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McCullouch et al.(10) **Pub. No.: US 2016/0262635 A1**(43) **Pub. Date: Sep. 15, 2016**(54) **COMPOSITIONS, DEVICES AND METHODS
FOR DIAGNOSING HEART FAILURE AND
FOR PATIENT-SPECIFIC MODELING TO
PREDICT OUTCOMES OF CARDIAC
RESYNCHRONIZATION THERAPY****Publication Classification**(51) **Int. Cl.***A61B 5/02* (2006.01)*G06F 19/00* (2006.01)*A61N 1/39* (2006.01)*A61B 5/00* (2006.01)*A61N 1/362* (2006.01)(52) **U.S. Cl.**CPC *A61B 5/02028* (2013.01); *A61B 5/4836*
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(2) Date: **May 12, 2016****Related U.S. Application Data**(60) Provisional application No. 61/905,138, filed on Nov.
15, 2013.(57) **ABSTRACT**

in alternative embodiments, provided are compositions, medical devices or products of manufacture, systems, diagnostic tools, and methods, including computer implemented methods, for predicting the response of patients with dyssynchronous heart failure (DHF) to cardiac resynchronization therapy (CRT), comprising: measuring or determining the fraction of the LV/septum performing negative work (MNW); and measuring or determining the coefficient of variation of external work density (COVW), wherein the MNW fraction performing negative work and coefficient of variation COVW (sd/mean) correlated strongly with observed reduction in end-systolic volume after CRT.

Fig. 1

- Patients classified as responders/non-responders based on changes in cardiac function 3-6 months after CRT procedure measured using echocardiography

- >10% reduction in end-systolic volume
- >5% absolute change in ejection fraction

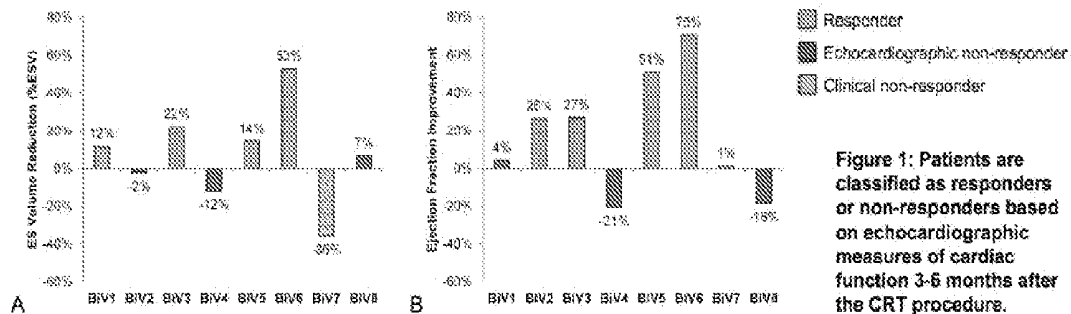


Fig. 2

- Baseline measures of mechanical and electrical function do not correlate well with functional improvement after CRT procedure

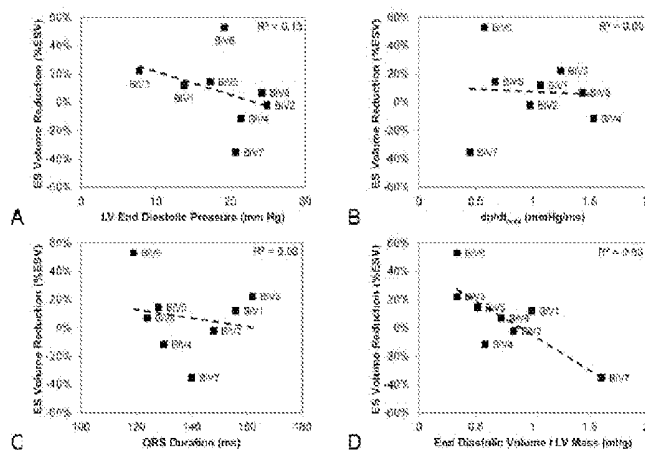


Figure 2: Measures of LV mechanical function such as end-diastolic pressure (A) and the maximum dp/dt (B) do not correlate with end-systolic volume reduction after CRT. The QRS duration (C) and the echocardiographic measure of dilatation (D) also do not correlate with functional improvement after CRT.

Fig. 3

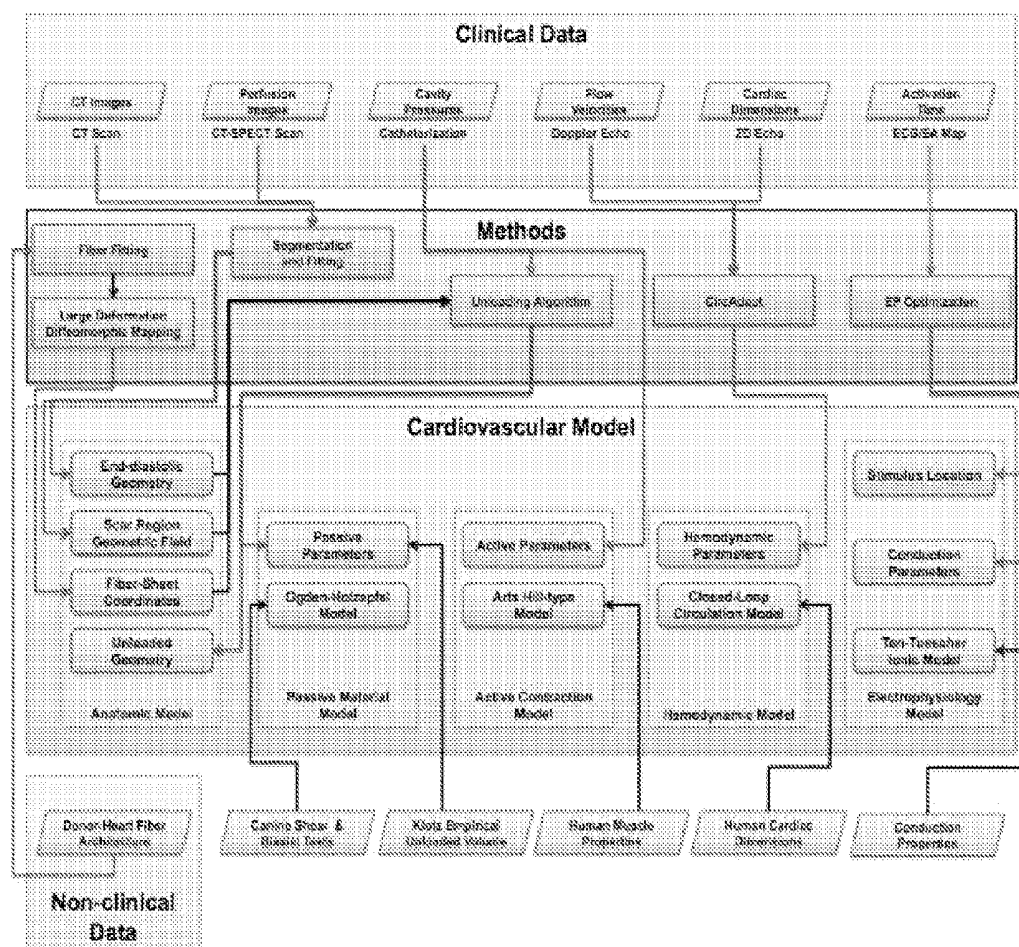


Figure 3: Different components of the patient-specific electromechanics model utilized in its construction.

Fig. 4

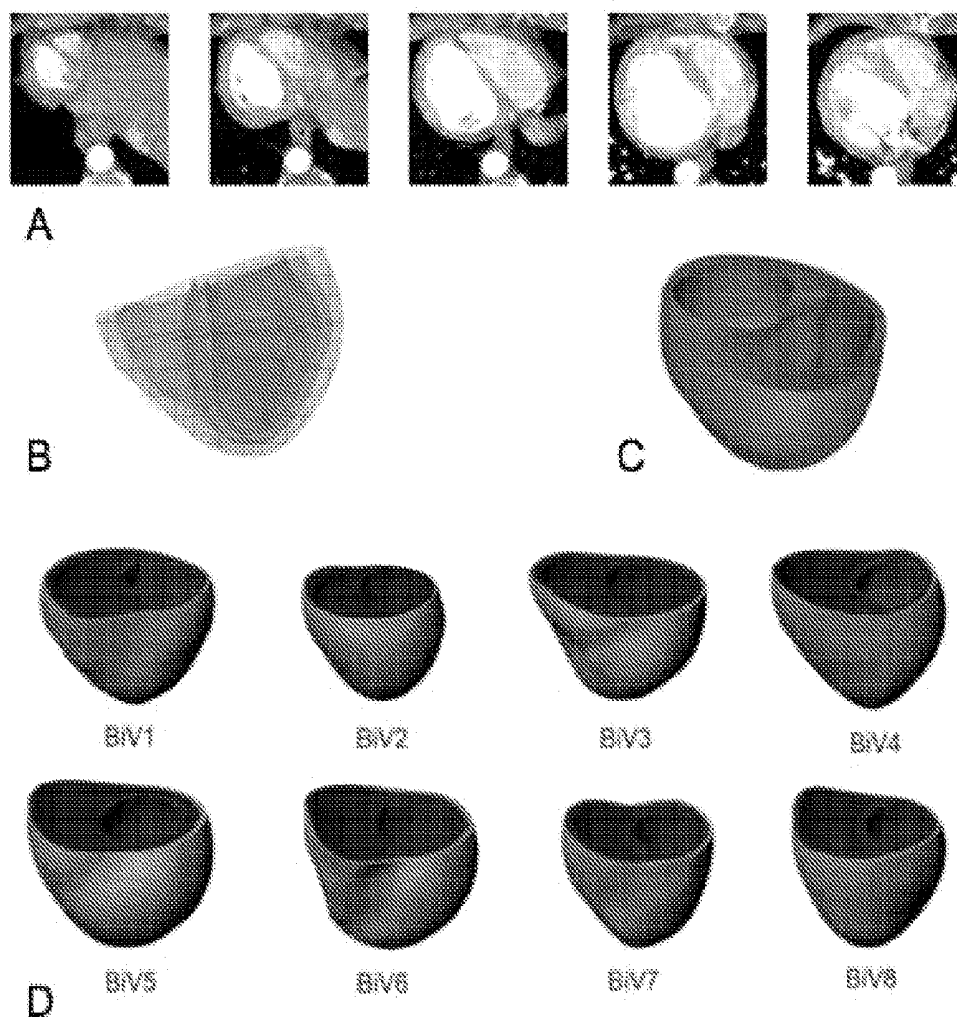


Figure 4: CT image slices (A) were segmented and the resulting data points are used to fit the surfaces of the geometric biventricular model (B). Patient-specific hexahedral finite element mesh (C) is constructed from the surfaces for different patients (D).

Fig. 5

Myofiber Architecture

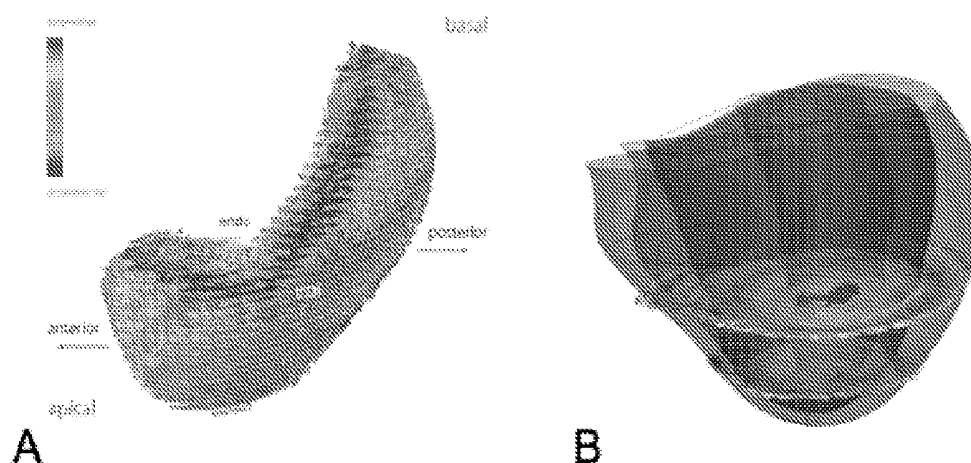


Figure 5: Reconstructed diffusion tensors in the explanted donor heart (A) fitted to the geometric model (B).

