patient indicates that electrical activation of the ventricles is leading to mechanical pulsatile activity that is being superseded by LVAD flow rates, then an LVAD output parameter such as, e.g., pump speed, RPM automaticity adaptation algorithms, or parameters to control periodic speed modulation, may be reduced or tailored.

[65] Further, for example, determining an LVAD output parameter 206 may include comparing the present, or current, generated electrical heterogeneity information 204 to the previously generated electrical heterogeneity information 204 when in the absence of LVAD therapy or using previous one or more LVAD output parameters. In this way, if the generated electrical heterogeneity information 204 indicates improvement in the electrical and/or mechanical cardiac functionality of the patient's heart, the exemplary method 200 may determine that the present one or more LVAD output parameters 206 are more effective than the absence of LVAD therapy or the previous one or more LVAD output parameters.

[66] In this way, the one or more LVAD output parameters may be titrated, or adjusted, 210 based on the generated electrical heterogeneity information 204 until optimal LVAD output parameters are found. For example, after determining one or more LVAD output parameters 206, the exemplary method 200 may adjust the LVAD based on, or using, the determined one or more LVAD output parameters 210 (e.g., a user may do so manually or the system may automatically perform the adjustment), and then the method 200 may loop to again monitor electrical activity during delivery of LVAD therapy 202, generate electrical heterogeneity information based on the monitored electrical activity 204, and determine LVAD output parameters based thereon. In other words, the exemplary method 200 may "try out" a plurality of different LVAD output parameters until determining which of the plurality of different LVAD output parameters are appropriate, acceptable, and/or optimal based on the generated electrical heterogeneity information. In one or more embodiments, it may be described that the method 200 provides feedback on speed control to avoid right ventricular dyssynchrony or other factors that may lead to right ventricular failures (right ventricle to left ventricular dyssynchrony).

[67] As described herein, the LVAD output parameters may include at least one of LVAD pump speed, LVAD pump throughput, LVAD pump power, LVAD pump current, LVAD pump voltage, pump inflow gimbal angle, automatic algorithmic responses to events such as pump suction, patient activity level changes, and physiologic parameter inputs, enabling/disabling periodic pump

speed modulation features such as the Lavare cycle, etc. In at least one embodiment, the method 200 may be described as adjusting LVAD pump speed based on the feedback of electrical heterogeneity information generated from the monitored electrical activity of the patient using a plurality of external electrodes. The electrical activity may be monitored during a plurality of different LVAD pump speeds, and electrical heterogeneity information may be generated for each set of electrical activity monitored during a plurality of different LVAD pump speeds. Thus, electrical heterogeneity information may be associated with each of the plurality of different LVAD pump speeds. The LVAD pump speed associated with, or having, optimal or acceptable electrical heterogeneity information may be determined as the LVAD pump speed to be used with the patient. In one embodiment, the LVAD pump speed having the best electrical heterogeneity information (e.g., lowest amount of dyssynchrony, lowest amount of right ventricular dyssynchrony, etc.) may be selected).

[68] Further, other factors may also distinguish one LVAD output parameter from another such as, e.g., settings to promote native heart recovery, such as flow rates selected to preserve native function or periodic adjustments down in RPM to shift more cardiac work to the native heart and to test for recovery which may allow, or enable, withdrawal of support of the LVAD. In other words, although one LVAD output parameter may provide the best, or most optimal, electrical heterogeneity information, a different LVAD output parameter may be determined, or selected, because the electrical information can support appropriate settings to encourage and accelerate native heart recovery which may lead to cessation of LVAD support and pump withdrawal without creating acute support deficit.

[69] Additionally, whenever LVAD output parameters are determined 206, the determined LVAD output parameters may be displayed 208 on a graphical user interface of a computing apparatus or device such as those shown and described with respect to FIGS. 1-3. A user may see the determined LVAD output parameters, and then may manually adjust the LVAD using a LVAD controller

according to the determined LVAD output parameters. In other embodiments, the LVAD output parameters may be automatically adjusted using the systems and methods described herein. In other words, feedback on the LVAD may be automated for “one-button” speed titration.

[70] The use of a LVAD may affect the volume of one or more heart chambers and may also affect the stretching of cardiac tissue. Further, the conduction of the cardiac tissue may further be affected from the volume changes and cardiac tissue stretching. Still further, activation patterns may also be impacted by changes in cardiac shape, not only dyssynchrony. Thus, the LVAD may affect pacing therapy that may be also delivered, or applied, to the patient.

[71] A LVAD may also be used in conjunction with cardiac pacing therapy, and as such, the LVAD and the cardiac pacing therapy may be adjusted, or titrated, at the same time to provide acceptable or optimal cardiac therapy to a patient. An exemplary method 250 of adjusting one or both of a LVAD output parameter and a pacing parameter is depicted in FIG. 5 using, e.g., the systems and apparatus depicted in FIGS. 1-3 and 7-10. As shown, the exemplary method 250 may include providing LVAD therapy 252, e.g., using the LVAD apparatus 151 described herein with respect to FIGS. 1 and 8 and providing pacing therapy 254, e.g., using the systems and apparatus described herein with respect to FIGS. 7-10. The LVAD therapy 252 may include a plurality of different output parameters that may be adjustable by the exemplary systems described herein and/or a user using the exemplary systems. Likewise, the pacing therapy 254 may include a plurality of different pacing parameters that may be adjustable by the exemplary systems described herein and/or a user using the exemplary systems. The plurality of different pacing parameters may include A-V interval, V-V interval, pacing pulse width, pacing vector, multipoint pacing vector, pacing voltage, pacing configuration (e.g., biventricular pacing, left ventricle only pacing, right ventricle only pacing), pacing rate, pacing rate response parameters, etc.

[72] Similar to method 200, the exemplary method 250 may include monitoring electrical activity 256 of the patient using a plurality of external electrodes such as, e.g., the electrode apparatus 110 described herein with reference to FIG. 1-3. The electrical activity 256 may be monitored for a plurality of cardiac cycles or heartbeats. Further, the electrical activity 256 may be monitored for a selected period of time such as, e.g., five seconds. The electrical activity can be monitored 256 in the absence of LVAD therapy, in the absence of cardiac pacing therapy, in the absence of both LVAD therapy and cardiac pacing therapy, during LVAD therapy, during cardiac pacing therapy, and during both LVAD therapy and cardiac pacing therapy. Also, similar to method 200, the method 250 may further include generating electrical heterogeneity information 258 from the monitored electrical activity 256. The generated electrical heterogeneity information 258 may then be used to adjust 260 one or both of the LVAD output parameters of the provided LVAD therapy 252 and the cardiac pacing therapy parameters of the provided cardiac pacing therapy 254.

[73] For instance, the exemplary method 250 may try one of a plurality of different combinations of LVAD output parameters and cardiac pacing parameters, and may generate electrical heterogeneity information 258 from the electrical activity monitored during the use of the “tried” combination of LVAD output parameters and cardiac pacing parameters. The generated electrical heterogeneity information may be compared to baseline electrical heterogeneity information or electrical heterogeneity information generated during the use of a different combination of LVAD output parameters and cardiac pacing parameters to determine whether the present, or current, combination of LVAD output parameters and cardiac pacing parameters results in acceptable or optimal therapy for the patient.

[74] More specifically, for example, the speed of the LVAD pump may be configured in a plurality of different pump speeds, and for each pump speed, the right ventricular preexcitation of the cardiac pacing therapy may be adjusted to a plurality of different right ventricular preexcitations. More specifically, right

ventricular (RV) preexcitation may be compared to left ventricular timing to minimize septal motion and may be adjusted by the timing of the A-V or V-V interval. In another embodiment, one or more device settings, which includes a combination of different device parameters described previously, may be adjusted to provide an optimal synchronized (e.g., most synchronized) right ventricular activation (e.g., measured by lowest RVAT or other metrics of right sided electrical heterogeneity) without impeding the LVAD operation (e.g., without causing suction at an operating LVAD speed). Thus, the LVAD and/or RV preexcitation may be programmed to optimize the contribution of the right ventricle. Electrical heterogeneity information may be generated for each different combination of LVAD pump speed and right ventricular preexcitation such that the LVAD pump speed and right ventricular preexcitation that results in acceptable (e.g., optimal) electrical heterogeneity information may be determined. The determined LVAD pump speed and right ventricular preexcitation may then be, e.g., displayed on a graphical user interface such that a practitioner may see the result and/or automatically used to program the LVAD and the cardiac pacing apparatus. Further, for example, LVAD responsive algorithms (such, e.g., a suction response or rate adaptation), periodic speed modulation, and/or operating mode features (such as the Lavare cycle) may be exercised to test acute impact on electrical activation patterns, which may occur during ambulatory operation.

[75] LVAD output parameters may also be adjusted using cardiac sound information such as, e.g., capturing using the acoustics sensors 120 as described herein with respect to the FIGS. 1-3. An exemplary method 270 of adjusting a LVAD based on one or both of electrical heterogeneity information and cardiac sounds is depicted in FIG. 6 using, e.g., the systems and apparatus depicted in FIGS. 1-3 and 7-10. Similar to method 250, the exemplary method 270 may include providing LVAD therapy 272, e.g., using the LVAD apparatus 151 described herein with respect to FIGS. 1 and 8. Although not depicted in FIG. 6, it is to be understood that the method 270 may also include providing pacing therapy, e.g., using the systems and apparatus described herein with respect to FIGS. 7-10, and adjust the pacing therapy using the same or similar methodology

and processes as method 270. Additionally, the LVAD cardiac therapy adjusted, or titrated, in the method 270 may be adjusted, or titrated, in conjunction with, or at the same time as, the cardiac pacing therapy based on one or both of the electrical heterogeneity information and cardiac sound information.

[76] Similar to method 200, the exemplary method 270 may include monitoring electrical activity 274 of the patient using a plurality of external electrodes such as, e.g., the electrode apparatus 110 described herein with reference to FIG. 1-3. The electrical activity 274 may be monitored for a plurality of cardiac cycles or heartbeats. Further, the electrical activity 274 may be monitored for a selected period of time such as, e.g., five seconds. The electrical activity can be monitored 274 in the absence of LVAD therapy or during LVAD therapy. Also, similar to method 200, the method 270 may further include generating electrical heterogeneity information 278 from the monitored electrical activity 274. The generated electrical heterogeneity information 288 may then be used to adjust 280 the LVAD output parameters of the provided LVAD therapy 280.

[77] The LVAD output parameters may also be adjusted 280 in view of, or based on, the cardiac sound information. For instance, the exemplary method 270 may further include monitoring cardiac sounds using acoustic sensors 276. The cardiac sounds may be monitored using a plurality of different types of apparatus and systems. In at least one embodiment, the cardiac sounds may be monitored using, e.g., the external acoustic sensors 120 described herein with respect to FIGS. 1-3. In other embodiments, the cardiac sounds may be monitored using one or more implantable devices or other sound monitoring devices that are not associated with (e.g., coupled to, part of, etc.) the electrode apparatus 110. Still, in other embodiments, the cardiac sounds may be measured, or monitored, using sound capture apparatus that is not contact with patient tissue (e.g., not in contact with the patient's skin, not attached to, not coupled to, or in proximity with cardiac tissue, etc.).

- [78]** The cardiac sound monitoring 276 may result in electrical signals representative of cardiac sounds from a plurality of different locations about the patient. Such cardiac sounds may be useful in determining one or both of LVAD output parameters and cardiac pacing parameters. The cardiac sounds may be useful in determine mechanical cardiac functionality (e.g., forces, timings, movement, etc.) such as, but not limited to, heart valves opening, heart valves closing, heart chambers contracting (e.g., during depolarization), heart chambers relaxing (e.g., during repolarization), valvular regurgitation, progression of right or left hear failure, arrhythmias such as atrial fibrillation or ventricular tachyarrhythmia/fibrillation, etc.
- [79]** The exemplary method 270 may further include adjusting one or more LVAD output parameters 280 based on one or both of the generated electrical heterogeneity information 278 and the monitored cardiac sounds 276. For example, the LVAD pump speed may be increased if the cardiac sounds indicate aortic valve opening and the electrical heterogeneity information indicates right ventricular activation in advance of hemodynamic emptying of the left ventricle. Further, for example, the LVAD pump speed may be changed if there is evidence of abnormal heart sounds, which may indicate progression of left or right heart failure. For instance, a right ventricular 3rd heart sound may be indicative of right ventricular dysfunction and LVAD speed may be titrated lower and/or pacing parameters may be adjusted to reduce electrical heterogeneity.
- [80]** In at least one embodiment, the exemplary method 200 may include determining whether at least one heart valve is open or closed based on the monitored cardiac sounds, and then adjusting the output parameter for the LVAD to allow at least some opening of the heart valves. More specifically, signatures of a second heart sound on the acoustic signal may be analyzed to detect the transition of the aortic valve from opening to closing, and changes in this second heart sound signature can be monitored for varying LVAD speeds to detect speeds at which the valve does not open. For instance, a threshold of programmable

LVAD speed may be set to a maximum speed that still allows the aortic valve to open.