Fig. 6

Scar Region

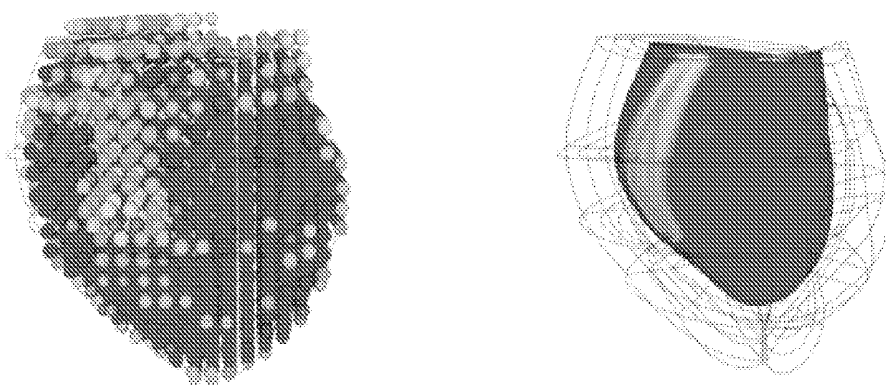


Figure 6: The voxel intensities of the MIBI scan were reconstructed in 3D space and aligned to the anatomical model; a scalar field was fitted to define the region of the scar.

Fig. 7

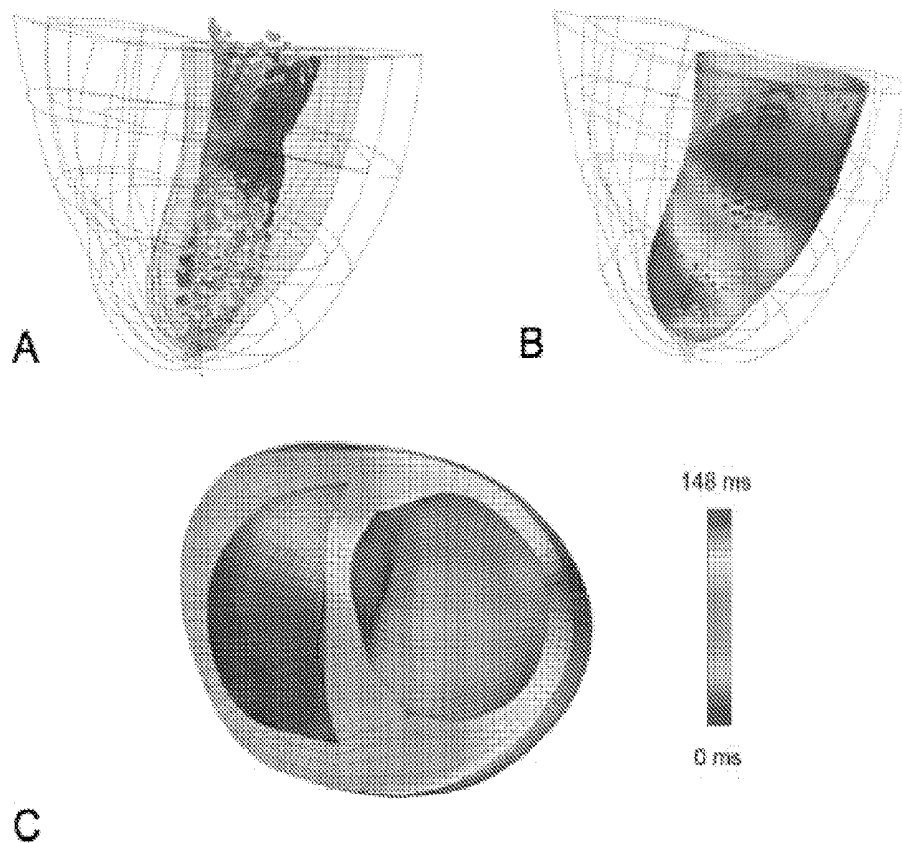


Figure 7: Electroanatomic activation time data (A) projected onto the LV surface of the finite element mesh and rendered as a field (B). Output of an electrophysiology simulation to generate myocardial activation times.

Fig. 8

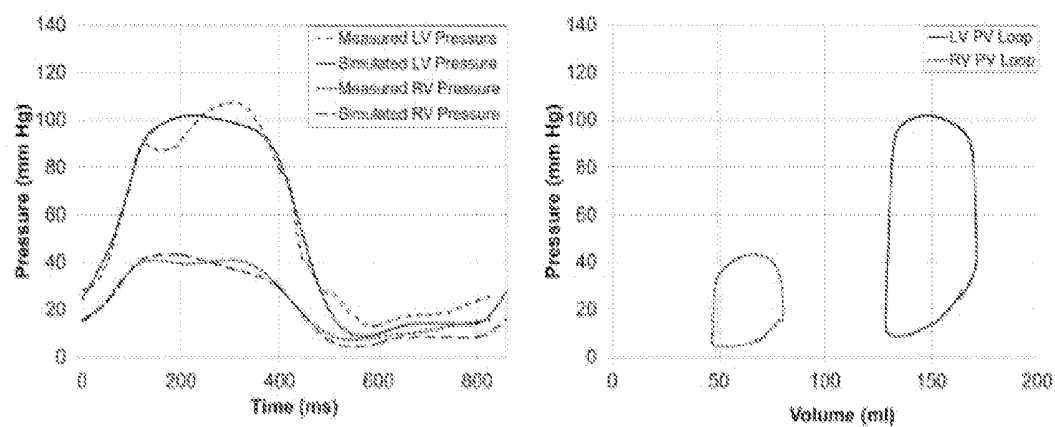


Figure 8: Simulated and Measured LV and RV Pressure and PV Loops.

Fig. 9

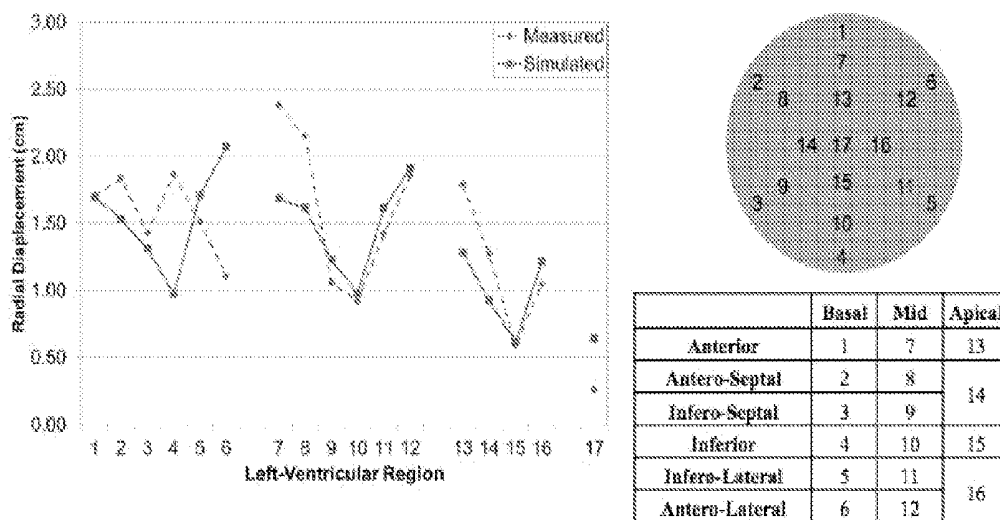


Figure 9: Radial displacement between end-diastole and end-systole from the measured and simulated geometries.

Fig. 10

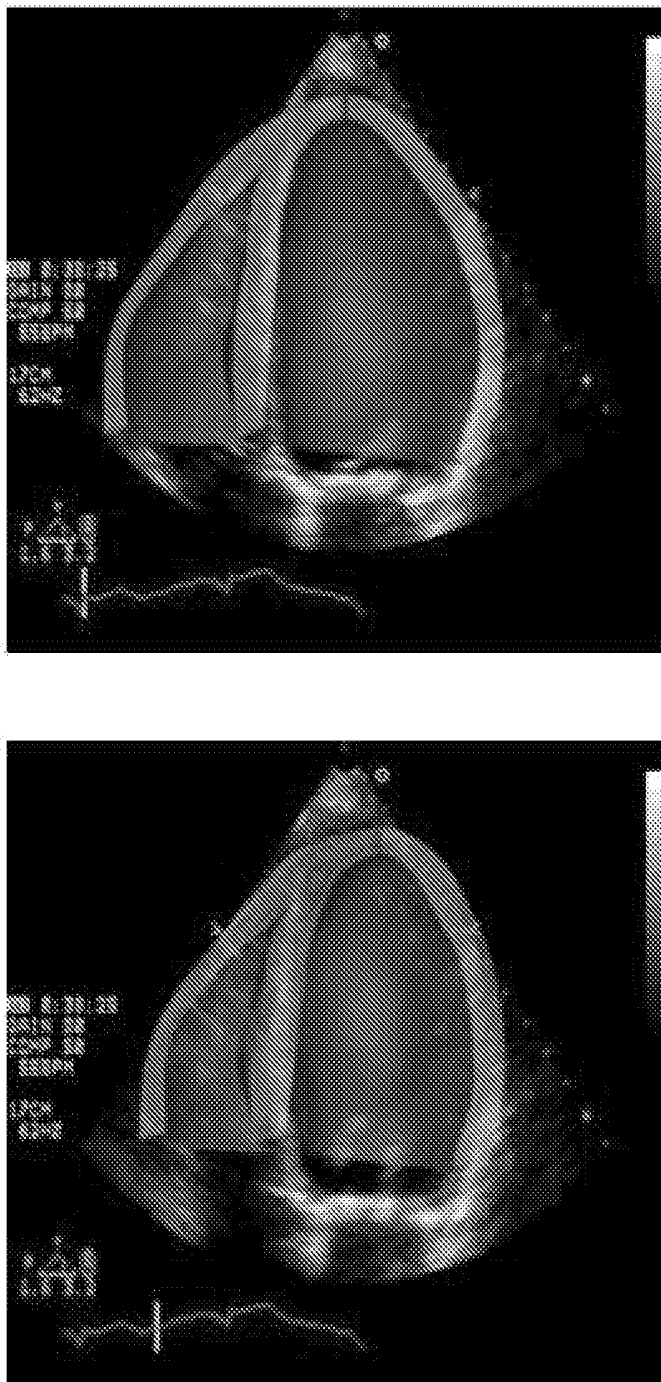


Fig. 11

Regional Stress-Strain Work Loops

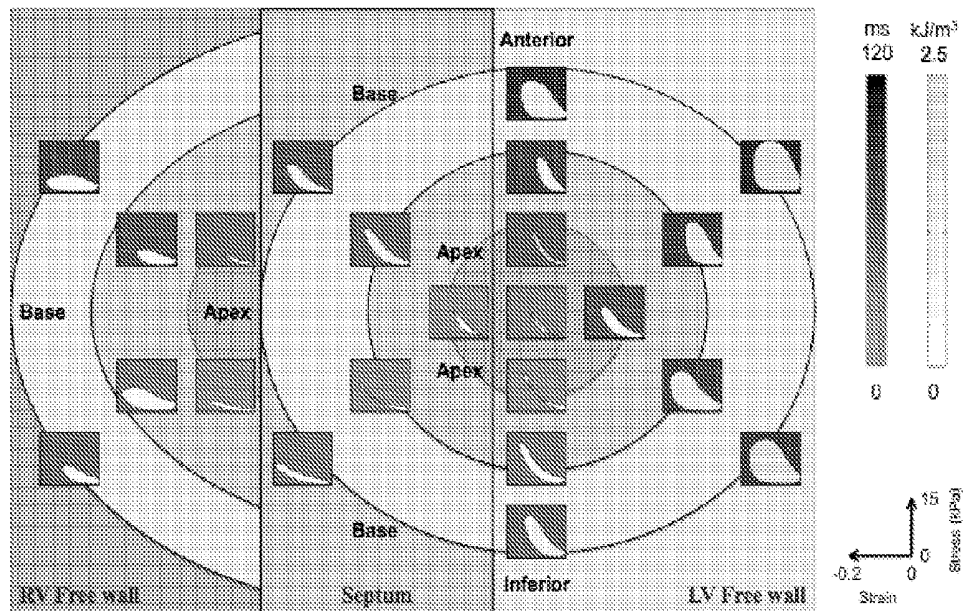


Figure 11: Stress-strain loops used to compute the regional work density in a heart failure patient. The septal region performs minimal or negative work in patients who responded better to CRT.