[81] The exemplary method 270 may adjust the LVAD, and then the method 270 may loop to again monitor electrical activity and cardiac sounds during delivery of LVAD therapy 274, 276, generate electrical heterogeneity information based on the monitored electrical activity 278, and further determine and adjusted LVAD output parameters 280 based thereon.

[82] the exemplary systems, apparatus, and methods described herein may also be useful in titrating, or adjusting, medications, which may be used with the LVAD and pacing therapies described herein. For example, certain medications may impact cardiac activation, and thus, the exemplary systems, apparatus, and methods may be used to titrate, or adjust, the LVAD, cardiac pacing therapy, and medications at the same, or similar, time for patients with, e.g., heart failure with a preserved ejection fraction, heart failure with a reduced ejection fraction, etc.

[83] further, the exemplary systems, apparatus, and methods described herein may also be useful titration, or adjustment of left atrium versus right atrium pacing in patients with atrial dyssynchrony.

[84] Also, the exemplary systems, apparatus, and methods described herein may also be useful in measuring, or monitoring, recovery of patients to, e.g., assist in assessing whether a LVAD may be removed from patients. In other words, the exemplary systems, apparatus, and methods may assist in determining whether LVAD cardiac therapy is still needed for patients.

[85] As described herein, the exemplary systems and methods described herein may be used with respect to the implantation and configuration of an implantable medical device (IMD) and/or a LVAD. For example, the exemplary systems and methods may be used in conjunction with an exemplary therapy system 10 described herein with reference to FIGS. 7-10.

[86] FIG. 7 is a conceptual diagram illustrating an exemplary therapy system 10 that may be used to deliver pacing therapy to a patient 14. Patient 14 may, but not necessarily, be a human. The therapy system 10 may include an implantable medical device 16 (IMD), which may be coupled to leads 18, 20, 22. The IMD 16 may be, e.g., an implantable pacemaker, cardioverter, and/or defibrillator, that delivers, or provides, electrical signals to and/or measures, or monitors electrical signals from the heart 12 of the patient 14 via electrodes coupled to one or more of the leads 18, 20, 22.

[87] The leads 18, 20, 22 extend into the heart 12 of the patient 14 to sense electrical activity of the heart 12 and/or to deliver electrical stimulation to the heart 12. In the example shown in FIG. 11, the right ventricular (RV) lead 18 extends through one or more veins (not shown), the superior vena cava (not shown), and the right atrium 26, and into the right ventricle 28. The left ventricular (LV) coronary sinus lead 20 extends through one or more veins, the vena cava, the right atrium 26, and into the coronary sinus 30 to a region adjacent to the free wall of the left ventricle 32 of the heart 12. The right atrial (RA) lead 22 extends through one or more veins and the vena cava, and into the right atrium 26 of the heart 12. Although the system 10 includes a RV lead 18, it is to be understood the exemplary systems and methods described herein may not utilize the electrodes located on the RV lead 18 for sensing and/or pacing. Further, it is to be understood that the system 10 is merely one example, and that the exemplary systems and methods described herein may utilize systems that do not include a RV lead 18 (e.g., for sensing and/or pacing).

[88] The IMD 16 may sense, among other things, electrical signals attendant to the depolarization and repolarization of the heart 12 via electrodes coupled to at least one of the leads 18, 20, 22. In some examples, the IMD 16 provides pacing therapy (e.g., pacing pulses) to the heart 12 based on the electrical signals sensed within the heart 12. The IMD 16 may be operable to adjust one or more parameters associated with the pacing therapy such as, e.g., A-V delay and other various timings, pulse width, amplitude, voltage, burst length, etc. Further, the

IMD 16 may be operable to use various electrode configurations to deliver pacing therapy, which may be unipolar, bipolar, quadripolar, or further multipolar. For example, a multipolar lead may include several electrodes that can be used for delivering pacing therapy. Hence, a multipolar lead system may provide, or offer, multiple electrical vectors to pace from. A pacing vector may include at least one cathode, which may be at least one electrode located on at least one lead, and at least one anode, which may be at least one electrode located on at least one lead (e.g., the same lead, or a different lead) and/or on the casing, or can, of the IMD. While improvement in cardiac function as a result of the pacing therapy may primarily depend on the cathode, the electrical parameters like impedance, pacing threshold voltage, current drain, longevity, etc. may be more dependent on the pacing vector, which includes both the cathode and the anode. The IMD 16 may also provide defibrillation therapy and/or cardioversion therapy via electrodes located on at least one of the leads 18, 20, 22. Further, the IMD 16 may detect arrhythmia of the heart 12, such as fibrillation of the ventricles 28, 32, and deliver defibrillation therapy to the heart 12 in the form of electrical pulses. In some examples, IMD 16 may be programmed to deliver a progression of therapies, e.g., pulses with increasing energy levels, until a fibrillation of heart 12 is stopped.

[89] FIG. 8 is a partially cut-away view of a patient's heart coupled to a IMD 16 via cardiac leads and additionally coupled to an exemplary LVAD 150. The LVAD 150 includes an inflow conduit 173 that is surgically inserted into the apical area of the LV such that the blood volume normally filling the LV is at least partially unloaded into a central pumping chamber 176 of LVAD 150. Upon actuation, the pumping chamber 176 ejects blood through outflow conduit 174 which is coupled to the arterial system, typically to the ascending or descending aorta. Inflow and outflow conduits 173 and 174 may include valves in order to control the direction of blood flow into and out of LVAD 150. Actuation of LVAD 150 may be pneumatic, hydraulic, electromagnetic, or by other means known in the art. The LVAD controller, or control and power unit, 152 may provide the power used for actuating LVAD 150. The controller 152 may additionally be configured to control, or execute, the actuation of LVAD 150 in

relation to time, pressure, flow rate, or other operating factors. The controller (e.g., control and power unit) 152 may be incorporated with LVAD 150 in a fully implantable system, or the controller 152 may be located external to the patient's body with any necessary connections for actuating LVAD 150 provided transcutaneously.

[90] In the embodiment shown in FIG. 9, a pressure transducer 168 is positioned in the left ventricle transmyocardially. Pressure transducer 168 is carried by a lead 166 coupled to the IMD 16 via a connector. During placement of an LVAD, exposure of the LV may allow an opportunity for placing a pressure sensor directly in the LV. Alternatively, a sensor may be positioned in a cardiac vein, as described previously, or elsewhere for measuring a correlate of LVP.

[91] Other similarly labeled components in FIG. 8 correspond to those in FIGS. 7 and 9-10. The IMD 14 in this embodiment may be described as receiving EGM and RVP signals from the lead 18 and LVP signals from the lead 166. RVP and LVP signals may be stored and processed in the IMD 16 for detecting a metric of ventricular synchronization. The IMD 16 as well as the computing apparatus 140 and the remote computing device 160 of FIG. 1 may be in telemetric communication with LVAD controller 150 such that LVAD operating parameters may be adjusted according to commands received from the IMD 16, the computing apparatus 140, and the remote computing device 160. Further, the LVAD controller 152 may receive pressure-related data transmitted from the IMD 16 and may process such data for determining a metric of ventricular synchronization and adjusting LVAD actuation time based on that metric.

[92] FIGS. 9A-9B are conceptual diagrams illustrating the IMD 16 and the leads 18, 20, 22 of therapy system 10 of FIG. 7 in more detail. The leads 18, 20, 22 may be electrically coupled to a therapy delivery module (e.g., for delivery of pacing therapy), a sensing module (e.g., for sensing one or more signals from one or more electrodes), and/or any other modules of the IMD 16 via a connector block 34. In some examples, the proximal ends of the leads 18, 20, 22 may include electrical

contacts that electrically couple to respective electrical contacts within the connector block 34 of the IMD 16. In addition, in some examples, the leads 18, 20, 22 may be mechanically coupled to the connector block 34 with the aid of set screws, connection pins, or another suitable mechanical coupling mechanism.

[93] Each of the leads 18, 20, 22 includes an elongated insulative lead body, which may carry a number of conductors (e.g., concentric coiled conductors, straight conductors, etc.) separated from one another by insulation (e.g., tubular insulative sheaths). In the illustrated example, bipolar electrodes 40, 42 are located proximate to a distal end of the lead 18. In addition, bipolar electrodes 44, 45, 46, 47 are located proximate to a distal end of the lead 20 and bipolar electrodes 48, 50 are located proximate to a distal end of the lead 22.

[94] The electrodes 40, 44, 45, 46, 47, 48 may take the form of ring electrodes, and the electrodes 42, 50 may take the form of extendable helix tip electrodes mounted retractably within the insulative electrode heads 52, 54, 56, respectively. Each of the electrodes 40, 42, 44, 45, 46, 47, 48, 50 may be electrically coupled to a respective one of the conductors (e.g., coiled and/or straight) within the lead body of its associated lead 18, 20, 22, and thereby coupled to a respective one of the electrical contacts on the proximal end of the leads 18, 20, 22.

[95] Additionally, electrodes 44, 45, 46 and 47 may have an electrode surface area of about 5.3 mm² to about 5.8 mm². Electrodes 44, 45, 46, and 47 may also be referred to as LV1, LV2, LV3, and LV4, respectively. The LV electrodes (i.e., left ventricle electrode 1 (LV1) 44, left ventricle electrode 2 (LV2) 45, left ventricle electrode 3 (LV3) 46, and left ventricle 4 (LV4) 47 etc.) on the lead 20 can be spaced apart at variable distances. For example, electrode 44 may be a distance of, e.g., about 21 millimeters (mm), away from electrode 45, electrodes 45 and 46 may be spaced a distance of, e.g., about 1.3mm to about 1.5 mm, away from each other, and electrodes 46 and 47 may be spaced a distance of, e.g. 20 mm to about 21 mm, away from each other.

[96] The electrodes 40, 42, 44, 45, 46, 47, 48, 50 may further be used to sense electrical signals (e.g., morphological waveforms within electrograms (EGM)) attendant to the depolarization and repolarization of the heart 12. The sensed electrical signals may be used to adjust one or more pacing parameters such as, e.g., A-V interval, V-V interval, etc. to provide optimal and/or effective cardiac functionality. The electrical signals are conducted to the IMD 16 via the respective leads 18, 20, 22. In some examples, the IMD 16 may also deliver pacing pulses via the electrodes 40, 42, 44, 45, 46, 47, 48, 50 to cause depolarization of cardiac tissue of the patient's heart 12. In some examples, as illustrated in FIG. 9A, the IMD 16 includes one or more housing electrodes, such as housing electrode 58, which may be formed integrally with an outer surface of a housing 60 (e.g., hermetically-sealed housing) of the IMD 16 or otherwise coupled to the housing 60. Any of the electrodes 40, 42, 44, 45, 46, 47, 48, 50 may be used for unipolar sensing or pacing in combination with the housing electrode 58. In other words, any of electrodes 40, 42, 44, 45, 46, 47, 48, 50, 58 may be used in combination to form a sensing vector, e.g., a sensing vector that may be used to evaluate and/or analyze the effectiveness of pacing therapy. It is to be understood by those skilled in the art that other electrodes can also be selected to define, or be used for, pacing and sensing vectors. Further, any of electrodes 40, 42, 44, 45, 46, 47, 48, 50, 58, when not being used to deliver pacing therapy, may be used to sense electrical activity during pacing therapy.

[97] As described in further detail with reference to FIG. 9A, the housing 60 may enclose a therapy delivery module that may include a stimulation generator for generating cardiac pacing pulses and defibrillation or cardioversion shocks, as well as a sensing module for monitoring electrical signals of the patient's heart (e.g., the patient's heart rhythm). The leads 18, 20, 22 may also include elongated electrodes 62, 64, 66, respectively, which may take the form of a coil. The IMD 16 may deliver defibrillation shocks to the heart 12 via any combination of the elongated electrodes 62, 64, 66 and the housing electrode 58. The electrodes 58, 62, 64, 66 may also be used to deliver cardioversion pulses to the heart 12. Further, the electrodes 62, 64, 66 may be fabricated from any suitable electrically

conductive material, such as, but not limited to, platinum, platinum alloy, and/or other materials known to be usable in implantable defibrillation electrodes. Since electrodes 62, 64, 66 are not generally configured to deliver pacing therapy, any of electrodes 62, 64, 66 may be used to sense electrical activity (e.g., for use in determining electrode effectiveness, for use in analyzing pacing therapy effectiveness, etc.) and may be used in combination with any of electrodes 40, 42, 44, 45, 46, 47, 48, 50, 58. In at least one embodiment, the RV elongated electrode 62 may be used to sense electrical activity of a patient's heart during the delivery of pacing therapy (e.g., in combination with the housing electrode 58, or defibrillation electrode-to-housing electrode vector).