Fig. 12

Distribution of External Work Density

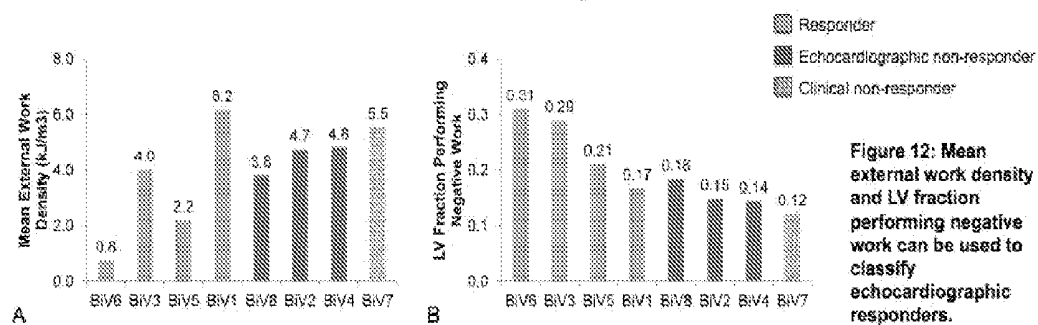


Fig. 13

Classification of Echocardiographic Response

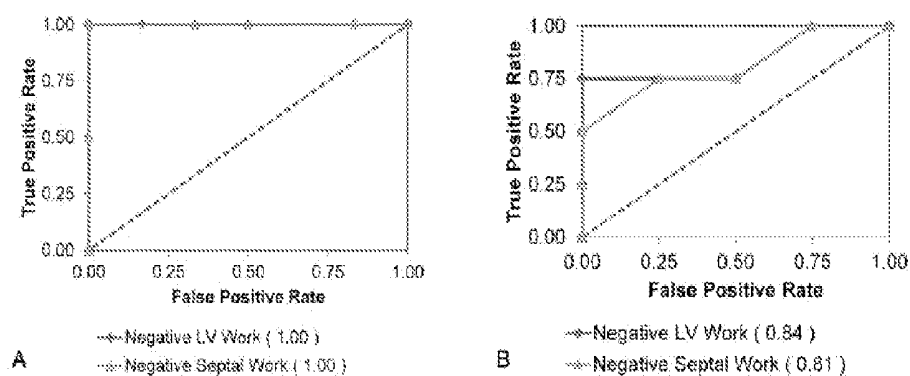


Figure 13: Receiver-operator characteristic (ROC) curves for using negative LV and septal work as classifiers of echocardiographic response to CRT. Echocardiographic response is classified using 10% reduction in end-systolic volume (A) or 5% absolute increase in ejection fraction (B).

Fig. 14

Biomarkers for Reverse Remodeling

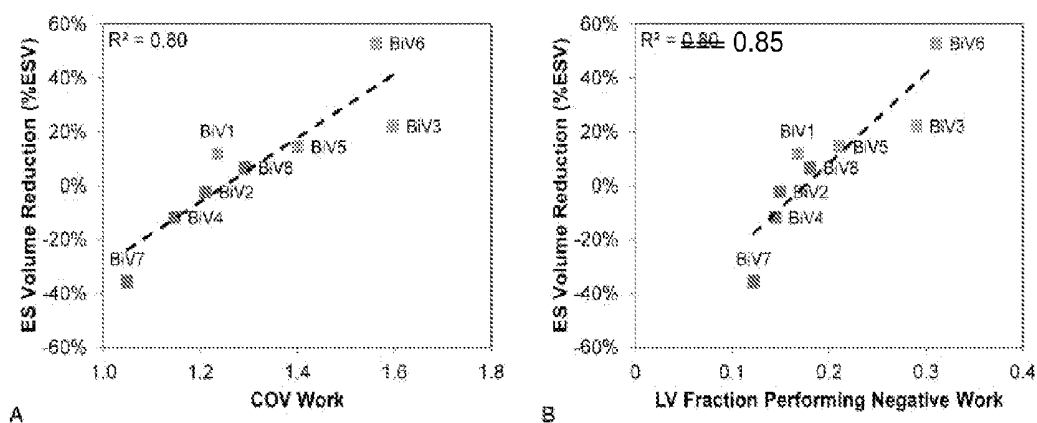
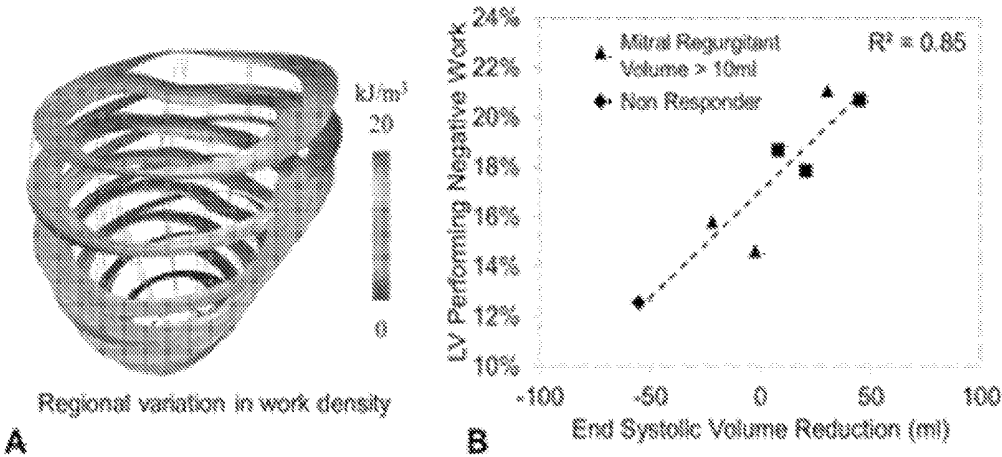


Figure 14: Both coefficient of variation of external work density (A) and fraction of LV performing negative work (B) predict quantitative measures of left-ventricular reverse remodeling.

Fig. 15



**COMPOSITIONS, DEVICES AND METHODS
FOR DIAGNOSING HEART FAILURE AND
FOR PATIENT-SPECIFIC MODELING TO
PREDICT OUTCOMES OF CARDIAC
RESYNCHRONIZATION THERAPY**

RELATED APPLICATIONS

[0001] This application claims the benefit of priority to U.S. Provisional Patent Application Ser. No. 61/905,138, filed Nov. 15, 2013. The aforementioned application is expressly incorporated herein by reference in its entirety and for all purposes.

**STATEMENT AS TO FEDERALLY SPONSORED
RESEARCH**

[0002] This invention was made with government support under Grant No. HL096544, awarded by the National Institutes of Health (NIH), DHHS. The government has certain rights in this invention.

TECHNICAL FIELD

[0003] This invention generally relates to diagnostics, medical devices and therapies used in dyssynchronous heart failure (DHF), including cardiac resynchronization therapy (CRT) and use of biventricular pacemakers (BVPs). In particular, in alternative embodiments, provided are compositions, diagnostic techniques, medical devices or products of manufacture, systems, and methods for diagnosing the severity of DHF, predicting the response of patients with DHF to therapy including CRT, improving the response to therapy by informing the choice of therapeutic parameters such as CRT pacing lead locations or ventriculo-ventricular (VV) delays, or comprising: computing, measuring or determining the distributions of regional myocardial work and deriving from these measures of work heterogeneity. The work heterogeneity can be computed, measured or assessed using alternative measures derived from these distributions including but not limited to, the coefficient of variation of regional work (COVW), the mass or volume fraction of the whole heart, left ventricular (LV) wall, right ventricular (RV) wall or septal wall in which regional work is less than or equal to zero (MNV).

BACKGROUND

[0004] Cardiac resynchronization therapy (CRT) is a treatment for dyssynchronous heart failure (DHF) in which a pacemaker system can pace the heart in a manner intended to improve the synchrony of electrical activation of the heart walls. By pacing in one, two or more locations, pacemaker therapy can resynchronize a heart whose walls do not contract in synchrony, which occurs in approximately 25 to 50% of heart failure patients. By adjusting the timing of pacemaker stimuli, the improvement of mechanical function in the heart can be altered and optimized.

[0005] Different indices of dyssynchrony are found from echocardiography, electrocardiography, cardiac catheterization, or cardiac imaging to classify responders and non-responders to CRT. However, these metrics have shown neither high specificity and sensitivity nor good correlations with patient outcomes.

[0006] Previous studies based on data from experimental animals suggest that electrical dyssynchrony produces increased heterogeneity in regional myocardial work density,

and model studies suggest that it could be a sensitive indicator of the mechanical deficit caused by electrical dyssynchrony. In a computational model of canine DHF, it was shown that the coefficient of variation (std. dev./mean) of the external work density (COVW) correlated well with measures of mechanical dyssynchrony. This metric was sensitive to the interaction effect between dilatation and electrical dyssynchrony that made mechanical dyssynchrony worse.

SUMMARY

[0007] In alternative embodiments, provided are compositions and methods for the clinical use of patient-specific computational models constructed from clinical data measured in patients clinically diagnosed with dyssynchronous heart failure (DHF) where the reduction of cardiac output or pumping performance occurs as a result of disorganized ventricular contraction and may be exacerbated by valve regurgitation. This invention for the first time found that patients having more heterogeneous regional work distributions are more able to benefit from therapy intended to decrease dyssynchrony, and that the greatest responses to therapy can be achieved by the greatest reductions in the magnitude of work heterogeneity. In alternative embodiments, these computations or measurements are made before therapy based on measurements obtained before therapy to assess the severity of dyssynchronous heart failure or to determine the likelihood of a patient to respond to a therapy. In alternative embodiments, computations or determinations made before therapy can include computational simulations of possible therapeutic interventions such as cardiac resynchronization therapy (CRT) using different possible therapeutic parameters such as alternative pacing lead locations or VV pacing delay times. In alternative embodiments, the results of such computations or predictions of regional myocardial work distributions are used to select or advise the choice of therapeutic parameters intended to achieve best possible clinic responses or therapeutics outcomes. In alternative embodiments, these computations, predictions, measurements and/or determinations of regional myocardial work distributions are used after therapy to assess the response to treatment.

[0008] In alternative embodiments, provided are diagnostic tools or methods, including computer implemented methods, for:

[0009] predicting and optimizing the response of patients with dyssynchronous heart failure (DHF) to cardiac resynchronization therapy (CRT), and/or

[0010] for diagnosing dyssynchronous heart failure or the degree of dyssynchrony in dyssynchronous heart failure, comprising:

[0011] measuring or determining indices derived from the regional distribution of myocardial external work density (RDMW) prior to treatment as a diagnostic assessment of the severity of dyssynchronous heart failure or the adverse impact of dyssynchrony

[0012] on ventricular mechanical performance,

[0013] wherein optionally the indices measured or determined are selected from the group consisting of:

[0014] (i) the fraction of ventricular wall mass or volume, or a part thereof, optionally left ventricle (LV), right ventricle (RV), or septum, performing negative work (myocardial negative work density fraction, or MNWF), optionally having work done on it by the surrounding heart wall,

- [0015] (ii) regions of the left ventricular wall mass performing negative work (LVNW),
- [0016] (iii) the coefficient of variation of external work density (COVW) or other measures of work dispersion or heterogeneity, optionally to predict amount of electromechanical dyssynchrony or the likely improvement in CRT response,
- [0017] (iv) the fraction of the septal wall performing negative work (change in STNW or Δ STNW), wherein a decrease in the fraction of the septal wall performing negative work (Δ STNW) computed after simulated CRT is a predictor of pump function improvement and CRT response, and
- [0018] (v) a combination thereof,
- [0019] and optionally predicting the potential response of patients with dyssynchronous heart failure (DHF) to cardiac resynchronization therapy (CRT), optionally predicting a reduction in end-systolic ventricular volume due to CRT, by using the myocardial negative work density fraction, or MNWF, or coefficient of variation (standard deviation divided by mean) of regional work density COVW or other measures of the heterogeneity or dispersion of RDMW, with greater values of heterogeneity corresponding to greater potential benefit of therapies that act to decrease dyssynchrony,
- [0020] and optionally the diagnostic tool or method is a computer implemented method,
- [0021] and optionally a value for COVW prior to therapy ranging from between about 1.0 to 1.25, indicates a low electromechanical dyssynchrony and predicts a weak CRT response,
- [0022] and optionally values in the range of between about 1.25 to 1.50 indicate a moderate electromechanical dyssynchrony and predicts a moderate CRT response,
- [0023] and optionally a value for COVW exceeding about 1.5 indicates a high mechanical dyssynchrony and predicts a strong CRT response,
- [0024] and optionally regions of the left ventricular wall mass performing negative work (LVNW) before therapy indicate an electromechanical dyssynchrony, and larger regions indicate more severe dyssynchrony and greater potential for benefit of CRT,
- [0025] and optionally values for LVNW below about 0.15 indicate low mechanical dyssynchrony and predict a weak CRT response,
- [0026] and optionally values for LVNW from between about 0.15 to 0.20 indicate moderate electromechanical dyssynchrony and predict a moderate CRT response,
- [0027] and optionally values for LVNW exceeding about 0.20 indicate a high electromechanical mechanical dyssynchrony and predict a strong CRT response,
- [0028] and optionally metrics for work heterogeneity can be used as a decision tool for choosing the correct intervention techniques for patients with DHF, where patients having high work heterogeneity, optionally $\text{COVW} > 1.5$ $\text{LVNW} > 0.20$ $\text{STNW} > 0.25$ at baseline are ideal candidates for CRT,
- [0029] and optionally CRT may not be effective in patients with low baseline work heterogeneity, optionally $\text{COVW} < 1.25$, $\text{LVNW} < 0.15$ $\text{STNW} < 0.15$,
- [0030] and optionally values for Δ STNW ranging from between about 0 to 0.06 predict a low improvement and therefore a weak CRT response,
- [0031] and optionally Δ STNW values from between about 0.06 to 0.12 indicate a moderate improvement and predict a moderate CRT response,
- [0032] and optionally Δ STNW value reductions of between about 0.12-0.18 indicate a high improvement and predict a strong CRT response.
- [0033] Any of these indices can be used as addition information aiding the clinical decision for the intervention technique. Based on the diagnostic embodiment, this exemplary method, or model, of the invention can aid in the decision as to whether or not a candidate would likely benefit from undergoing an ICD implantation procedure to apply CRT. Optimal CRT settings would reduce these quantities as closely as possible to zero.
- [0034] In alternative embodiments, methods of the invention for computing the decrease in measures of the heterogeneity of regional work density can predict optimal therapeutic settings such as pacing lead locations and ventricle-to-ventricle (VV) delay times by simulating various settings and finding those settings that reduce the COVW, LVNW, STNW or other measures of the heterogeneity of RDMW to minimum values.
- [0035] In alternative embodiments, provided are diagnostic tools or methods, including computer implemented methods, for predicting and/or optimizing the response of patients with dyssynchronous heart failure (DHF) to cardiac resynchronization therapy (CRT), comprising:
- [0036] (a) measuring or determining indices derived from the regional distribution of myocardial external work density (RDMW) prior to treatment,
- [0037] wherein optionally the indices measured or determined are selected from the group consisting of:
- [0038] (i) the fraction of ventricular wall mass or volume, or a part thereof, optionally left ventricle (LV), right ventricle (RV), or septum, performing negative work (myocardial negative work density fraction, or MNWF), optionally having work done on it by the surrounding heart wall,
- [0039] (ii) regions of the left ventricular wall mass performing negative work (LVNW),
- [0040] (iii) the coefficient of variation of external work density (COVW) or other measures of work dispersion or heterogeneity, optionally to predict amount of electromechanical dyssynchrony or the likely improvement in CRT response,
- [0041] (iv) the fraction of the septal wall performing negative work (change in STNW or Δ STNW), wherein a decrease in the fraction of the septal wall performing negative work (Δ STNW) computed after simulated CRT is a predictor of pump function improvement and CRT response, and
- [0042] (v) a combination thereof,
- [0043] and
- [0044] (b) computing the change in these indices of work heterogeneity following the simulated application of CRT in a computational model,
- [0045] wherein optionally change in these indices of work heterogeneity comprise:
- [0046] (i) a decrease in the fraction of myocardium (or LV, RV, or septal myocardium) performing negative work (MNWF) of about 0.1 or greater; or
- [0047] (ii) a decrease in the coefficient of variation of external work density (COVW) of about 0.5 or greater,

[0048] wherein optionally a computed decrease in the fraction of the septum performing negative work correlates strongly with a positive response to therapy and an observed reduction in end-systolic volume, optionally approximately 3 to 6 months after CRT,

[0049] wherein this correlation is based on the fact that higher values of the change correlate (with a correlation coefficient r^2 greater than 0.7) with better reductions in end-systolic relations; and lower values imply or predict less improvement, and these relations also show that a decrease of greater than 0.6 predicts a significant clinical improvement,

[0050] and optionally a value for COVW prior to therapy ranging from between about 1.0 to 1.25, indicates a low electromechanical dyssynchrony and predicts a weak CRT response,

[0051] and optionally values in the range of between about 1.25 to 1.50 indicate a moderate electromechanical dyssynchrony and predicts a moderate CRT response,

[0052] and optionally a value for COVW exceeding about 1.5 indicates a high mechanical dyssynchrony and predicts a strong CRT response,

[0053] and optionally regions of the left ventricular wall mass performing negative work (LVNW) before therapy indicate an electromechanical dyssynchrony, and larger regions indicate more severe dyssynchrony and greater potential for benefit of CRT,

[0054] and optionally values for LVNW below about 0.15 indicate low mechanical dyssynchrony and predict a weak CRT response,

[0055] and optionally values for LVNW from between about 0.15 to 0.20 indicate moderate electromechanical dyssynchrony and predict a moderate CRT response,

[0056] and optionally values for LVNW exceeding about 0.20 indicate a high electromechanical mechanical dyssynchrony and predict a strong CRT response,

[0057] and optionally metrics for work heterogeneity can be used as a decision tool for choosing the correct intervention techniques for patients with DHF, where patients having high work heterogeneity (optionally COVW>1.5, LVNW>0.20 SNW>0.25 at baseline are ideal candidates for CRT,

[0058] and optionally CRT may not be effective in patients with low baseline work heterogeneity (optionally COVW<1.25, LVNW<0.15, STNW<0.15,

[0059] and optionally values for Δ STNW ranging from between about 0 to 0.06 predict a low improvement and therefore a weak CRT response,

[0060] and optionally Δ STNW values from between about 0.06 to 0.12 indicate a moderate improvement and predict a moderate CRT response,

[0061] and optionally Δ STNW value reductions of between about 0.12-0.18 indicate a high improvement and predict a strong CRT response.

[0062] An optimization protocol seeks pacing conditions including pacing lead locations and/or VV delays that reduce the magnitude of one or any combination of the measures of regional heterogeneity of myocardial work density to as close as possible to zero.

[0063] In alternative embodiments, provided are diagnostic tools or methods, including computer implemented methods, for improving and/or optimizing the response of patients with dyssynchronous heart failure (DHF) to cardiac resynchronization therapy (CRT), comprising:

[0064] (a) measuring or determining indices derived from the regional distribution of myocardial external work density (RDMW) prior to treatment,

[0065] wherein optionally the indices measured or determined are selected from the group consisting of:

[0066] (i) the fraction of ventricular myocardium, or a part thereof, optionally left ventricle (LV), right ventricle (RV), or septum, performing negative work (myocardial negative work density fraction, or MNWF), optionally having work done on it by the surrounding heart wall,

[0067] (ii) the coefficient of variation of external work density (COVW) or other measures of work dispersion or heterogeneity, optionally comprising the standard deviation, quartiles or extrema of the regional work distributions,

[0068] (iii) and a combination thereof,

[0069] and

[0070] (b) computing the change in these indices of work heterogeneity under varied therapeutic conditions, optionally comprising varied pacing lead locations and varied VV delay times between stimulation of left and right ventricular pacing electrodes,

[0071] wherein optionally:

[0072] (i) a decrease of at least 0.06 for STNW and/or 0.1 for LVNW in the fraction of myocardium (or LV, RV, or septal myocardium) performing negative work (MNWF) in response to various numbers and locations of pacing leads or various different delay times between stimulation of different pacing allows assessment of which therapeutic parameters (e.g., what numbers and locations of pacing leads or what different delay times between stimulation of different pacing sites) will result in the greatest decrease in absolute MNWF; or

[0073] (ii) a decrease of at least 0.5 in the coefficient of variation of external work density (COVW) in response to various numbers and locations of pacing leads or various different delay times between stimulation of different pacing allows assessment of which therapeutic parameters (e.g., what numbers and locations of pacing leads or what different delay times between stimulation of different pacing sites) will result in the greatest decrease in absolute COVW,

[0074] wherein optionally the computed decrease in the fraction of the septum performing negative work correlates strongly, or $r^2>0.7$, with a positive response to therapy and observed reduction in end-systolic volume about 3 to 6 months after CRT,

[0075] wherein optionally an alteration of pacing lead locations and delay times significantly effects the predicted decrease in work heterogeneity indices,

[0076] and optionally, for an optimal response to therapy, vary the VV delay of the simulated CRT in the model until one or any combination of the indices COVW, LVNW or STNW is reduced to the lowest absolute value, realizing that as delays are varied too much the heart could be made dyssynchronous in the opposite direction, which would not be beneficial.

[0077] In alternative embodiments, provided are computer program products for processing data, the computer program product comprising: computer-executable logic or algorithms contained on (optionally embedded or non-transitory on) a computer-readable medium and configured for causing

the following computer-executed step to occur: at least one method, or computer-implemented method, of the invention.

[0078] In alternative embodiments, provided are computer systems comprising a processor and a data storage device wherein said data storage device has stored thereon: a computer program product for implementing a computer-implemented method of the invention, wherein optionally the computer-executable logic or algorithms for executing the computer-implemented methods are embedded or are non-transitory on the computer system.

[0079] In alternative embodiments, provided are Graphical User Interface (GUI) computer program products comprising: a computer program product for implementing a computer-implemented method of the invention, wherein optionally the computer-executable logic or algorithms for executing the computer-implemented method are embedded or are non-transitory on the GUI computer program product.

[0080] In alternative embodiments, provided are computer systems comprising a processor and a data storage device wherein said data storage device has stored thereon: (a) a computer program product for implementing a computer-implemented method of the invention; (b) a computer program product for processing data generated by a method of the invention; (c) a Graphical User Interface (GUI) computer program product of the invention; or, (d) a combination thereof.

[0081] In alternative embodiments, provided are non-transitory memory media comprising program instructions for running, processing and/or implementing: (a) a computer program product for implementing a computer-implemented method of the invention; (b) a computer program product for processing data generated by a method of the invention; (c) a Graphical User Interface (GUI) computer program product of the invention; (d) a computer system of the invention, or (e) a combination thereof.

[0082] In alternative embodiments, provided are computer-readable storage media comprising a set of or a plurality of computer-readable instructions that, when executed by a processor of a computing device, cause the computing device to run, process and/or implement: (a) a computer program product for implementing a computer-implemented method of the invention; (b) a computer program product for processing data generated by a method of the invention; (c) a Graphical User Interface (GUI) computer program product of the invention; (d) a computer system of the invention, (e) a non-transitory memory medium of the invention, or (f) a combination thereof.