[98] The configuration of the exemplary therapy systems 10 illustrated in FIGS. 7-10 are merely a couple of examples. In other examples, the therapy system may include epicardial leads and/or patch electrodes instead of or in addition to the transvenous leads 18, 20, 22 illustrated in FIG. 9A. Additionally, in other examples, the therapy system 10 may be implanted in/around the cardiac space without transvenous leads (e.g., leadless/wireless pacing systems) or with leads implanted (e.g., implanted transvenously or using approaches) into the left chambers of the heart (in addition to or replacing the transvenous leads placed into the right chambers of the heart as illustrated in FIG. 9A). An exemplary leadless system may be described in U.S. Pat. App. Ser. No. 14/173,288 filed on February 5, 2014 and entitled “Systems and Methods for Leadless Cardiac Resynchronization Therapy,” which is incorporated herein by reference in its entirety. Further, in one or more embodiments, the IMD 16 need not be implanted within the patient 14. For example, the IMD 16 may deliver various cardiac therapies to the heart 12 via percutaneous leads that extend through the skin of the patient 14 to a variety of positions within or outside of the heart 12. In one or more embodiments, the system 10 may utilize wireless pacing (e.g., using energy transmission to the intracardiac pacing component(s) via ultrasound, inductive coupling, RF, etc.) and sensing cardiac activation using electrodes on the can/housing and/or on subcutaneous leads.

[99] In other examples of therapy systems that provide electrical stimulation therapy to the heart 12, such therapy systems may include any suitable number of leads coupled to the IMD 16, and each of the leads may extend to any location within or proximate to the heart 12. For example, other examples of therapy systems may include less than or more than three transvenous leads. In at least one embodiment, the therapy system that provides pacing, or electrical stimulation, therapy to the heart 12 may only provide left univentricular pacing therapy with using, or including, sensing or pacing electrodes located in the left ventricle. In these left univentricular pacing systems, at least one pacing and/or sensing electrode may be located in the patient's left ventricle and at least one pacing and/or sensing electrode may be located in one or both the right atrium and left atrium. Still further, other therapy systems may include a single lead that extends from the IMD 16 into the right atrium 26 or the right ventricle 28, or two leads that extend into a respective one of the right atrium 26 and the right ventricle 28.

[100] FIG. 10A is a functional block diagram of one exemplary configuration of the IMD 16. As shown, the IMD 16 may include a control module 81, a therapy delivery module 84 (e.g., which may include a stimulation generator), a sensing module 86, and a power source 90.

[101] The control module 81 may include a processor 80, memory 82, and a telemetry module 88. The memory 82 may include computer-readable instructions that, when executed, e.g., by the processor 80, cause the IMD 16 and/or the control module 81 to perform various functions attributed to the IMD 16 and/or the control module 81 described herein. Further, the memory 82 may include any volatile, non-volatile, magnetic, optical, and/or electrical media, such as a random-access memory (RAM), read-only memory (ROM), non-volatile RAM (NVRAM), electrically-erasable programmable ROM (EEPROM), flash memory, and/or any other digital media. An exemplary capture management module may be the left ventricular capture management (LVCM) module described in U.S. Pat. No. 7,684,863 entitled "LV THRESHOLD

MEASUREMENT AND CAPTURE MANAGEMENT" and issued March 23, 2010, which is incorporated herein by reference in its entirety.

[102] The processor 80 of the control module 81 may include any one or more of a microprocessor, a controller, a digital signal processor (DSP), an application specific integrated circuit (ASIC), a field-programmable gate array (FPGA), and/or equivalent discrete or integrated logic circuitry. In some examples, the processor 80 may include multiple components, such as any combination of one or more microprocessors, one or more controllers, one or more DSPs, one or more ASICs, and/or one or more FPGAs, as well as other discrete or integrated logic circuitry. The functions attributed to the processor 80 herein may be embodied as software, firmware, hardware, or any combination thereof.

[103] The control module 81 may control the therapy delivery module 84 to deliver therapy (e.g., electrical stimulation therapy such as pacing) to the heart 12 according to a selected one or more therapy programs, which may be stored in the memory 82. More, specifically, the control module 81 (e.g., the processor 80) may control various parameters of the electrical stimulus delivered by the therapy delivery module 84 such as, e.g., A-V delays, V-V delays, pacing pulses with the amplitudes, pulse widths, frequency, or electrode polarities, etc., which may be specified by one or more selected therapy programs (e.g., A-V and/or V-V delay adjustment programs, pacing therapy programs, pacing recovery programs, capture management programs, etc.). As shown, the therapy delivery module 84 is electrically coupled to electrodes 40, 42, 44, 45, 46, 47, 48, 50, 58, 62, 64, 66, e.g., via conductors of the respective lead 18, 20, 22, or, in the case of housing electrode 58, via an electrical conductor disposed within housing 60 of IMD 16. Therapy delivery module 84 may be configured to generate and deliver electrical stimulation therapy such as pacing therapy to the heart 12 using one or more of the electrodes 40, 42, 44, 45, 46, 47, 48, 50, 58, 62, 64, 66.

[104] For example, therapy delivery module 84 may deliver pacing stimulus (e.g., pacing pulses) via ring electrodes 40, 44, 45, 46, 47, 48 coupled to leads 18, 20, 22

and/or helical tip electrodes 42, 50 of leads 18, 22. Further, for example, therapy delivery module 84 may deliver defibrillation shocks to heart 12 via at least two of electrodes 58, 62, 64, 66. In some examples, therapy delivery module 84 may be configured to deliver pacing, cardioversion, or defibrillation stimulation in the form of electrical pulses. In other examples, therapy delivery module 84 may be configured deliver one or more of these types of stimulation in the form of other signals, such as sine waves, square waves, and/or other substantially continuous time signals.

[105] The IMD 16 may further include a switch module 85 and the control module 81 (e.g., the processor 80) may use the switch module 85 to select, e.g., via a data/address bus, which of the available electrodes are used to deliver therapy such as pacing pulses for pacing therapy, or which of the available electrodes are used for sensing. The switch module 85 may include a switch array, switch matrix, multiplexer, or any other type of switching device suitable to selectively couple the sensing module 86 and/or the therapy delivery module 84 to one or more selected electrodes. More specifically, the therapy delivery module 84 may include a plurality of pacing output circuits. Each pacing output circuit of the plurality of pacing output circuits may be selectively coupled, e.g., using the switch module 85, to one or more of the electrodes 40, 42, 44, 45, 46, 47, 48, 50, 58, 62, 64, 66 (e.g., a pair of electrodes for delivery of therapy using a bipolar or multipolar pacing vector). In other words, each electrode can be selectively coupled to one of the pacing output circuits of the therapy delivery module using the switching module 85.

[106] The sensing module 86 is coupled (e.g., electrically coupled) to sensing apparatus, which may include, among additional sensing apparatus, the electrodes 40, 42, 44, 45, 46, 47, 48, 50, 58, 62, 64, 66 to monitor electrical activity of the heart 12, e.g., electrocardiogram (ECG)/electrogram (EGM) signals, etc. The ECG/EGM signals may be used to measure or monitor activation times (e.g., ventricular activation times, etc.), heart rate (HR), heart rate variability (HRV), heart rate turbulence (HRT), deceleration/acceleration capacity, deceleration

sequence incidence, T-wave alternans (TWA), P-wave to P-wave intervals (also referred to as the P-P intervals or A-A intervals), R-wave to R-wave intervals (also referred to as the R-R intervals or V-V intervals), P-wave to QRS complex intervals (also referred to as the P-R intervals, A-V intervals, or P-Q intervals), QRS-complex morphology, ST segment (i.e., the segment that connects the QRS complex and the T-wave), T-wave changes, QT intervals, electrical vectors, etc.

[107] The switch module 85 may also be used with the sensing module 86 to select which of the available electrodes are used, or enabled, to, e.g., sense electrical activity of the patient's heart (e.g., one or more electrical vectors of the patient's heart using any combination of the electrodes 40, 42, 44, 45, 46, 47, 48, 50, 58, 62, 64, 66). Likewise, the switch module 85 may also be used with the sensing module 86 to select which of the available electrodes are not to be used (e.g., disabled) to, e.g., sense electrical activity of the patient's heart (e.g., one or more electrical vectors of the patient's heart using any combination of the electrodes 40, 42, 44, 45, 46, 47, 48, 50, 58, 62, 64, 66), etc. In some examples, the control module 81 may select the electrodes that function as sensing electrodes via the switch module within the sensing module 86, e.g., by providing signals via a data/address bus.

[108] In some examples, sensing module 86 includes a channel that includes an amplifier with a relatively wider pass band than the R-wave or P-wave amplifiers. Signals from the selected sensing electrodes may be provided to a multiplexer, and thereafter converted to multi-bit digital signals by an analog-to-digital converter for storage in memory 82, e.g., as an electrogram (EGM). In some examples, the storage of such EGMs in memory 82 may be under the control of a direct memory access circuit.

[109] In some examples, the control module 81 may operate as an interrupt driven device, and may be responsive to interrupts from pacer timing and control module, where the interrupts may correspond to the occurrences of sensed P-waves and R-waves and the generation of cardiac pacing pulses. Any necessary mathematical

calculations may be performed by the processor 80 and any updating of the values or intervals controlled by the pacer timing and control module may take place following such interrupts. A portion of memory 82 may be configured as a plurality of recirculating buffers, capable of holding one or more series of measured intervals (e.g., intrinsic A-V conduction times), which may be analyzed by, e.g., the processor 80 in response to the occurrence of a pace or sense interrupt to determine whether the patient's heart 12 is presently exhibiting atrial or ventricular tachyarrhythmia.

[110] The pacer timing and control module may include programmable counters which control the basic time intervals associated with DDD, VVI, DVI, VDD, AAI, DDI, DDDR, VVIR, DVIR, VDDR, AAIR, DDIR and other modes of single and dual chamber pacing. In the aforementioned pacing modes, "D" may indicate dual chamber, "V" may indicate a ventricle, "I" may indicate inhibited pacing (e.g., no pacing), and "A" may indicate an atrium. The first letter in the pacing mode may indicate the chamber that is paced, the second letter may indicate the chamber in which an electrical signal is sensed, and the third letter may indicate the chamber in which the response to sensing is provided.

[111] The telemetry module 88 of the control module 81 may include any suitable hardware, firmware, software, or any combination thereof for communicating with another device, such as a programmer. For example, under the control of the processor 80, the telemetry module 88 may receive downlink telemetry from and send uplink telemetry to a programmer with the aid of an antenna, which may be internal and/or external. The processor 80 may provide the data to be uplinked to a programmer and the control signals for the telemetry circuit within the telemetry module 88, e.g., via an address/data bus. In some examples, the telemetry module 88 may provide received data to the processor 80 via a multiplexer.

[112] The various components of the IMD 16 are further coupled to a power source 90, which may include a rechargeable or non-rechargeable battery. A non-rechargeable battery may be selected to last for several years, while a rechargeable

battery may be inductively charged from an external device, e.g., on a daily or weekly basis.

[113] FIG. 10B is another embodiment of a functional block diagram for IMD 16. FIG. 10B depicts bipolar RA lead 22, bipolar RV lead 18, and bipolar LV CS lead 20 without the LA CS pace/sense electrodes and coupled with an implantable pulse generator (IPG) circuit 31 having programmable modes and parameters of a bi-ventricular DDD/R type known in the pacing art. In turn, the sensor signal processing circuit 91 indirectly couples to the timing circuit 43 and via data and control bus to microcomputer circuitry 33. The IPG circuit 31 is illustrated in a functional block diagram divided generally into a microcomputer circuit 33 and a pacing circuit 21. The pacing circuit 21 includes the digital controller/timer circuit 43, the output amplifiers circuit 51, the sense amplifiers circuit 55, the RF telemetry transceiver 41, the activity sensor circuit 35 as well as a number of other circuits and components described below.

[114] Crystal oscillator circuit 89 provides the basic timing clock for the pacing circuit 21 while battery 29 provides power. Power-on-reset circuit 87 responds to initial connection of the circuit to the battery for defining an initial operating condition and similarly, resets the operative state of the device in response to detection of a low battery condition. Reference mode circuit 37 generates stable voltage reference and currents for the analog circuits within the pacing circuit 21. Analog-to-digital converter (ADC) and multiplexer circuit 39 digitize analog signals and voltage to provide, e.g., real time telemetry of cardiac signals from sense amplifiers 55 for uplink transmission via RF transmitter and receiver circuit 41. Voltage reference and bias circuit 37, ADC and multiplexer 39, power-on-reset circuit 87, and crystal oscillator circuit 89 may correspond to any of those used in exemplary implantable cardiac pacemakers.