[0083] In alternative embodiments, provided are computer program products comprising: a computer-readable storage medium; and program instructions residing in said storage medium which, when executed by a computer, run, process and/or implement: (a) a computer program product for implementing a computer-implemented method of the invention; (b) a computer program product for processing data generated by a method of the invention; (c) a Graphical User Interface (GUI) computer program product of the invention; (d) a computer system of the invention, (e) a non-transitory memory medium of the invention; (f) a computer-readable storage medium of the invention, or (g) a combination thereof.

[0084] In alternative embodiments, provided are computer program storage devices, embodied on a tangible computer readable medium, comprising: (a) a computer program product for implementing a computer-implemented method of the

invention; (b) a computer program product for processing data generated by a method of the invention; (c) a Graphical User Interface (GUI) computer program product of the invention; (d) a computer system of the invention, (e) a non-transitory memory medium of the invention; (f) a computer-readable storage medium of the invention; (g) a computer program product of the invention; or (h) a combination thereof.

[0085] In alternative embodiments, provided are computer or equivalent electronic systems, comprising: a memory; and a processor operatively coupled to the memory, the processor adapted to execute program code stored in the memory to: run, process and/or implement: (a) a computer program product for implementing a computer-implemented method of the invention; (b) a computer program product for processing data generated by a method of the invention; (c) a Graphical User Interface (GUI) computer program product of the invention; (d) a computer system of the invention, (e) a non-transitory memory medium of the invention; (f) a computer-readable storage medium of the invention; (g) a computer program product of the invention; (h) a computer program storage device of the invention; or (i) a combination thereof.

[0086] In alternative embodiments, provided are products of manufacture, medical devices, pacemakers, or biventricular pacemakers, comprising, or having embedded or non-transiently contained therein: (a) a computer program product for implementing a computer-implemented method of the invention; (b) a computer program product for processing data generated by a method of the invention; (c) a Graphical User Interface (GUI) computer program product of the invention; (d) a computer system of the invention, (e) a non-transitory memory medium of the invention; (f) a computer-readable storage medium of the invention; (g) a computer program product of the invention; (h) a computer program storage device of the invention; or (i) a combination thereof.

[0087] In alternative embodiments, the products of manufacture, medical devices, pacemakers or biventricular pacemakers of the invention are manufactured or configured as a programmable implantable cardioverter-defibrillator (ICD) or CRT-D including a defibrillator in case defibrillation is needed, an implantable defibrillator, a dual-chamber defibrillator or a single-chamber defibrillator, or a CRT-P where there is no defibrillator but the CRT-P has a pacing system alone without the defibrillator.

[0088] In alternative embodiments, the products of manufacture, medical devices, pacemakers or biventricular pacemakers of the invention further comprises a computer, or a minicomputer, or circuitry comprising or have embedded or intransiently configured therein: (a) a computer program product for implementing a computer-implemented method of the invention; (b) a computer program product for processing data generated by a method of the invention; (c) a Graphical User Interface (GUI) computer program product of the invention; (d) a computer system of the invention, (e) a non-transitory memory medium of the invention; (f) a computer-readable storage medium of the invention; (g) a computer program product of the invention; (h) a computer program storage device of the invention; or (i) a combination thereof.

[0089] In alternative embodiments, provided are products of manufacture, medical devices, pacemakers or biventricular pacemakers manufactured or configured as comprising a remote communication device for remotely and operably interacting with: (a) a computer program product for implementing a computer-implemented method of the invention;

(b) a computer program product for processing data generated by a method of the invention; (c) a Graphical User Interface (GUI) computer program product of the invention; (d) a computer system of the invention, (e) a non-transitory memory medium of the invention; (f) a computer-readable storage medium of the invention; (g) a computer program product of the invention; (h) a computer program storage device of the invention; or (i) a combination thereof, wherein optionally the remote communication is by internet or telephone. In alternative embodiments, the products of manufacture, medical devices, pacemakers or biventricular pacemakers are manufactured or configured as a programmable implantable cardioverter-defibrillator (ICD) or CRT-D including a defibrillator in case defibrillation is needed, an implantable defibrillator, a dual-chamber defibrillator or a single-chamber defibrillator, or a CRT-P where there is no defibrillator but the CRT-P has a pacing system alone without the defibrillator.

[0090] In alternative embodiments, provided are systems or methods comprising:

[0091] (1) a product of manufacture, medical device, or biventricular pacemaker, and

[0092] (2) (a) a computer program product for implementing a computer-implemented method of the invention; (b) a computer program product for processing data generated by a method of the invention; (c) a Graphical User Interface (GUI) computer program product of the invention; (d) a computer system of the invention, (e) a non-transitory memory medium of the invention; (f) a computer-readable storage medium of the invention; (g) a computer program product of the invention; (h) a computer program storage device of the invention; or (i) a combination thereof, wherein the product of manufacture, medical device, or biventricular pacemaker is manufactured or configured as comprising a remote communication device for remotely operably interacting with any one or several elements of (2), wherein optionally the remote communication is by internet or telephone or equivalent electronic device.

[0093] In alternative embodiments, provided are compositions, medical devices or products of manufacture, systems and methods for predicting the response of patients with dyssynchronous heart failure to cardiac re-synchronization therapy (CRT), comprising: (a) measuring or determining the fraction of the LV/septum performing negative work (LVNW); and, (b) measuring or determining the coefficient of variation of external work density (COVW), wherein the LVNW fraction performing negative work and coefficient of variation COVW (sd/mean) correlated strongly with observed reduction in end-systolic volume after CRT.

[0094] In alternative embodiments, provided are computer-implemented methods for predicting the response of patients with dyssynchronous heart failure to cardiac re-synchronization therapy (CRT), comprising: (a) measuring or determining the fraction of the LV/septum performing negative work (LVNW); and (b) measuring or determining the coefficient of variation of external work density (COVW), wherein the LVNW fraction performing negative work and coefficient of variation COVW (sd/mean) correlated strongly with observed reduction in end-systolic volume after CRT.

[0095] In alternative embodiments, provided are computer program products for processing data, the computer program product comprising: computer-executable logic and/or algorithms contained on a computer-readable medium and con-

figured for causing the following computer-executed step to occur: for executing the computer-implemented method of the invention.

[0096] In alternative embodiments, provided are computer systems comprising a processor and a data storage device wherein said data storage device has stored thereon: a computer program product for implementing a computer-implemented method of the invention.

[0097] In alternative embodiments, provided are products of manufacture, or a medical device, or a biventricular pacemaker, comprising elements for carrying out or executing the computer-implemented method of the invention, including embedded or non-transitory memory medium, or embedded or non-transitory computer program products, of the invention for executing the computer-implemented method.

[0098] In alternative embodiments, provided are uses of a product of manufacture, or a medical device, or a biventricular pacemaker for carrying out or executing the computer-implemented method of the invention.

[0099] The details of one or more embodiments of the invention are set forth in the accompanying drawings and the description below. Other features, objects, and advantages of the invention will be apparent from the description and drawings, and from the claims.

[0100] All publications, patents, patent applications cited herein are hereby expressly incorporated by reference for all purposes.

BRIEF DESCRIPTION OF THE DRAWINGS

[0101] The drawings set forth herein are illustrative of embodiments of the invention and are not meant to limit the scope of the invention as encompassed by the claims.

[0102] FIG. 1 graphically illustrates data of: ES volume reduction as % ESV (FIG. 1A) and ejection fraction improvement (FIG. 1B), where patients are classified as responders or non-responders based on echocardiographic measures of cardiac function 3 to 6 months after a CRT procedure; as discussed in detail in Example 1, below.

[0103] FIG. 2 graphically illustrates measures of LV mechanical function: FIG. 2(A) measures ES volume reduction as % ESV as a function of LV end diastolic pressure; FIG. 2(B) measures ES volume reduction as % ESV as a function of dp/dt_{max} ; FIG. 2(C) measures ES volume reduction as % ESV as a function of QRS duration; FIG. 2(D) measures ES volume reduction as % ESV as a function of end diastolic volume; as discussed in detail in Example 1, below.

[0104] FIG. 3 schematically illustrates different components of an exemplary patient-specific electromechanics model, or method (including a computer-implemented method, of the invention; as discussed in detail in Example 1, below.

[0105] FIG. 4 schematically illustrates: images of CT image slices FIG. 4(A) that were segmented and the resulting data points are used to fit the surfaces of the geometric ventricular model, as illustrated in FIG. 4(B); and patient-specific hexahedral finite element mesh, as illustrated in FIG. 4(C), is constructed from the surfaces for different patients, as illustrated in FIG. 4(D); as discussed in detail in Example 1, below.

[0106] FIG. 5 schematically illustrates reconstructed diffusion tensors in the explanted donor heart, as illustrated in FIG. 5(A), fitted to the geometric model, as illustrated in FIG. 5(B); as discussed in detail in Example 1, below.

[0107] FIG. 6 schematically illustrates how the voxel intensities of the MIBI scan were reconstructed in 3D space, as illustrated in FIG. 6(A), and aligned to the anatomical model, as illustrated in FIG. 6(B); as discussed in detail in Example 1, below.

[0108] FIG. 7 schematically illustrates electroanatomic activation time data, as illustrated in FIG. 7(A), projected onto the LV surface of the finite element mesh and rendered as a field, as illustrated in FIG. 7(B), and aligned to an anatomical model, as illustrated in FIG. 7(C); as discussed in detail in Example 1, below.

[0109] FIGS. 8 and 9 graphically illustrate a comparison of global and local cardiac function: FIG. 8 illustrates simulated and measured LV and RV pressure and PV loops, with FIG. 8A measuring pressure as a function of time; and FIG. 8B measuring pressure as a function of volume; and, FIG. 9 illustrates radial displacement between end-diastole and end-systole from the measured and simulated geometries, with FIG. 9A measuring (measured and simulated) radial displacement as a function of the left ventricular region; and FIG. 9B graphically and as a table displays the data of FIG. 9A; as discussed in detail in Example 1, below.

[0110] FIG. 10 schematically illustrates a comparison of ventricular geometry of the simulated heart overlaid on the clinical echocardiographic images of the same heart at end-diastole, as illustrated in FIG. 10(A), and end-systole, as illustrated in FIG. 10(B); as discussed in detail in Example 1, below.

[0111] FIG. 11 schematically illustrates stress-strain loops used to compute regional work density; the schematic demonstrates that the septal region performs minimal or negative work in patients who responded better to CRT; FIG. 11(A) illustrates RV free wall stress-strain loops; FIG. 11(B) illustrates septum stress-strain loops; FIG. 11(C) illustrates anterior-posterior and LV free wall stress-strain loops; as discussed in detail in Example 1, below.

[0112] FIG. 12 illustrates mean external work density and LV fraction performing negative work can be used to classify echocardiographic responders; where FIG. 12(A) graphically illustrates the measurement of mean external work density in responders, echocardiographic non-responders and clinical non-responders; and FIG. 12(B) graphically illustrates the measurement of LV fraction performing negative work in the same patient samples as FIG. 12(A); as discussed in detail in Example 1, below.

[0113] FIG. 13 illustrates receiver-operator characteristic (ROC) curves for using negative LV and septal work as classifiers of echocardiographic response to CRT; where FIG. 13(A) graphically illustrates data measuring true positive rate and a function of false positive rate of negative LV work (at 1.00) and negative septal work (at 1.00); and FIG. 13(B) graphically illustrates data measuring true positive rate and a function of false positive rate of negative LV work (at 0.84) and negative septal work (at 0.81); as discussed in detail in Example 1, below.

[0114] FIG. 14 graphically illustrates both coefficient of variation of external work density, as illustrated in FIG. 14(A), and fraction of LV performing negative work, as illustrated in FIG. 14(B); where FIG. 14(A) measures ES volume reduction as a function of COV work; and FIG. 14B measures ES volume reduction as a function of LV fraction performing negative work); as discussed in detail in Example 1, below.