[115] If the IPG is programmed to a rate responsive mode, the signals output by one or more physiologic sensors are employed as a rate control parameter (RCP) to derive a physiologic escape interval. For example, the escape interval is

adjusted proportionally to the patient's activity level developed in the patient activity sensor (PAS) circuit 35 in the depicted, exemplary IPG circuit 31. The patient activity sensor 27 is coupled to the IPG housing and may take the form of a piezoelectric crystal transducer. An output signal of the patient activity sensor 27 may be processed and used as a RCP. Sensor 27 generates electrical signals in response to sensed physical activity that are processed by activity circuit 35 and provided to digital controller/timer circuit 43. Activity circuit 35 and associated sensor 27 may correspond to the circuitry disclosed in U.S. Pat. No. 5,052,388 entitled "METHOD AND APPARATUS FOR IMPLEMENTING ACTIVITY SENSING IN A PULSE GENERATOR" and issued on October 1, 1991 and U.S. Pat. No. 4,428,378 entitled "RATE ADAPTIVE PACER" and issued on January 31, 1984, each of which is incorporated herein by reference in its entirety. Similarly, the exemplary systems, apparatus, and methods described herein may be practiced in conjunction with alternate types of sensors such as oxygenation sensors, pressure sensors, pH sensors, and respiration sensors for use in providing rate responsive pacing capabilities. Alternately, QT time may be used as a rate indicating parameter, in which case no extra sensor is required. Similarly, the exemplary embodiments described herein may also be practiced in non-rate responsive pacemakers.

[116] Data transmission to and from the external programmer is accomplished by way of the telemetry antenna 57 and an associated RF transceiver 41, which serves both to demodulate received downlink telemetry and to transmit uplink telemetry. Uplink telemetry capabilities may include the ability to transmit stored digital information, e.g., operating modes and parameters, EGM histograms, and other events, as well as real time EGMs of atrial and/or ventricular electrical activity and marker channel pulses indicating the occurrence of sensed and paced depolarizations in the atrium and ventricle.

[117] Microcomputer 33 contains a microprocessor 80 and associated system clock and on-processor RAM and ROM chips 82A and 82B, respectively. In addition, microcomputer circuit 33 includes a separate RAM/ROM chip 82C to

provide additional memory capacity. Microprocessor 80 normally operates in a reduced power consumption mode and is interrupt driven. Microprocessor 80 is awakened in response to defined interrupt events, which may include A-TRIG, RV-TRIG, LV-TRIG signals generated by timers in digital timer/controller circuit 43 and A-EVENT, RV-EVENT, and LV-EVENT signals generated by sense amplifiers circuit 55, among others. The specific values of the intervals and delays timed out by digital controller/timer circuit 43 are controlled by the microcomputer circuit 33 by way of data and control bus from programmed-in parameter values and operating modes. In addition, if programmed to operate as a rate responsive pacemaker, a timed interrupt, e.g., every cycle or every two seconds, may be provided in order to allow the microprocessor to analyze the activity sensor data and update the basic A-A, V-A, or V-V escape interval, as applicable. In addition, the microprocessor 80 may also serve to define variable, operative A-V delay intervals and/or V-V intervals, and the energy delivered to the ventricles and/or atria.

[118] In one embodiment, microprocessor 80 is a custom microprocessor adapted to fetch and execute instructions stored in RAM/ROM unit 82 in a conventional manner. It is contemplated, however, that other implementations may be suitable to practice the present invention. For example, an off-the-shelf, commercially available microprocessor or microcontroller, or custom application-specific, hardwired logic, or state-machine type circuit may perform the functions of microprocessor 80.

[119] Digital controller/timer circuit 43 operates under the general control of the microcomputer 33 to control timing and other functions within the pacing circuit 321 and includes a set of timing and associated logic circuits of which certain ones pertinent to the present invention are depicted. The depicted timing circuits include URI/LRI timers 83A, V-V delay timer 83B, intrinsic interval timers 83C for timing elapsed V-EVENT to V-EVENT intervals or V-EVENT to A-EVENT intervals or the V-V conduction interval, escape interval timers 83D for timing A-A, V-A, and/or V-V pacing escape intervals, an A-V delay interval timer 83E for

timing the A-LVp delay (or A-RVp delay) from a preceding A-EVENT or A-TRIG, a post-ventricular timer 83F for timing post-ventricular time periods, and a date/time clock 83G.

[120] The A-V delay interval timer 83E is loaded with an appropriate delay interval for one ventricular chamber (e.g., either an A-RVp delay or an A-LVp delay) to time-out starting from a preceding A-PACE or A-EVENT. The interval timer 83E triggers pacing stimulus delivery, and can be based on one or more prior cardiac cycles (or from a data set empirically derived for a given patient).

[121] The post-event timer 83F times out the post-ventricular time period following an RV-EVENT or LV-EVENT or a RV-TRIG or LV-TRIG and post-atrial time periods following an A-EVENT or A-TRIG. The durations of the post-event time periods may also be selected as programmable parameters stored in the microcomputer 33. The post-ventricular time periods include the PVARP, a post-atrial ventricular blanking period (PAVBP), a ventricular blanking period (VBP), a post-ventricular atrial blanking period (PVARP) and a ventricular refractory period (VRP) although other periods can be suitably defined depending, at least in part, on the operative circuitry employed in the pacing engine. The post-atrial time periods include an atrial refractory period (ARP) during which an A-EVENT is ignored for the purpose of resetting any A-V delay, and an atrial blanking period (ABP) during which atrial sensing is disabled. It should be noted that the starting of the post-atrial time periods and the A-V delays can be commenced substantially simultaneously with the start or end of each A-EVENT or A-TRIG or, in the latter case, upon the end of the A-PACE which may follow the A-TRIG. Similarly, the starting of the post-ventricular time periods and the V-A escape interval can be commenced substantially simultaneously with the start or end of the V-EVENT or V-TRIG or, in the latter case, upon the end of the V-PACE which may follow the V-TRIG. The microprocessor 80 also optionally calculates A-V delays, V-V delays, post-ventricular time periods, and post-atrial time periods that vary with the sensor-based escape interval established in response to

the RCP(s), intrinsic A-V conduction times, intrinsic heart rate, and/or any other parameter or metric.

[122] The output amplifiers circuit 51 contains a RA pace pulse generator (and a LA pace pulse generator if LA pacing is provided), a RV pace pulse generator, a LV pace pulse generator, and/or any other pulse generator configured to provide atrial and ventricular pacing. In order to trigger generation of an RV-PACE or LV-PACE pulse, digital controller/timer circuit 43 generates the RV-TRIG signal at the time-out of the A-RVp delay (in the case of RV pre-excitation) or the LV-TRIG at the time-out of the A-LVp delay (in the case of LV pre-excitation) provided by AV delay interval timer 83E (or the V-V delay timer 83B). Similarly, digital controller/timer circuit 43 generates an RA-TRIG signal that triggers output of an RA-PACE pulse (or an LA-TRIG signal that triggers output of an LA-PACE pulse, if provided) at the end of the V-A escape interval timed by escape interval timers 83D.

[123] The output amplifiers circuit 51 includes switching circuits for coupling selected pace electrode pairs from among the lead conductors and the IND-CAN electrode 20 to the RA pace pulse generator (and LA pace pulse generator if provided), RV pace pulse generator and LV pace pulse generator. Pace/sense electrode pair selection and control circuit 53 selects lead conductors and associated pace electrode pairs to be coupled with the atrial and ventricular output amplifiers within output amplifiers circuit 51 for accomplishing RA, LA, RV, and LV pacing.

[124] The sense amplifiers circuit 55 contains sense amplifiers for atrial and ventricular pacing and sensing. High impedance P-wave and R-wave sense amplifiers may be used to amplify a voltage difference signal that is generated across the sense electrode pairs by the passage of cardiac depolarization wavefronts. The high impedance sense amplifiers use high gain to amplify the low amplitude signals and rely on pass band filters, time domain filtering and amplitude threshold comparison to discriminate a P-wave or R-wave from

background electrical noise. Digital controller/timer circuit 43 controls sensitivity settings of the atrial and ventricular sense amplifiers 55.

[125] The sense amplifiers may be uncoupled from the sense electrodes during the blanking periods before, during, and after delivery of a pace pulse to any of the pace electrodes of the pacing system to avoid saturation of the sense amplifiers. The sense amplifiers circuit 55 includes blanking circuits for uncoupling the selected pairs of the lead conductors and the IND-CAN electrode 20 from the inputs of the RA sense amplifier (and LA sense amplifier if provided), RV sense amplifier and LV sense amplifier during the ABP, PVABP and VBP. The sense amplifiers circuit 55 also includes switching circuits for coupling selected sense electrode lead conductors and the IND-CAN electrode 20 to the RA sense amplifier (and LA sense amplifier if provided), RV sense amplifier and LV sense amplifier. Again, sense electrode selection and control circuit 53 selects conductors and associated sense electrode pairs to be coupled with the atrial and ventricular sense amplifiers within the output amplifiers circuit 51 and sense amplifiers circuit 55 for accomplishing RA, LA, RV, and LV sensing along desired unipolar and bipolar sensing vectors.

[126] Right atrial depolarizations or P-waves in the RA-SENSE signal that are sensed by the RA sense amplifier result in a RA-EVENT signal that is communicated to the digital controller/timer circuit 43. Similarly, left atrial depolarizations or P-waves in the LA-SENSE signal that are sensed by the LA sense amplifier, if provided, result in a LA-EVENT signal that is communicated to the digital controller/timer circuit 43. Ventricular depolarizations or R-waves in the RV-SENSE signal are sensed by a ventricular sense amplifier result in an RV-EVENT signal that is communicated to the digital controller/timer circuit 43. Similarly, ventricular depolarizations or R-waves in the LV-SENSE signal are sensed by a ventricular sense amplifier result in an LV-EVENT signal that is communicated to the digital controller/timer circuit 43. The RV-EVENT, LV-EVENT, and RA-EVENT, LA-SENSE signals may be refractory or non-

refractory, and can inadvertently be triggered by electrical noise signals or aberrantly conducted depolarization waves rather than true R-waves or P-waves.

[127] The techniques described in this disclosure, including those attributed to the IMD 16, the computing apparatus 140, the remote computing device 160, and/or various constituent components, may be implemented, at least in part, in hardware, software, firmware, or any combination thereof. For example, various aspects of the techniques may be implemented within processing circuitry and/or one or more processors including one or more microprocessors, DSPs, ASICs, FPGAs, or any other equivalent integrated or discrete logic circuitry, as well as any combinations of such components, embodied in programmers, such as physician or patient programmers, stimulators, image processing devices, or other devices. The term "module," "processor," or "processing circuitry" may generally refer to any of the foregoing logic circuitry, alone or in combination with other logic circuitry, or any other equivalent circuitry.

[128] Such hardware, software, and/or firmware may be implemented within the same device or within separate devices to support the various operations and functions described in this disclosure. In addition, any of the described units, modules, or components may be implemented together or separately as discrete but interoperable logic devices. Depiction of different features as modules or units is intended to highlight different functional aspects and does not necessarily imply that such modules or units must be realized by separate hardware or software components. Rather, functionality associated with one or more modules or units may be performed by separate hardware or software components, or integrated within common or separate hardware or software components.

[129] When implemented in software, the functionality ascribed to the systems, devices and techniques described in this disclosure may be embodied as instructions on a computer-readable medium such as RAM, ROM, NVRAM, EEPROM, FLASH memory, magnetic data storage media, optical data storage

media, or the like. The instructions may be executed by one or more processors to support one or more aspects of the functionality described in this disclosure.

ILLUSTRATIVE EMBODIMENTS

- [130]** Embodiment 1: A system comprising:
- electrode apparatus comprising a plurality of external electrodes to monitor cardiac electrical activity from tissue of a patient; and
 - computing apparatus comprising processing circuitry and coupled to the electrode apparatus and configured to:
 - monitor cardiac electrical activity using the plurality of external electrodes at least during delivery of cardiac therapy using a left ventricular assist device (LVAD);
 - generate electrical heterogeneity information based on the monitored electrical activity; and
 - determine an output parameter for the LVAD based the generated electrical heterogeneity information.
- [131]** Embodiment 2: A method comprising:
- monitoring electrical activity from tissue of a patient using a plurality of electrodes at least during delivery of cardiac therapy using a left ventricular assist device (LVAD);
 - generating electrical heterogeneity information based on the monitored electrical activity; and
 - determining an output parameter for the LVAD based the generated electrical heterogeneity information.
- [132]** Embodiment 3: The system or method as set forth in any one of embodiments 1-2, wherein the plurality of external electrodes comprises surface electrodes positioned in an array configured to be located proximate skin of a torso of the patient.

- [133]** Embodiment 4: The system or method as set forth in any one of embodiments 1-3, wherein the system further comprises a display, wherein the display comprises a graphical user interface configured to assist a user in evaluating patient cardiac health, wherein the computing apparatus is further configured to display electrical heterogeneity information and the determined output parameter for the LVAD on the graphical user interface.
- [134]** Embodiment 5: The system or method as set forth in any one of embodiments 1-4, wherein the computing apparatus is further configured to execute or the method further comprises adjusting the LVAD in accordance with the determined output parameter.
- [135]** Embodiment 6: The system or method as set forth in any one of embodiments 1-5, wherein the electrical heterogeneity information comprises right ventricular electrical heterogeneity information indicative of right ventricular dyssynchrony generated using electrical activity monitored by a right set of external electrodes of the plurality of external electrodes positioned proximate the right torso of the patient.
- [136]** Embodiment 7: The system or method of embodiment 6, wherein the electrical heterogeneity information comprises a mean of the right ventricular electrical activation times monitored by the right set of external electrodes.
- [137]** Embodiment 8: The system or method as set forth in any one of embodiments 1-7, wherein the electrical heterogeneity information comprises septal electrical heterogeneity information indicative of septal dyssynchrony generated using electrical activity monitored by a central set of external electrodes of the plurality of external electrodes positioned proximate the sternum or spine of the patient.
- [138]** Embodiment 9: The system or method of embodiment 8, wherein determining an output parameter for the LVAD based the generated electrical heterogeneity information comprises comparing the septal central electrical

heterogeneity information to other electrical heterogeneity information generated from a set of external electrodes to the right or left of the sternum or spine of the patient.

[139] Embodiment 10: The system or method as set forth in any one of embodiments 1-9, wherein the computing apparatus is further configured to execute or the method further comprises determining one or more cardiac pacing parameters to be used in cardiac pacing therapy in conjunction with the LVAD based on the generated electrical heterogeneity information.

[140] Embodiment 11: The system or method of embodiment 10, wherein the one or more pacing parameters comprises right ventricular preexcitation.

[141] Embodiment 12: The system or method as set forth in any one of embodiments 1-11, further comprising or providing an acoustic sensor comprising at least one transducer to monitor cardiac sounds of the patient, wherein the computing apparatus is further configured to execute or the method further comprises determining the output parameter for the LVAD based on the monitored cardiac sounds of the patient during delivery of cardiac therapy using the LVAD.

[142] Embodiment 13: The system or method of embodiment 12, wherein determining the output parameter for the LVAD based on the monitored cardiac sounds of the patient during delivery of cardiac therapy using the LVAD comprises:

determining whether heart valves are open or closed based on the monitored cardiac sounds; and

adjusting the output parameter for the LVAD to allow at least some opening of the heart valves.

[143] Embodiment 14: The system or method as set forth in any one of embodiments 12-13, further comprising a display or providing a display, wherein the display comprises a graphical user interface configured to assist a user in evaluating patient cardiac health, wherein the computing apparatus is further

configured to display cardiac sound information based on the monitored cardiac sounds of the patient during delivery of cardiac therapy using the LVAD.

[144] This disclosure has been provided with reference to illustrative embodiments and is not meant to be construed in a limiting sense. As described previously, one skilled in the art will recognize that other various illustrative applications may use the techniques as described herein to take advantage of the beneficial characteristics of the apparatus and methods described herein. Various modifications of the illustrative embodiments, as well as additional embodiments of the disclosure, will be apparent upon reference to this description.

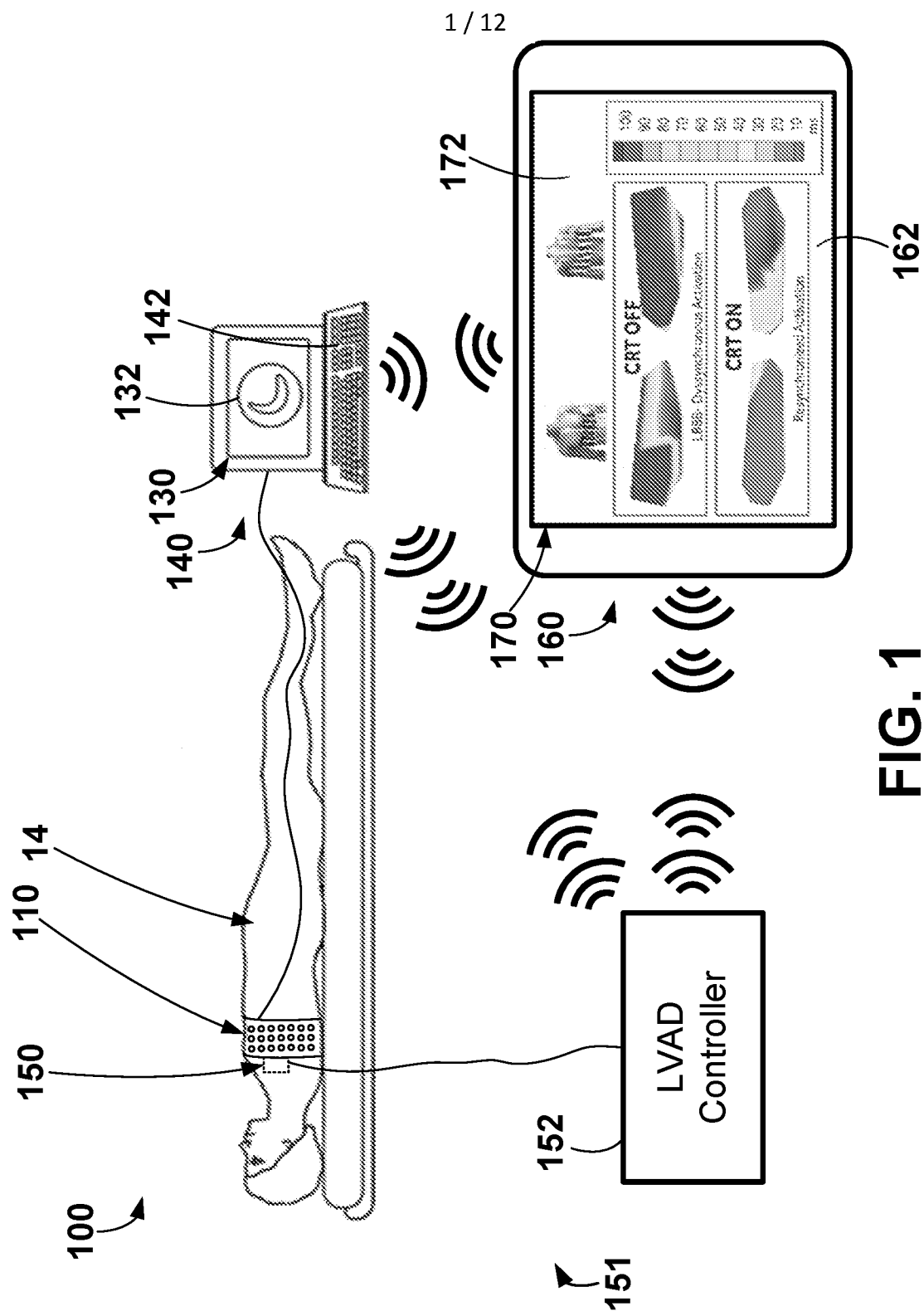
CLAIMS

What is claimed:

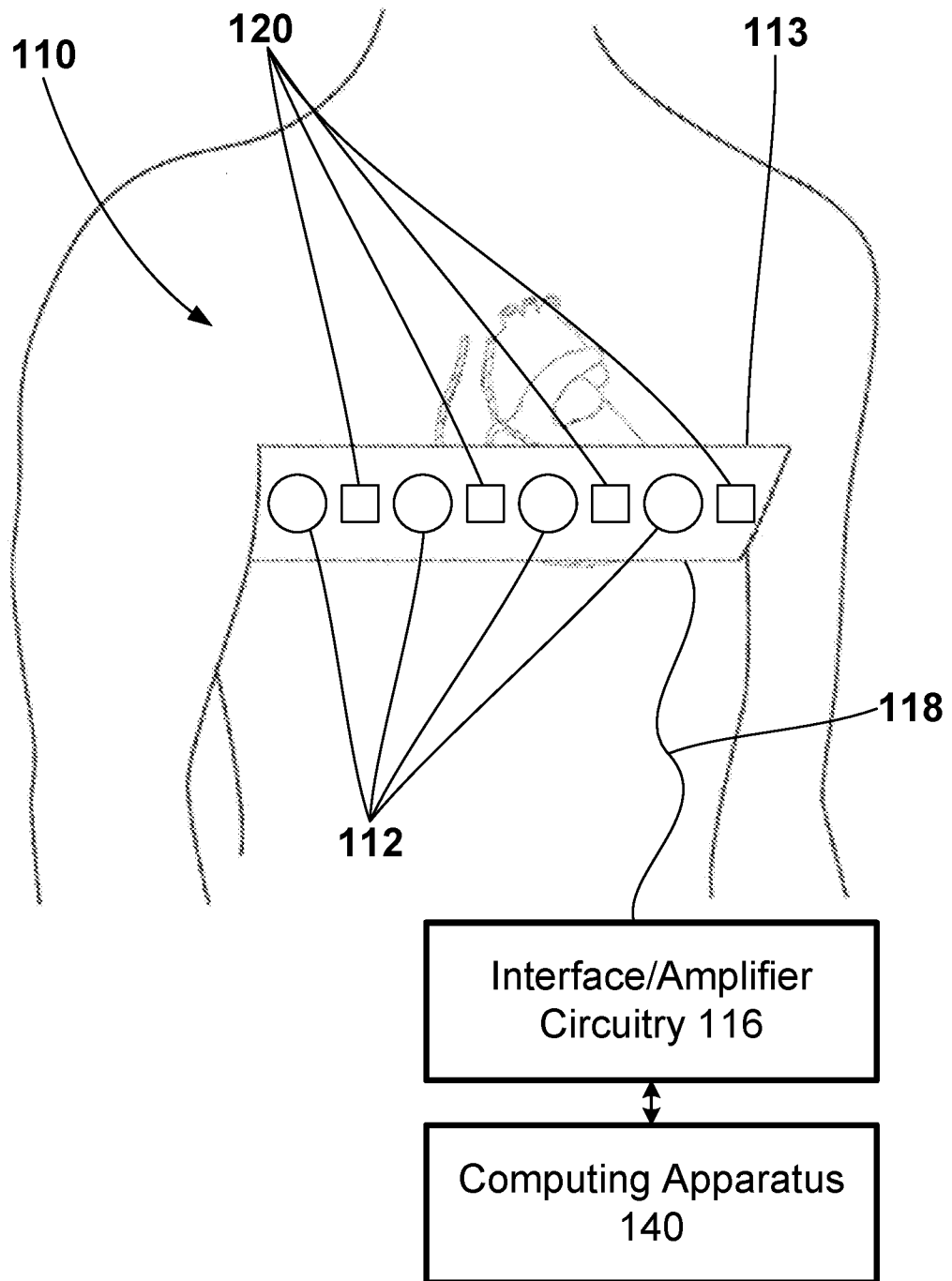
1. A system comprising:
 - electrode apparatus comprising a plurality of external electrodes to monitor cardiac electrical activity from tissue of a patient; and
 - computing apparatus comprising processing circuitry and coupled to the electrode apparatus and configured to:
 - monitor cardiac electrical activity using the plurality of external electrodes at least during delivery of cardiac therapy using a left ventricular assist device (LVAD);
 - generate electrical heterogeneity information based on the monitored electrical activity; and
 - determine an output parameter for the LVAD based the generated electrical heterogeneity information.
2. A method comprising:
 - monitoring electrical activity from tissue of a patient using a plurality of electrodes at least during delivery of cardiac therapy using a left ventricular assist device (LVAD);
 - generating electrical heterogeneity information based on the monitored electrical activity; and
 - determining an output parameter for the LVAD based the generated electrical heterogeneity information.
3. The system or method as set forth in any one of claims 1-2, wherein the plurality of external electrodes comprises surface electrodes positioned in an array configured to be located proximate skin of a torso of the patient.

4. The system or method as set forth in any one of claims 1-3, wherein the controller is further configured to execute or the method further comprises displaying electrical heterogeneity information and the determined output parameter for the LVAD on a graphical user interface to assist a user in evaluating patient cardiac health.
5. The system or method as set forth in any one of claims 1-4, wherein the controller is further configured to execute or the method further comprises adjusting the LVAD in accordance with the determined output parameter.
6. The system or method as set forth in any one of claims 1-5, wherein the electrical heterogeneity information comprises right ventricular electrical heterogeneity information indicative of right ventricular dyssynchrony generated using electrical activity monitored by a right set of external electrodes of the plurality of external electrodes positioned proximate the right torso of the patient.
7. The system or method of claim 6, wherein the electrical heterogeneity information comprises a mean of the right ventricular electrical activation times monitored by the right set of external electrodes.
8. The system or method as set forth in any one of claims 1-7, wherein the electrical heterogeneity information comprises septal electrical heterogeneity information indicative of septal dyssynchrony generated using electrical activity monitored by a central set of external electrodes of the plurality of external electrodes positioned proximate the sternum or spine of the patient.
9. The system or method set forth in any one of claim 8, wherein determining an output parameter for the LVAD based the generated electrical heterogeneity information comprises comparing the septal central electrical heterogeneity information to other electrical heterogeneity information generated from a set of external electrodes to the right or left of the sternum or spine of the patient.