[0115] FIG. 15 illustrates results of using exemplary patient-specific (PS) computational models of the invention:

as schematically illustrated in FIG. 15A, spatial distribution of myocardial work density was computed from baseline models; and as graphically illustrated in FIG. 15B, two measures of the distribution, LV fraction performing negative work and coefficient of variation (sd/mean) correlated strongly with observed reduction in end-systolic volume after CRT, respectively; as discussed in detail in Example 1, below.

[0116] Like reference symbols in the various drawings indicate like elements.

[0117] Reference will now be made in detail to various exemplary embodiments of the invention, examples of which are illustrated in the accompanying drawings. The following detailed description is provided to give the reader a better understanding of certain details of aspects and embodiments of the invention, and should not be interpreted as a limitation on the scope of the invention.

DETAILED DESCRIPTION

[0118] In alternative embodiments, provided are compositions, medical devices or products of manufacture, systems, diagnostic tools, and methods (including computer implemented methods) for assessing the severity of dyssynchronous heart failure, for identifying the clinical candidates best indicated for CRT or other therapy intended to reduce dyssynchrony, and for optimizing outcomes of therapy including by identifying most effective pacing protocols or electrode locations for a specific patient. In alternative embodiments, the compositions, medical devices or products of manufacture, systems and methods (including computer implemented methods) of the invention are used to assess the severity of or predict the response of patients with DHF to CRT by using a patient-specific computational model.

[0119] In alternative embodiments, the compositions, medical devices or products of manufacture, systems, diagnostic tools, and methods (including computer implemented methods) of the invention are used to predict the response of patients with DHF to CRT or other therapy using a patient-specific computational model to compute biomarkers by using indices derived from the regional distribution of myocardial external work density RDMW, for example, by using the fraction of the whole myocardium, the LV free wall or the septum performing negative work (MNV) or the coefficient of variation of external work density (COVW) using patient data obtained before therapy, or other properties of the regional distribution of myocardial work, stress, or strain or their changes as predicted by the computer model simulating CRT or pacemaker or other therapy.

[0120] In alternative embodiments, by using these biomarkers, methods of this invention can be significantly better than existing predictors of the response to CRT as measured by the reduction in end-systolic left ventricular volume three to six months after pacemaker implantation, and methods of this invention can more accurately discriminate clinical responders from non-responders. Since about 30% to 50% of CRT candidates are non-responders to therapy, the methods of the invention can identify best clinical candidates for CRT and help optimize outcomes of CRT by varying pacing protocols and electrode locations.

[0121] In alternative embodiments, provided are methods (including computer-implemented methods) for constructing patient-specific electromechanical finite-element models of the cardiovascular system, and methods for estimating their parameters from clinically available measurements made

before the CRT procedure. In alternative embodiments, methods of the invention comprise:

- [0122] Constructing patient-specific finite-element meshes from patient cardiac images;
- [0123] Incorporating measurements of human ventricular myofiber architecture;
- [0124] Estimating the cardiac electrical activation parameters using patient body surface or heart surface electrical recordings and using these for three-dimensional simulations of cardiac electrical activation patterns;
- [0125] Estimating patient-specific resting myocardial material properties using hemodynamic and cardiac functional measurements by adjusting parameters of the resting myocardial constitutive model to achieve normalized pressure-volume relations consistent with human measurements, such as those described by Klotz et al., 2006, *American Journal of Physiology-Heart and Circulatory Physiology*, 291:H403-H12;
- [0126] Computing patient-specific model of unloaded ventricular geometry using a dual or inverse method such as that described by Krishnamurthy et al., 2013 (2013) *J. Comput. Physics* 244:4-21;
- [0127] Estimating or optimizing parameters of cardiac muscle contraction using patient-specific measurements of cardiac performance such as ventricular pressures and volume changes from cardiac catheterization, non-invasive blood pressure measurement, echocardiography or other clinical methods.
- [0128] Estimating parameters of a close-loop model of the circulation using hemodynamic and cardiac functional measurements from cardiac catheterization, echocardiography, non-invasive blood pressure measurement or other methods together with an optimization or adaptation scheme, such as the CircAdapt model of the cardiovascular system, as described e.g., by Arts et al, *American Journal of Physiology—Heart and Circulatory Physiology*, 288 (4) (2005), p. H1943, and coupling the finite element biventricular model to circulation model using methods algorithms, e.g., such as those described by Kerckhoffs et al, (2007) *Ann Biomed Eng* 35:1-18;
- [0129] Computing specific results derived from the cardiac model analysis of the patient before treatment that serve as diagnostic indicators of the functional severity of cardiac dyssynchrony or as predictive biomarkers of response to a therapy such as CRT.
- [0130] These exemplary models of the invention have been validated by comparing the pressure time course from cardiac catheterization and regional displacements from echocardiography with patient-specific model computations.
- [0131] In alternative embodiments, provided are compositions, medical devices or products of manufacture, systems, diagnostic tools, and methods (including computer-implemented methods) to generate the stress-strain values and loops at different regions of the left ventricle to compute the external work density of different regions in the myocardium. In alternative embodiments, using this distribution of fiber or myocardial work density, the fraction of the LV or the septum performing negative work, the COVW, or other measure of the distribution, is computed as a biomarker for the regional mechanical heterogeneity. This biomarker is then used to assess the severity of dyssynchrony, to classify whether a patient will be a responder or a non-responder, or to predict

the improvement in ventricular function resulting from therapy. In addition, in alternative embodiments, the relative magnitude of this biomarker predicts the degree of left ventricular reverse remodeling as measured by end-systolic volume reduction.

[0132] In alternative embodiments, provided are compositions, medical devices or products of manufacture, systems, diagnostic tools, and methods (including computer-implemented methods) to simulate the CRT procedure to predict differential responses to different CRT pacing lead sites, as well as timing parameters and protocols.

[0133] The efficacy of the invention has been validated in eight patients with DHF. The work heterogeneity metrics were all able to discriminate the non-responders based on end-systolic volume reduction, as illustrated in FIG. 14. In addition, the area under the receiver-operator characteristic (ROC) curves for these metrics for identifying the responders from the non-responders using different echocardiographic measures of response were all greater than 0.8, as illustrated in FIG. 13.

[0134] In alternative embodiments, devices, appliances and products of manufacture of the invention, or any components thereof, are scaled to different proportional dimensions to accommodate the differing patients of all ages and physical dimensions. In alternative embodiments, devices, appliances and products of manufacture of the invention, or any components thereof, can be designed to have optimum dimensional relationships, to include variations in size, materials, shape, form, function and manner of operation, assembly and use, as are deemed readily apparent to one skilled in the art, and all equivalent relationships to those illustrated in the drawings and described in the specification are intended to be encompassed by the present inventive subject matter.

Computer Systems and Data Storage Devices

[0135] In alternative embodiments, computer-implemented methods of the invention, in whole or in part, will implement, or require the implementation of, using a machine, a computer, a computer system or equivalents, within which a set of instructions for causing the computer, computer system or machine to perform any one or more of the protocols or methodologies of the invention may be executed. In alternative embodiments, the machine may be connected (e.g., networked) to other machines, e.g., in a Local Area Network (LAN), an intranet, an extranet, or the Internet, or any equivalents thereof. The machine may operate in the capacity of a server or a client machine in a client-server network environment, or as a peer machine in a peer-to-peer (or distributed) network environment. The machine may be a personal computer (PC), a tablet PC, a set-top box (STB), a Personal Digital Assistant (PDA), a cellular telephone, a web appliance, a server, a network router, switch or bridge, or any machine capable of executing a set of instructions (sequential or otherwise) that specify actions to be taken by that machine. The term “machine” shall also be taken to include any collection of machines, computers or products of manufacture that individually or jointly execute a set (or multiple sets) of instructions to perform any one or more of the methodologies of the invention.

[0136] In alternative embodiments, an exemplary computer system of the invention comprises a processing device (processor), a main memory (e.g., read-only memory (ROM), flash memory, dynamic random access memory (DRAM) such as synchronous DRAM (SDRAM) or Rambus DRAM

(RDRAM), etc.), a static memory (e.g., flash memory, static random access memory (SRAM), etc.), and a data storage device, which communicate with each other via a bus.

[0137] In alternative embodiments, a processor represents one or more general-purpose processing devices such as a microprocessor, central processing unit, or the like. More particularly, the processor may be a complex instruction set computing (CISC) microprocessor, reduced instruction set computing (RISC) microprocessor, very long instruction word (VLIW) microprocessor, or a processor implementing other instruction sets or processors implementing a combination of instruction sets. The processor may also be one or more special-purpose processing devices such as an application specific integrated circuit (ASIC), a field programmable gate array (FPGA), a digital signal processor (DSP), network processor, or the like. In alternative embodiments the processor is configured to execute the instructions (e.g., processing logic) for performing the operations and steps discussed herein.

[0138] In alternative embodiments the computer system further comprises a network interface device. The computer system also may include a video display unit (e.g., a liquid crystal display (LCD) or a cathode ray tube (CRT)), an alphanumeric input device (e.g., a keyboard), a cursor control device (e.g., a mouse), and a signal generation device (e.g., a speaker).

[0139] In alternative embodiments, the data storage device (e.g., drive unit) comprises a computer-readable storage medium on which is stored one or more sets of instructions (e.g., software) embodying any one or more of the protocols, methodologies or functions of this invention. The instructions may also reside, completely or at least partially, within the main memory and/or within the processor during execution thereof by the computer system, the main memory and the processor also constituting machine-accessible storage media. The instructions may further be transmitted or received over a network via the network interface device.

[0140] In alternative embodiments the computer-readable storage medium is used to store data structure sets that define user identifying states and user preferences that define user profiles. Data structure sets and user profiles may also be stored in other sections of computer system, such as static memory.

[0141] In alternative embodiments, while the computer-readable storage medium in an exemplary embodiment is a single medium, the term “machine-accessible storage medium” can be taken to include a single medium or multiple media (e.g., a centralized or distributed database, and/or associated caches and servers) that store the one or more sets of instructions. In alternative embodiments the term “machine-accessible storage medium” can also be taken to include any medium that is capable of storing, encoding or carrying a set of instructions for execution by the machine and that cause the machine to perform any one or more of the methodologies of the present invention. In alternative embodiments the term “machine-accessible storage medium” shall accordingly be taken to include, but not be limited to, solid-state memories, and optical and magnetic media.

[0142] Those of skill in the art would understand that information and signals may be represented using any of a variety of different technologies and techniques. For example, data, instructions, commands, information, signals, bits, symbols, and chips that may be referenced throughout the above description may be represented by voltages, currents, elec-

tromagnetic waves, magnetic fields or particles, optical fields or particles, or any combination thereof.

[0143] Those of skill would further appreciate that the various illustrative logical blocks, modules, circuits, and algorithm steps described in connection with the embodiments disclosed herein may be implemented as electronic hardware, computer software, or combinations of both. To clearly illustrate this interchangeability of hardware and software, various illustrative components, blocks, modules, circuits, and steps have been described above generally in terms of their functionality. Whether such functionality is implemented as hardware or software depends upon the particular application and design constraints imposed on the overall system. Skilled artisans may implement the described functionality in varying ways for each particular application, but such implementation decisions should not be interpreted as causing a departure from the scope of the present invention.

[0144] The following examples, and the figures, are intended to clarify the invention, and to demonstrate and further illustrate certain preferred embodiments and aspects without restricting the subject of the invention to the examples and figures.

EXAMPLES

Example 1

Exemplary Methods and Products of Manufacture

[0145] The following example describes exemplary methods and devices of the invention.

[0146] We developed patient-specific (PS) computational models of 8 male patients aged >60 years with NYHA class III heart failure, ejection fraction <33%, left bundle branch block with QRS duration >120 ms, mitral regurgitation >10 ml (in 3 patients), and myocardial infarction (in 5 patients). Bi-ventricular geometry segmented from end-diastolic cardiac CT images, hemodynamic measurements from cardiac catheterization, electrophysiological measurements from ECG and electroanatomic mapping were used to construct detailed PS finite-element models of ventricular electromechanics coupled to a closed-loop circulation model. Spatial distribution of myocardial work density computed from baseline models (as illustrated in FIG. 11) varied significantly between patients (mean 0.7-5.3, sd 1.0-6.5 kJ/m³). Two measures of the distribution, LV fraction performing negative work and coefficient of variation (sd/mean) correlated strongly with observed reduction in end-systolic volume after CRT ($R^2=0.85$, 0.80 respectively; as illustrated in FIG. 14). Clinical indices based on model-computed strains such as internal stretch fraction (ISF) and circumferential uniformity ratio estimate (CURE) as well as the measured QRS duration did not correlate as well (ISF 0.15; CURE 0.23; QRS 0.22) possibly due to infarction.

[0147] In conclusion, functional improvement following CRT is greatest in patients with the largest region of LV performing negative work before treatment.

[0148] Echocardiographic Response:

[0149] Patients classified as responders/non-responders based on changes in cardiac function 3-6 months after CRT procedure measured using echocardiography: >10% reduction in end-systolic volume; >5% absolute change in ejection fraction.

[0150] FIG. 1 graphically illustrates data of: ES volume reduction as % ESV (FIG. 1A) and ejection fraction improve-

ment (FIG. 1B), where patients are classified as responders or non-responders based on echocardiographic measures of cardiac function 3 to 6 months after the CRT procedure. Baseline measures of mechanical and electrical function do not correlate well with functional improvement after CRT procedure. [0151] FIG. 2 graphically illustrates measures of LV mechanical function, such as: end-diastolic pressure, as illustrated in FIG. 2(A), and the maximum rate of change of left ventricular pressure (dp/dt), as illustrated in FIG. 2(B), do not correlate with end-systolic volume reduction after CRT. The QRS duration, as illustrated in FIG. 2(C), and the echocardiographic measure of dilatation, as illustrated in FIG. 2(D), also do not correlate with functional improvement after CRT.

Construction of Comprehensive Patient-Specific Model:

[0152] FIG. 3 illustrates different components of an exemplary patient-specific electromechanics model, or method (including a computer-implemented method, of the invention, including use of clinical data, a cardiovascular model and non-clinical data.

[0153] Bi-Ventricular Geometry:

[0154] FIG. 4 illustrates images of CT image slices FIG. 4(A) that were segmented and the resulting data points are used to fit the surfaces of the geometric ventricular model, as illustrated in FIG. 4(B). Patient-specific hexahedral finite element mesh, as illustrated in FIG. 4(C), is constructed from the surfaces for different patients, as illustrated in FIG. 4(D).

[0155] Myofiber Architecture:

[0156] FIG. 5 illustrates reconstructed diffusion tensors in the explanted donor heart, as illustrated in FIG. 5(A), fitted to the geometric model, as illustrated in FIG. 5(B).

[0157] Scar Region:

[0158] FIG. 6 illustrates how the voxel intensities of the MIBI (methoxy-isobutyl-isonitrile) scan were reconstructed in 3D space, as illustrated in FIG. 6(A), and aligned to the anatomical model, as illustrated in FIG. 6(B); a scalar field was fitted to define the region of the scar.

[0159] Activation Time:

[0160] FIG. 7 illustrates electroanatomic activation time data, as illustrated in FIG. 7(A), projected onto the LV surface of the finite element mesh and rendered as a field, as illustrated in FIG. 7(B), and aligned to an anatomical model, as illustrated in FIG. 7(C). This figure illustrates that output of an electrophysiology simulation can generate myocardial activation times.

[0161] Comparison of Global and Local Cardiac Function:

[0162] Model generated pressures and stroke volumes match measured data;

[0163] Radial displacement of different segments of the LV match with displacements measured using echocardiographic images

[0164] FIG. 8 illustrates simulated and measured LV and RV pressure and PV loops, with FIG. 8A measuring pressure as a function of time; and FIG. 8B measuring pressure as a function of volume.

[0165] FIG. 9 illustrates radial displacement between end-diastole and end-systole from the measured and simulated geometries, with FIG. 9A measuring (measured and simulated) radial displacement as a function of the left ventricular region; and FIG. 9B graphically and as a table displays the data of FIG. 9A.

[0166] FIG. 10 illustrates a comparison of ventricular geometry of the simulated heart (brown), overlaid on the

clinical echocardiographic images of the same heart at end-diastole, as illustrated in FIG. 10(A), and end-systole, as illustrated in FIG. 10(A).

[0167] Regional Stress-Strain Work Loops:

[0168] FIG. 11 illustrates stress-strain loops used to compute regional work density; the schematic demonstrates that the septal region performs minimal or negative work in patients who responded better to CRT; FIG. 11(A) illustrates RV free wall stress-strain loops; FIG. 11(B) illustrates septum stress-strain loops; FIG. 11(C) illustrates anterior-posterior and LV free wall stress-strain loops.

[0169] Distribution of External Work Density:

[0170] FIG. 12 illustrates mean external work density and LV fraction performing negative work can be used to classify echocardiographic responders; where FIG. 12(A) graphically illustrates the measurement of mean external work density in responders, echocardiographic non-responders and clinical non-responders; and FIG. 12(B) graphically illustrates the measurement of LV fraction performing negative work in the same patient samples as FIG. 12(A).

[0171] Classification of Echocardiographic Response:

[0172] FIG. 13 illustrates receiver-operator characteristic (ROC) curves for using negative LV and septal work as classifiers of echocardiographic response to CRT; the echocardiographic response is classified using 10% reduction in end-systolic volume, as illustrated in FIG. 13(A), or 5% absolute increase in ejection fraction, as illustrated in FIG. 13(B); where FIG. 13(A) graphically illustrates data measuring true positive rate and a function of false positive rate of negative LV work (at 1.00) and negative septal work (at 1.00); and FIG. 13(B) graphically illustrates data measuring true positive rate and a function of false positive rate of negative LV work (at 0.84) and negative septal work (at 0.81).

[0173] Biomarkers for Reverse Remodeling:

[0174] FIG. 14 illustrates that both coefficient of variation of external work density, as illustrated in FIG. 14(A), and fraction of LV performing negative work, as illustrated in FIG. 14(B), can predict quantitative measures of left-ventricular reverse remodeling; this is a strong indication that these abnormally enlarged hearts have decreased in size with prolonged application of CRT, i.e., a successful therapy.

[0175] Comprehensive Patient-Specific Computational Models:

[0176] We have demonstrated the viability of creating detailed patient-specific models to perform electromechanics simulations in DHF patients; models which are capable of realistically replicating patient-specific global and regional cardiac functions as well as local left ventricular wall displacements.

[0177] Classification Based on Echocardiographic Response to CRT:

[0178] Regional work heterogeneity can be used as a sensitive indicator of mechanical dyssynchrony. Fraction of the myocardium performing negative work can be used as a metric of regional work heterogeneity; negative work locations in the left ventricle can further be localized to the septal region in DHF patients; fraction of the LV and septum performing negative work can be used as classifiers to distinguish between echocardiographic responders and non-responders with high accuracy (area under ROC curves >0.8).

[0179] Prediction of Reverse Remodeling:

[0180] Functional improvement following CRT is greatest in patients with the largest region of LV performing negative work; and Left ventricular negative work fraction can quan-

titatively predict echocardiographic measures of left ventricular reverse remodeling in DHF patients.

[0181] In alternative embodiment, exemplary computational patient-specific models of the invention for cardiovascular systems are used to measure model-derived metrics that can better predict CRT response. For example, in one exemplary computational patient-specific models of the invention: in DHF patients, functional improvements in response to CRT are greater in subjects with higher baseline heterogeneity of regional work.

[0182] To demonstrate, we developed multi-scale, patient-specific, computational, cardiovascular models that can replicate baseline cardiac function in DHF patients. These exemplary comprehensive finite-element models of the invention take into account detailed patient measurements (such as bi-ventricular geometry, myofiber architecture, cardiac pressures, infarct/scar location, etc.) and replicate both global and local baseline cardiac function. We tested this hypothesis in ten DHF patients (8 with follow-up) who are part of an ongoing CRT study at the VA Hospital, San Diego. We have identified with high correlation that functional improvement following CRT is greatest in patients with the largest region of the left ventricle or septum performing negative work.

[0183] This exemplary patient-specific electromechanical model computes the myocardial external work density regional distribution in the ventricle. It has been shown that the degree of mechanical dyssynchrony as measured by indices derived from the regional work distribution correlate with the degree of echocardiographic CRT response (FIG. 14). The myocardial external work density regional distribution is calculated from the model as:

$$W = \oint_{\text{cardiac cycle}} \sum_{i=1}^3 \sum_{j=1}^3 \sigma_{ij} d\epsilon_{ij}$$

[0184] in general, or specifically in these results by the equation:

$$W = \oint_{\text{cardiac cycle}} \sigma_{ff} d\epsilon_{ff} + \oint_{\text{cardiac cycle}} \sigma_{cc} d\epsilon_{cc} + \oint_{\text{cardiac cycle}} \sigma_{ss} d\epsilon_{ss}$$

[0185] where sigma and epsilon are Cauchy stress and natural strain in the fiber direction (f), cross-fiber direction (c), and the direction perpendicular to the former two (s). Examples of indices derived from the regional work distribution compute the distribution heterogeneity and total cardiac cycle work.

[0186] In this exemplary patient-specific electromechanical model, the coefficient of variation of work (COVW) is a measure of the heterogeneity of the myocardial external work density distribution, and COVW is computed as:

$$COVW = \frac{W_{\sigma}}{W_{\pi}}$$

[0187] High COVW indicates increased mechanical dyssynchrony. Values for COVW range from 1.0-1.25 for low mechanical dyssynchrony (weak CRT response), 1.25-1.50 for moderate mechanical dyssynchrony (moderate CRT response), and 1.5-1.7 for high mechanical dyssynchrony (strong CRT responders) at baseline (FIG. 14 A).

[0188] A local negative value of total cardiac cycle work is a direct measure of local lost pump efficiency. The fraction of the left ventricular mass performing negative work (LVNW) at baseline is indicative of the existing severity of mechanical dyssynchrony. Values for LVNW approximately range from

0.1-0.15 for low mechanical dyssynchrony (weak CRT response), 0.15-0.20 for moderate mechanical dyssynchrony (moderate CRT response), and 0.2-0.25 for high mechanical dyssynchrony (strong CRT response) at baseline (FIG. 14 B).

[0189] A causal mechanism of CRT is the recruitment of septal myocardial regions which had originally performed negative work at baseline to perform positive work. The change (positive reduction) in the fraction of septum performing negative work (ASTNW) after CRT is a direct measure of pump function improvement and correlates with positive CRT response. Values for Δ STNW approximately range from 0 to 0.06 for low improvement (weak CRT response), 0.06 to 0.12 for moderate improvement (moderate CRT response), and 0.12 to 0.18 for high improvement (strong CRT response) (FIG. 14 C).

Four Categories of Model Clinical Utility

[0190] In alternative embodiments, the clinical utility of patient-specific electromechanical models of the invention are comprised of four main categories:

[0191] 1. Diagnostic support

[0192] Work heterogeneity metrics can be used as supporting diagnostic measure that can supplement existing diagnostics (such as QRS duration >120 ms, electrocardiographic features, low dp/dt) to characterize dyssynchronous heart failure (DHF). Patients with high work heterogeneity can be classified separately from patients with low work heterogeneity. This can help the clinicians in deciding on the appropriate therapeutic response to different DHF patients by estimating the severity of the existing heart failure using COVW and LVNW.

[0193] 2. Clinical decision support

[0194] The metrics for work heterogeneity can be used as a decision tool for choosing the correct intervention techniques for patients with DHF. Patients having high work heterogeneity (COVW>1.4, LVNW>16%, SNW>25%) at baseline are ideal candidates for CRT. Similarly, CRT may not be effective in patients with low baseline work heterogeneity (COVW<1.2, LVNW<12%, SNW<15%). This can be used as additional information aiding the clinical decision for the intervention technique. Based on the diagnostic, the model may aid in the decision as to whether or not a candidate would likely benefit from undergoing an ICD implantation procedure to apply CRT.