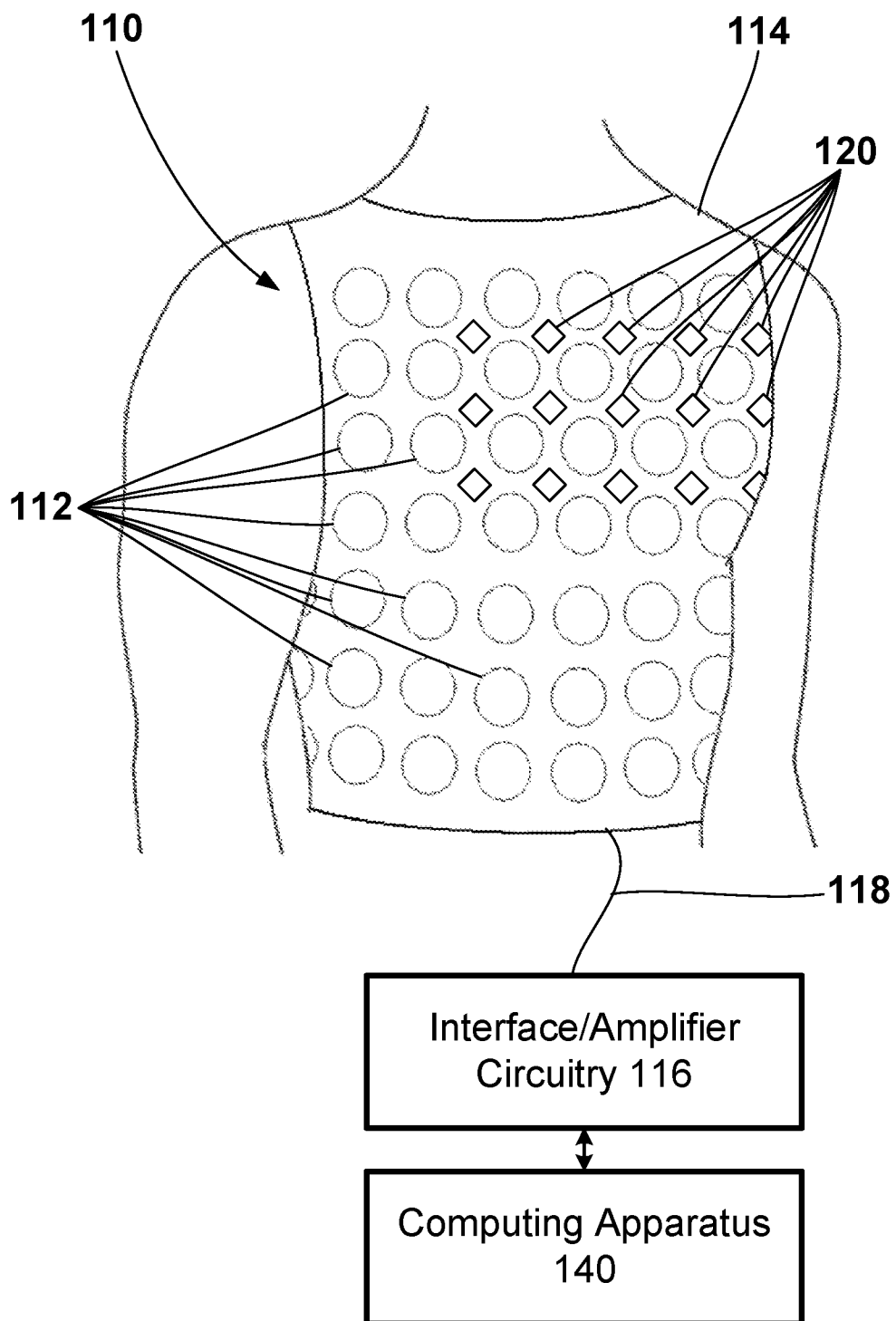
10. The system or method as set forth in any one of claims 1-9, wherein the controller is further configured to execute or the method further comprises determining one or more cardiac pacing parameters to be used in cardiac pacing therapy in conjunction with the LVAD based on the generated electrical heterogeneity information.
11. The system or method of claim 10, wherein the one or more pacing parameters comprises right ventricular preexcitation.
12. The system or method as set forth in any one of claims 1-11, wherein the controller is further configured to execute or the method further comprises:
 - monitoring cardiac sounds of the patient using an acoustic sensor during delivery of cardiac therapy using the LVAD; and
 - determining the output parameter for the LVAD based on monitored cardiac sounds of the patient during delivery of cardiac therapy using the LVAD.
13. The system or method of claim 12, wherein determining the output parameter for the LVAD based on the monitored cardiac sounds of the patient during delivery of cardiac therapy using the LVAD comprises:
 - determining whether heart valves are open or closed based on the monitored cardiac sounds; and
 - adjusting the output parameter for the LVAD to allow at least some opening of the heart valves.
14. The system or method as set forth in any one of claims 12-13, wherein the controller is further configured to execute or the method further comprises displaying cardiac sound information based on the monitored cardiac sounds of the patient during delivery of cardiac therapy using the LVAD on a graphical user interface to assist a user in evaluating patient cardiac health.



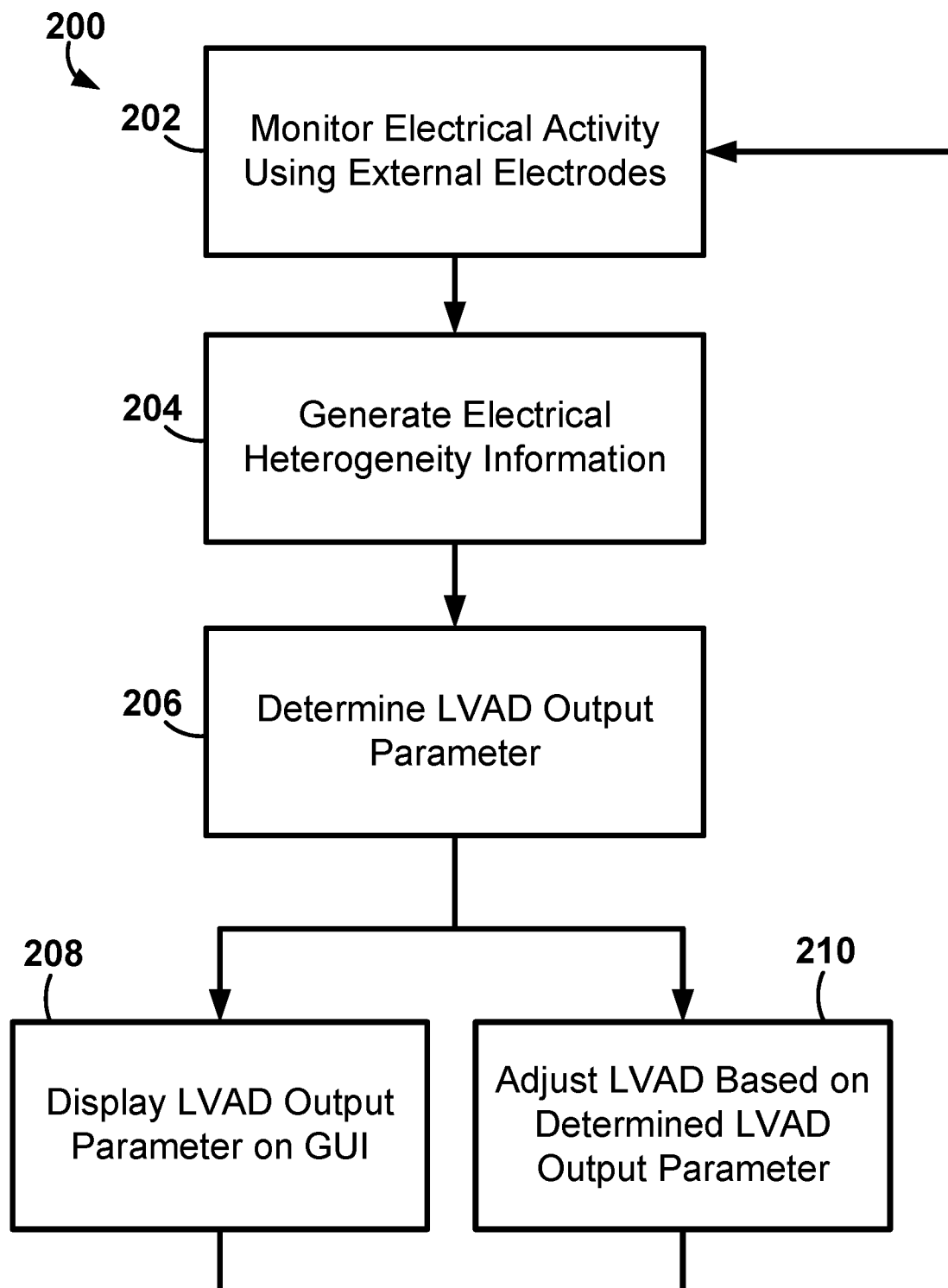
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**FIG. 2**

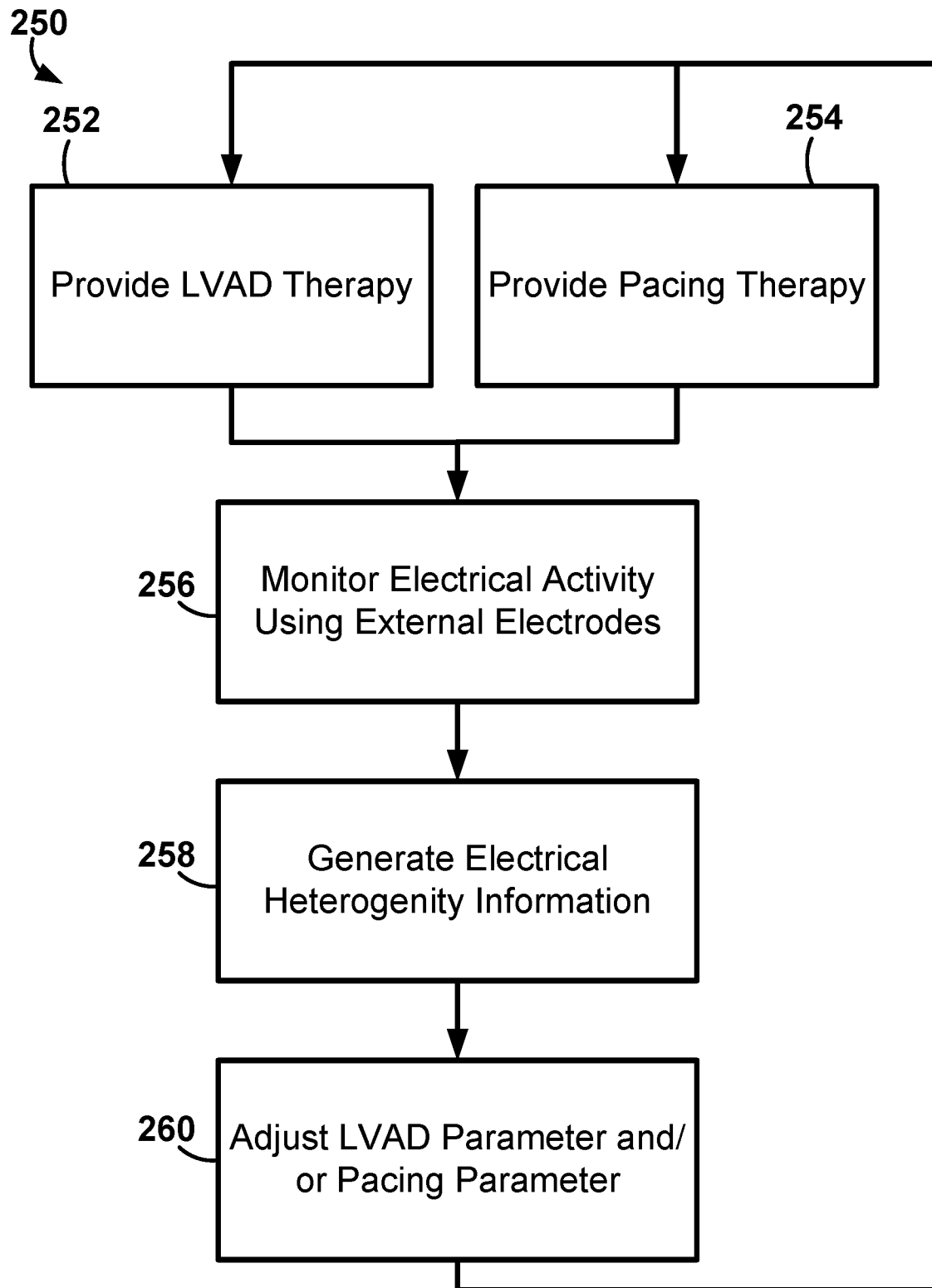
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**FIG. 3**

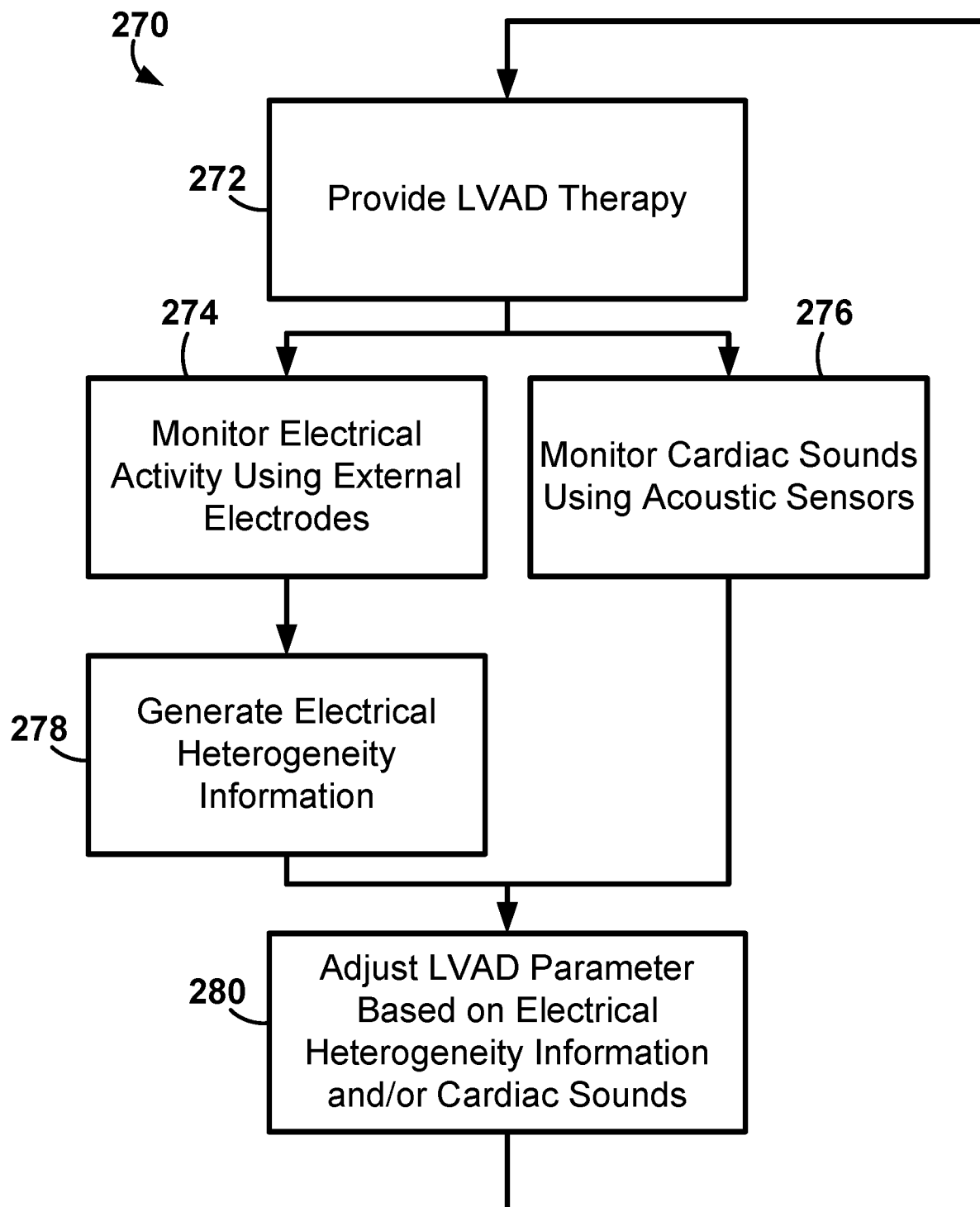
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**FIG. 4**

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**FIG. 5**

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**FIG. 6**

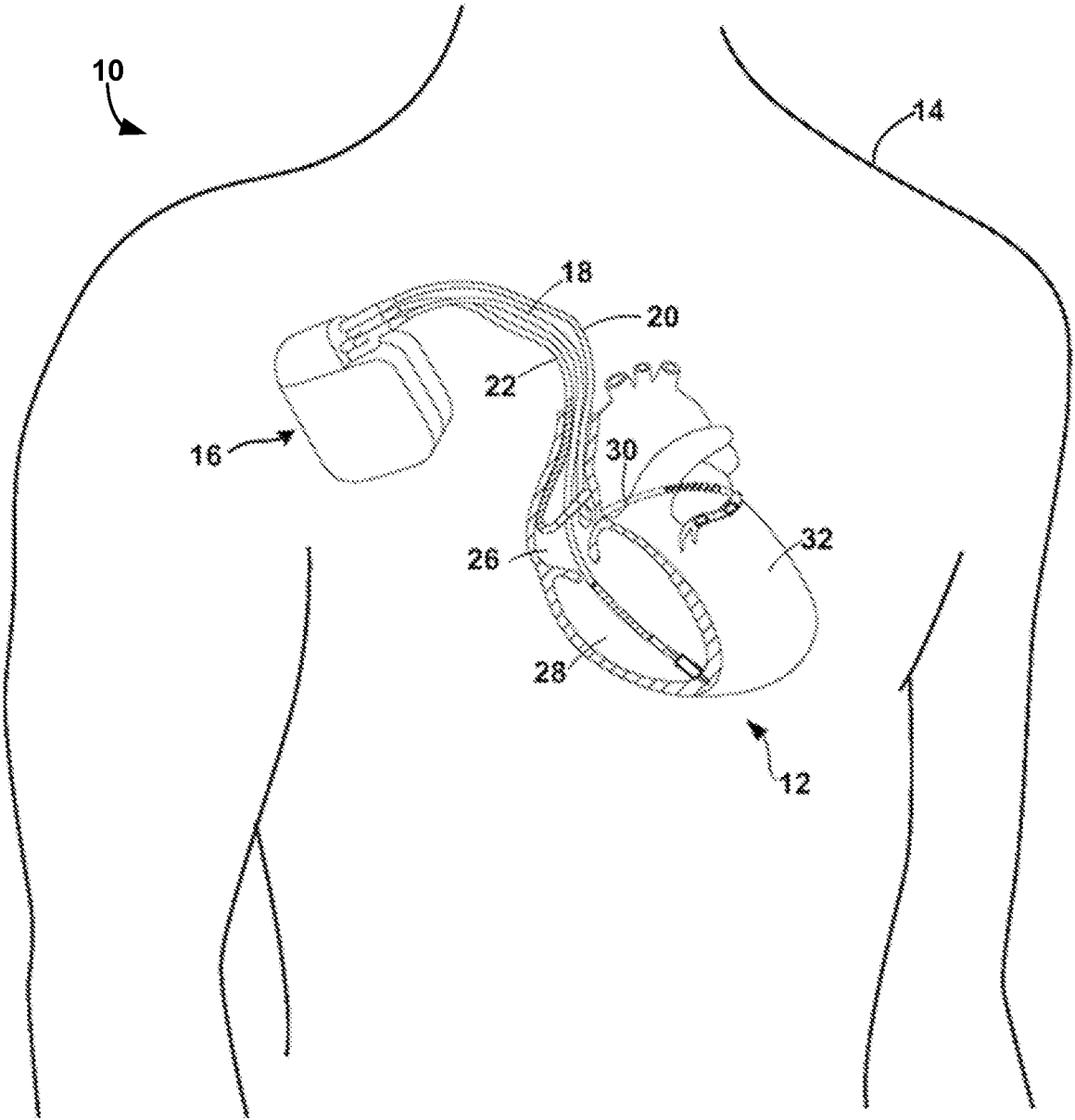
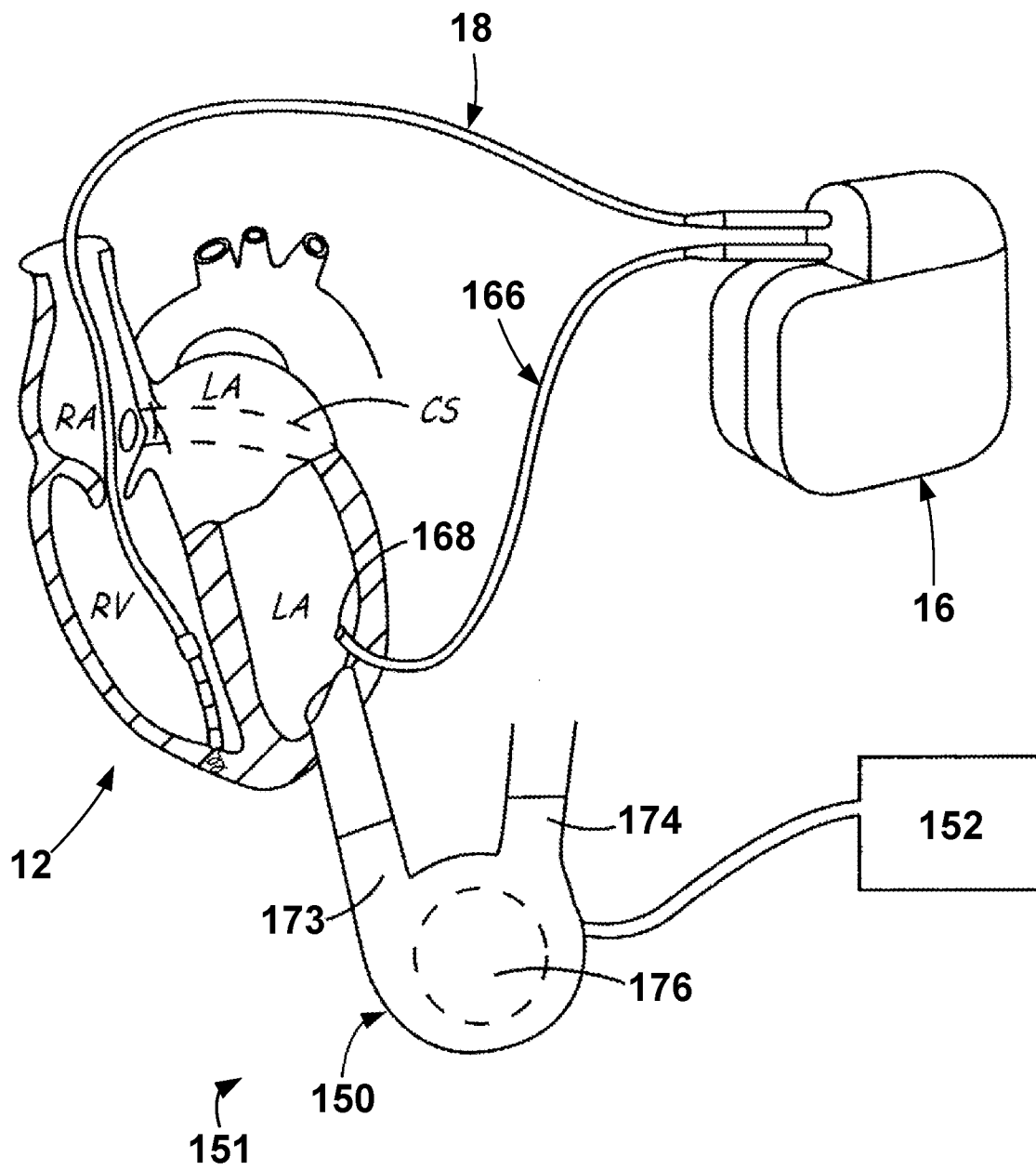