[0195] 3. Clinical optimization

[0196] Modeling the response to different parameters of the CRT intervention helps in optimizing the intervention procedure for a particular patient. Therapeutic parameters and protocols include but are not limited to optimal lead placement and the relative timing of lead stimulus application. Therapeutic outcomes may be predicted by simulation before implantation to estimate the best possible CRT response, as computed by mechanical dyssynchrony indices such as Δ STNW.

[0197] 4. Follow-up

[0198] Work heterogeneity metrics can be used as follow-up diagnostic measures to assess the success or failure of CRT in a particular patient. A successful CRT procedure may only reduce the end-systolic volume but may also reduce the work heterogeneity. In alternative embodiments, the reduction in work heterogeneity is

- computed immediately after the procedure, thus providing a faster assessment of the therapy.
- [0199] FIG. 3 (addendum) summarizes the clinical data, registration methods, and model components.
- [0200] In alternative embodiments, models for designing methods of the invention are constructed from patient clinical data. The clinical data included:
- [0201] Digital images of cardiac and thoracic anatomy
- [0202] Computed tomography images, magnetic resonance images, diffusion tensor magnetic resonance images, transthoracic echocardiographic images
- [0203] Ventricular cavity pressures
- [0204] Intracardiac catheterization
- [0205] Electrical activation pattern
- [0206] Electrocardiograms, electroanatomic mapping.
- [0207] In alternative embodiments, the four main components of exemplary patient-specific computer cardiovascular models or methods of the invention are: the anatomy (Anatomic Model), electrophysiology (Electrophysiology Model), biomechanics (Passive Material Model, Active Contraction Model), and hemodynamics (Hemodynamics model) (FIG. 3).
- [0208] General methods to register the clinical data to the model subcomponents are listed next to the category name in parenthesis, below. Examples of particular methods that can be used to practice the methods of this invention are described, e.g., in Aguado-Sierra et al., 2011; Krishnamurthy et al., 2012; Villongco et al., 2014, see below.
- [0209] Anatomical Model
- [0210] Model left and right ventricular geometry from patient cardiac images from MRI, CT, echocardiography or other imaging modalities (Image segmentation and mesh fitting or mesh generation)
- [0211] Incorporate ventricular muscle fiber architecture using human data from cadaver hearts or other sources (Fiber angle or tensor field fitting, Large deformation diffeomorphic mapping to map fibers to patient-specific geometry)
- [0212] Model shape and location of myocardial infarcts or ischemic zones from MIBI-SPECT, Gd delayed-enhancement MRI or other clinical data (image segmentation and fitting of patient-specific infarct or ischemic zone geometry). The myocardial infarct or ischemic region is modeled as a region of altered mechanical and electrical properties based on physical alterations associated with ischemia or infarction.
- [0213] Electrophysiology model
- [0214] Use an ionic model of the human ventricular action potential adjusted for changes associated with heart failure
- [0215] Model electrical conduction by identifying electrical stimulus location(s) and regional myocardial electrical conductivities of bulk left and right ventricular myocardium, left and right ventricular endocardium, infarct or ischemic tissue making use of patient electrophysiology recordings such as 12-lead ECG (Electrical model parameter optimization to match predicted and measured ECG, VCG or electrical recordings)
- [0216] Solve for three-dimensional action potential wave propagation to obtain three-dimensional distri-

bution of regional electrical activation times used to trigger mechanical contraction model

- [0217] Biomechanics model
- [0218] Identify patient-specific resting myocardial mechanical properties making use of measured or estimated diastolic ventricular pressures and volumes. Match model passive pressure-volume relation to human measurements, for example, to the normalized relation observed by Klotz et al, *Am J Physiol*, 2006. Solve for unloaded ventricular geometry making use of measured geometry (typically at end-diastole), known or estimated left ventricular end-diastolic pressure and volume, and a dual or inverse solution (e.g. as given by Krishnamurthy et al., *J Comp Phys*, 2013)
- [0219] Identify patient-specific active contractile myocardial properties such as peak systolic stiffness, rate of tension development and rate of diastolic tension decline making use of estimated or recorded ventricular and/or arterial blood pressures, and systolic ventricular volume changed. Adjust these parameters or solve for them using numerical optimization methods to minimize the differences between measured and computed ventricular systolic pressures and volume changes.
- [0220] Hemodynamics model
- [0221] Formulate and parameterize a closed loop circulation model and identify parameters to match patient measurements of arterial pressure waveforms.
- [0222] Make use of measured patient recordings including mitral and aortic valve dimensions and mitral regurgitant volume from echocardiography. Solve a numerical optimization or use an adaptive model such as CircAdapt (Arts et al., *Am J Physiol*, 2005).
- [0223] Integrated model
- [0224] Couple hemodynamic model to ventricular mechanics model using the algorithm of Kerchoffs et al. (*Ann Biomed Eng*, 2007).
- [0225] Couple electrical model top biomechanical model by using electrical depolarization times as times for initiation of systolic tension development, or use a fully coupled electromechanical model in which the ionic model includes intracellular calcium transients and a model of myofilament activation to tension development.
- [0226] Use model to solve for distributions of regional wall motions, pressures, stress and strain throughout the cardiac cycle. Integrate stress strain loops to obtain regional myocardial work density distributions. Derive from distributions predictive indices of heterogeneity including COVW, fraction of myocardium performing negative work or fraction of septum performing negative work (i.e. regions having work performed on them by surrounding regions).
- [0227] Use the model to simulate possible therapeutic interventions such as cardiac resynchronization using biventricular pacing. Specify pacing lead locations or VV delay times between lead stimuli and adjust these to maximize the decrease in measures of regional myocardial work density heterogeneity, e.g. to eliminate all negative work regions and to reduce the magnitude of work heterogeneity as much as possible.

REFERENCES

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- [0229] 2. Kerckhoffs, R. C., et al. (2010). Ventricular dilation and electrical dyssynchrony synergistically increase regional mechanical non-uniformity but not mechanical dyssynchrony a computational model. *Circulation: Heart Failure*, 3(4), 528-536.
- [0230] 3. Krishnamurthy, A., et al. (2013). Patient-specific models of cardiac biomechanics. *Journal of computational physics*, 244, 4-21.
- [0231] 4. Strauss, D. G., et al. (2011). Defining left bundle branch block in the era of cardiac resynchronization therapy. *The American journal of cardiology*, 107(6), 927-934.
- [0232] 5. Villongco, C. T. et al. (2014). Patient-specific modeling of ventricular activation pattern using surface ECG-derived vector-cardiogram in bundle branch block. *Progress in biophysics and molecular biology*.
- [0233] A number of embodiments of the invention have been described. Nevertheless, it will be understood that various modifications may be made without departing from the spirit and scope of the invention. Accordingly, other embodiments are within the scope of the following claims.

1. A method comprising:

predicting and optimizing the response of patients with dyssynchronous heart failure (DHF) to cardiac resynchronization therapy (CRT), and/or

diagnosing dyssynchronous heart failure or the degree of dyssynchrony in dyssynchronous heart failure, comprising:

measuring or determining indices derived from the regional distribution of myocardial external work density (RDMW) prior to treatment as a diagnostic assessment of the severity of dyssynchronous heart failure or the adverse impact of dyssynchrony on ventricular mechanical performance, wherein the indices measured or determined are selected from the group consisting of:

- (i) the fraction of ventricular wall mass or volume, or a part thereof, left ventricle (LV), right ventricle (RV), or septum, performing negative work (myocardial negative work density fraction, or MNWF), having work done on it by the surrounding heart wall,
- (ii) regions of the left ventricular wall mass performing negative work (LVNW),
- (iii) the coefficient of variation of external work density (COVW) or other measures of work dispersion or heterogeneity, to predict amount of electromechanical dyssynchrony or the likely improvement in CRT response,
- (iv) the fraction of the septal wall performing negative work, wherein a decrease in the fraction of the septal wall performing negative work computed after simulated CRT is a predictor of pump function improvement and CRT response, and
- (v) a combination thereof.

2. A method for predicting and/or optimizing the response of patients with dyssynchronous heart failure (DHF) to cardiac resynchronization therapy (CRT), comprising:

measuring or determining indices derived from the regional distribution of myocardial external work density (RDMW) prior to treatment,

wherein the indices measured or determined are selected from the group consisting of:

- (i) the fraction of ventricular wall mass or volume, or a part thereof, left ventricle (LV), right ventricle (RV), or septum, performing negative work (myocardial negative work density fraction, or MNWF), having work done on it by the surrounding heart wall,
- (ii) regions of the left ventricular wall mass performing negative work (LVNW),
- (iii) the coefficient of variation of external work density (COVW) or other measures of work dispersion or heterogeneity, optionally to predict amount of electromechanical dyssynchrony or the likely improvement in CRT response,
- (iv) the fraction of the septal wall performing negative, wherein a decrease in the fraction of the septal wall performing negative work computed after simulated CRT is a predictor of pump function improvement and CRT response, and
- (v) a combination thereof and;

computing the change in these indices of work heterogeneity following the simulated application of CRT in a computational model.

3. A method for improving and/or optimizing the response of patients with dyssynchronous heart failure (DHF) to cardiac resynchronization therapy (CRT), comprising:

measuring or determining indices derived from the regional distribution of myocardial external work density (RDMW) prior to treatment,

wherein the indices measured or determined are selected from the group consisting of:

- (i) the fraction of ventricular myocardium, or a part thereof, left ventricle (LV), right ventricle (RV), or septum, performing negative work (myocardial negative work density fraction, or MNWF), having work done on it by the surrounding heart wall,
- (ii) the coefficient of variation of external work density (COVW) or other measures of work dispersion or heterogeneity, comprising the standard deviation, quartiles or extrema of the regional work distributions,
- (iii) and a combination thereof; and

computing the change in these indices of work heterogeneity under varied therapeutic conditions, comprising varied pacing lead locations and varied delay times between stimulation of left and right ventricular pacing electrodes.

- 4. (canceled)
- 5. (canceled)
- 6. (canceled)
- 7. (canceled)
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- 13. (canceled)
- 14. (canceled)
- 15. (canceled)
- 16. (canceled)
- 17. (canceled)

18. (canceled)

19. The method of claim 1 further comprising:

predicting the potential response of patients with dyssynchronous heart failure (DHF) to cardiac resynchronization therapy (CRT) by at least predicting a reduction in end-systolic ventricular volume due to CRT by at least using the myocardial negative work density fraction and/or coefficient of variation of regional work density COVW or other measures of the heterogeneity or dispersion of RDMW, with greater values of heterogeneity corresponding to greater potential benefit of therapies that act to decrease dyssynchrony.

* * * * *

专利名称(译)	用于诊断心力衰竭和用于患者特异性建模以预测心脏再同步化疗法的结果的组合物，装置和方法		
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摘要(译)

在替代实施例中，提供了组合物，医疗设备或制造的产品，系统，诊断工具和方法，包括计算机实现的方法，用于预测患者dyssynchronous心脏10衰竭（DHF）心脏再同步化治疗（CRT）的反应，包括：测量或确定的LV/隔膜进行负功（MNW）的分数；并测量或确定外功密度（COVW），其中MNW分数进行消极的工作和变化COVW（SD/平均值）的系数在CRT后收缩末期容积减少观察密切相关的变异系数。

Fig. 1

- Patients classified as responders/non-responders based on changes in cardiac function 3-6 months after CRT procedure measured using echocardiography
 - >10% reduction in end-systolic volume
 - >5% absolute change in ejection fraction

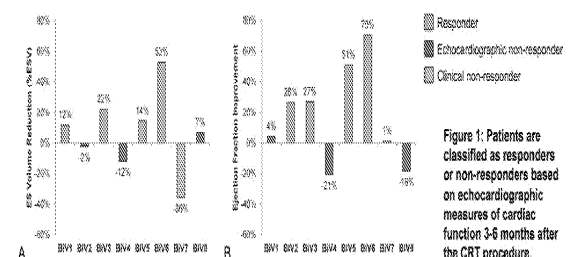


Figure 1: Patients are classified as responders or non-responders based on echocardiographic measures of cardiac function 3-6 months after the CRT procedure.