FIG. 7

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**FIG. 8**

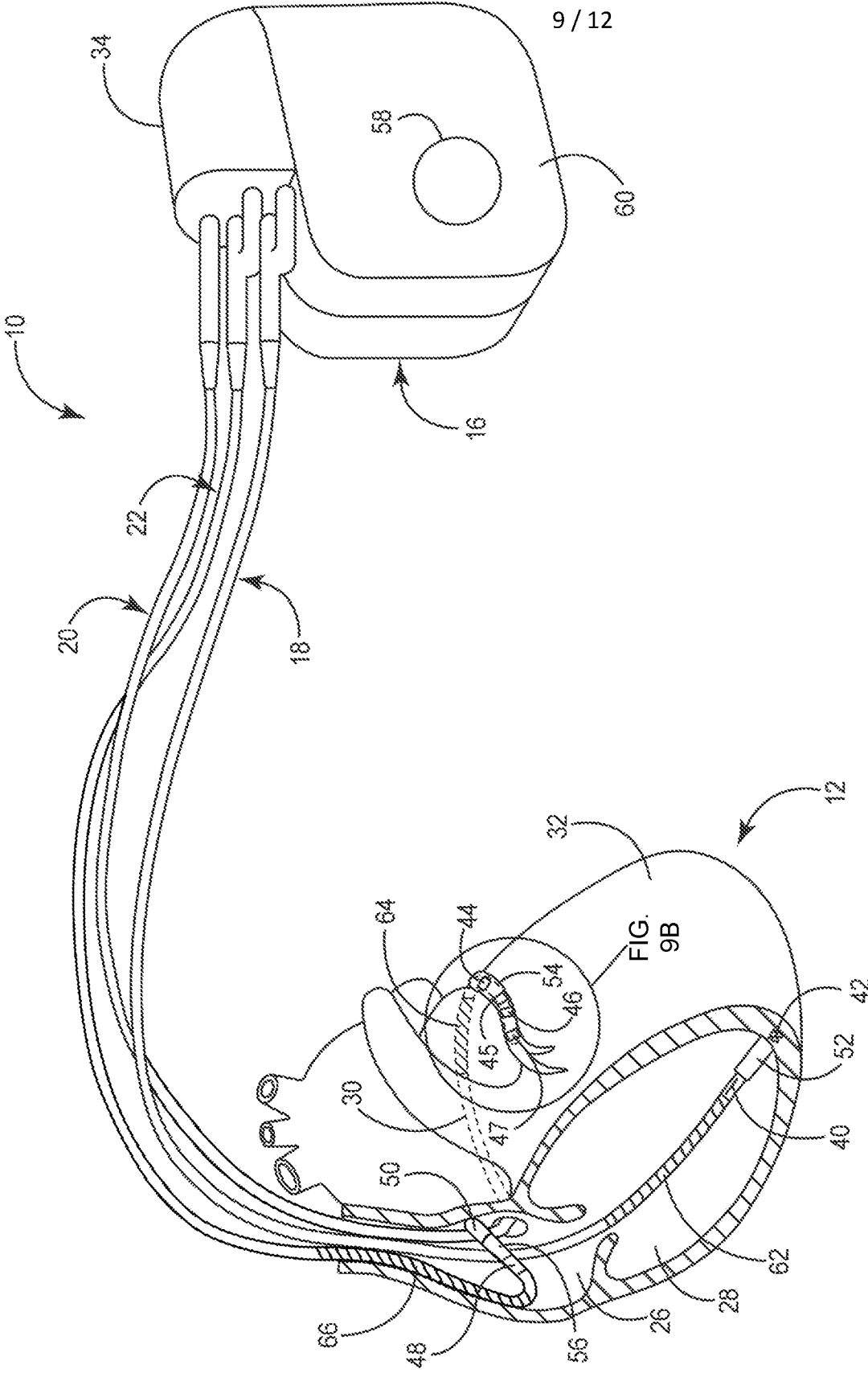


FIG. 9A

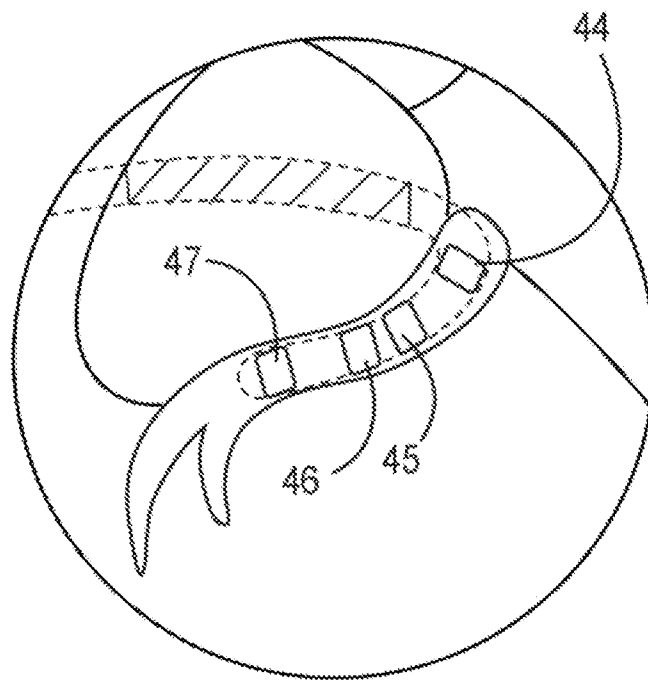
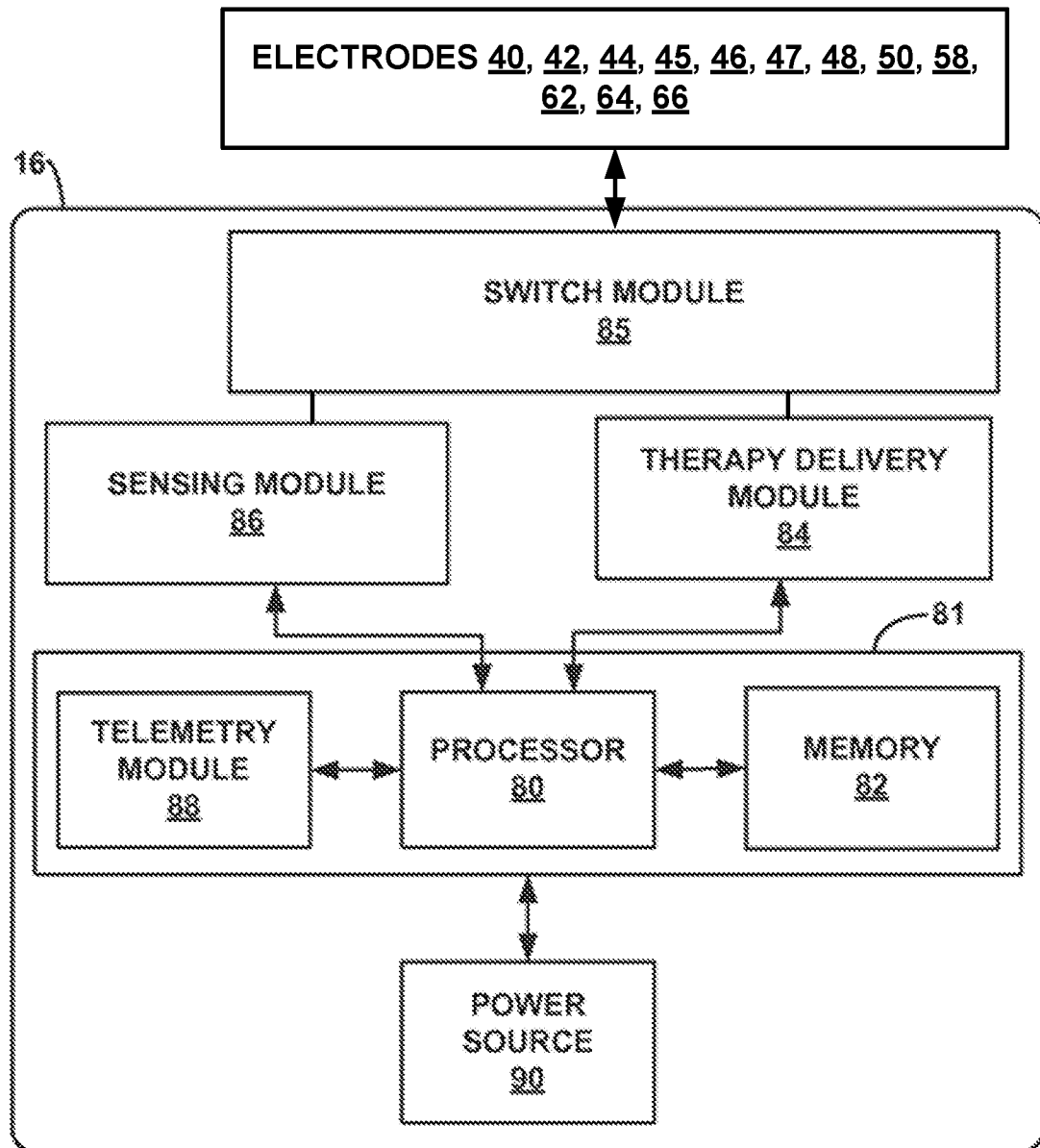


FIG. 9B

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**FIG. 10A**

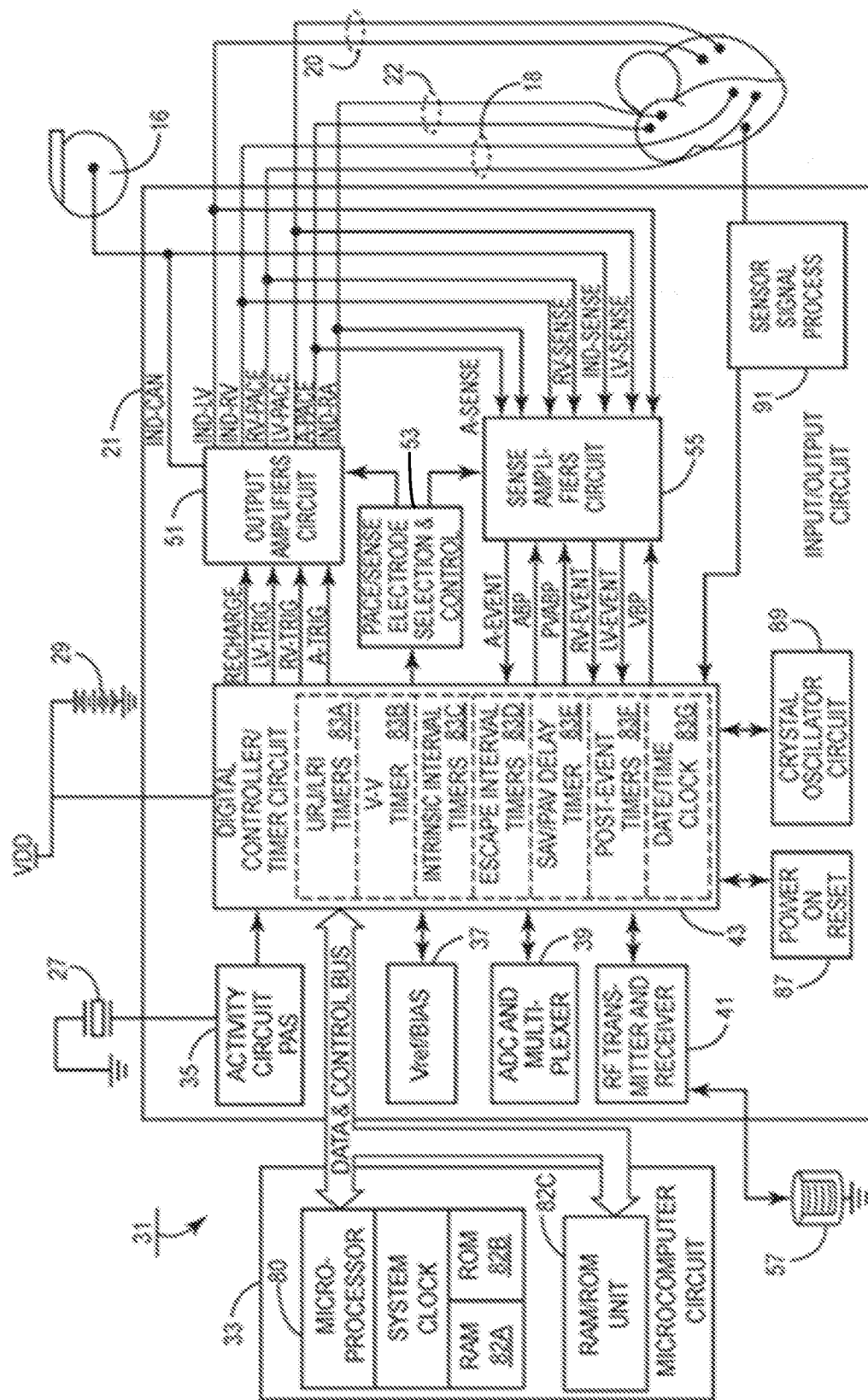


FIG. 10B

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2019/024862

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B5/0408 A61N1/362 A61M1/12
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61B A61N A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2016/045737 A1 (GHOSH SUBHAM [US] ET AL) 18 February 2016 (2016-02-18) paragraphs [0036] - [0095]; figures 1-7 -----	1-14
X	US 2016/045738 A1 (GHOSH SUBHAM [US] ET AL) 18 February 2016 (2016-02-18) paragraphs [0041] - [0099]; figures 1-6 -----	1-14
A	US 2015/328466 A1 (PETERS WILLIAM SUTTLE [NZ] ET AL) 19 November 2015 (2015-11-19) the whole document -----	1-14
A	US 2016/045744 A1 (GILLBERG JEFFREY [US] ET AL) 18 February 2016 (2016-02-18) the whole document -----	1-14
A	US 2016/030751 A1 (GHOSH SUBHAM [US] ET AL) 4 February 2016 (2016-02-04) the whole document -----	1-14



Further documents are listed in the continuation of Box C.



See patent family annex.

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

2 July 2019

Date of mailing of the international search report

10/07/2019

Name and mailing address of the ISA/

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Authorized officer

Smit, Jos

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2019/024862

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2016045737	A1	18-02-2016	NONE
US 2016045738	A1	18-02-2016	NONE
US 2015328466	A1	19-11-2015	AU 2004284842 A1 12-05-2005 CN 1874821 A 06-12-2006 DK 1677872 T3 15-02-2016 EP 1677872 A1 12-07-2006 EP 3028739 A1 08-06-2016 ES 2561354 T3 25-02-2016 JP 5196786 B2 15-05-2013 JP 2007509653 A 19-04-2007 US 2007060787 A1 15-03-2007 US 2010324354 A1 23-12-2010 US 2014051909 A1 20-02-2014 US 2015328466 A1 19-11-2015 WO 2005042089 A1 12-05-2005
US 2016045744	A1	18-02-2016	NONE
US 2016030751	A1	04-02-2016	NONE