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(54) **METHOD AND ALGORITHM FOR DEFINING THE PATHOLOGIC STATE FROM A PLURALITY OF INTRINSICALLY AND EXTRINSICALLY DERIVED SIGNALS**

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(57) **ABSTRACT**

The present invention describes methods and algorithms for processing a plurality of clinically relevant signals/data/genotypes intrinsic to a given patient and/or signals/data derived from external diagnostic equipment. The intrinsic signals can be acquired from device-based sensors and analogous extrinsic data can be obtained from imaging equipment. These signals/data are input into software algorithms that use digital signal processing in order to output informational data sets of clinical and technical relevance after comparisons are made to patients with access to this technology whose outcome under varying treatments is known. This data is used to define prognosis, guide clinical decision-making, make treatment suggestions, and direct programming of cardiac devices. Evaluation of an implanted device using such technology will confirm appropriately programmed settings within such a device. Application of these methodologies and algorithms to analyze signals obtained by an implanted device allows for closed loop programming of such a device based on multiple parameters using digital signal processing. These technologies will also allow for open connectivity between external imaging equipment and implanted devices as to derive a plethora of diagnostic and prognostic information. Comparisons of large data sets of intrinsically and extrinsically derived parameters are used to develop a translation function that relates device based indices to analogous, conventional indices that are currently state of the art. Multiple indices reflecting a plurality of diagnostic information are input into such software algorithms (intrinsically and/or extrinsically derived) in order to generate prognostic information and present therapeutic options based on evidence based medicine.

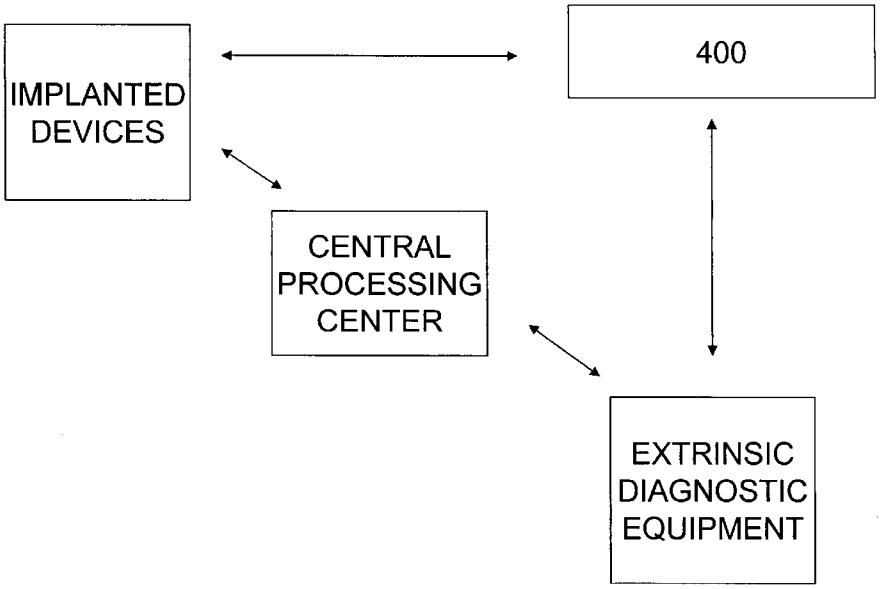
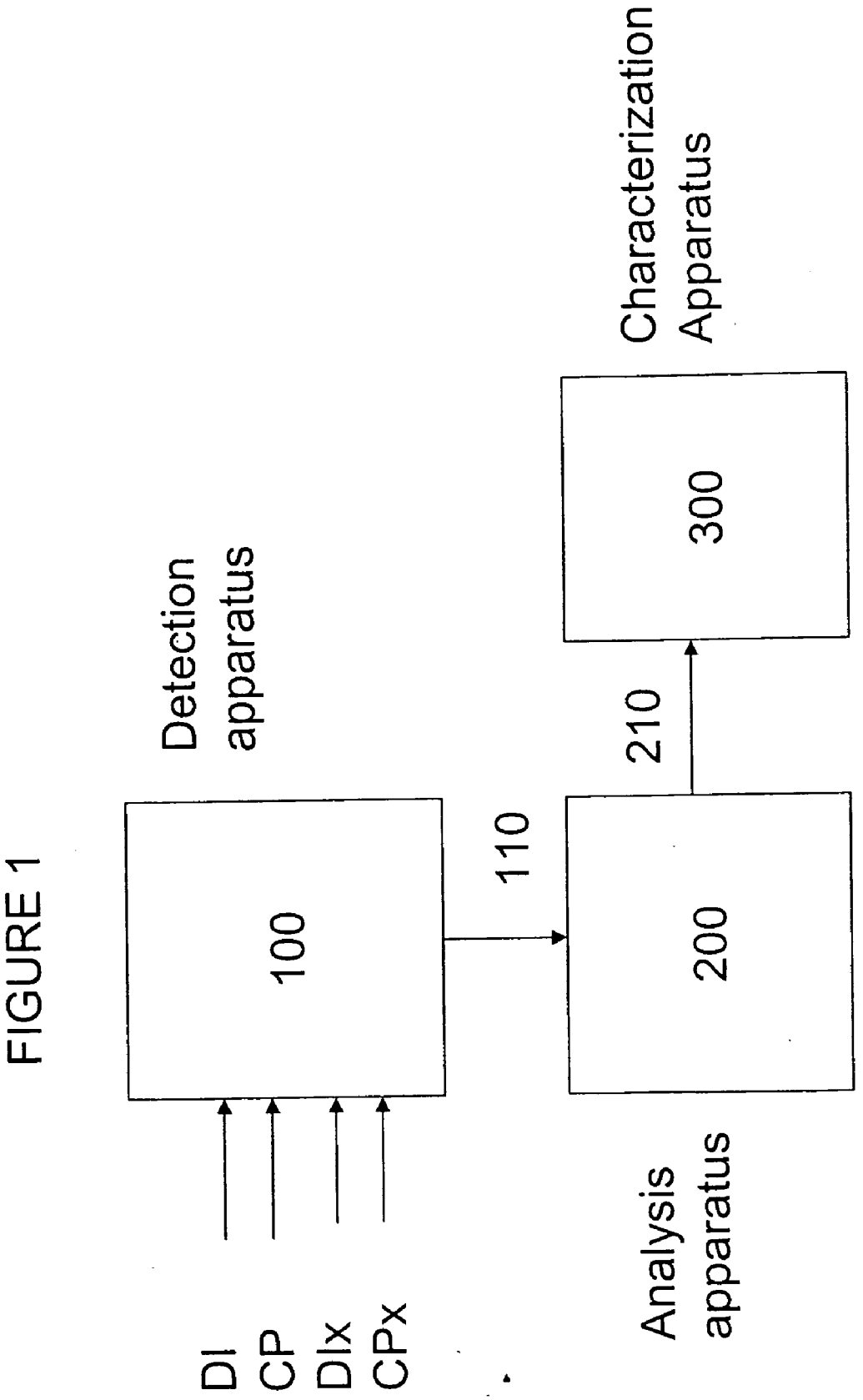


FIGURE 1


Detection apparatus
100
110
Analysis apparatus
200
210
Characterization Apparatus
300
DI
CP
DIx
CPx

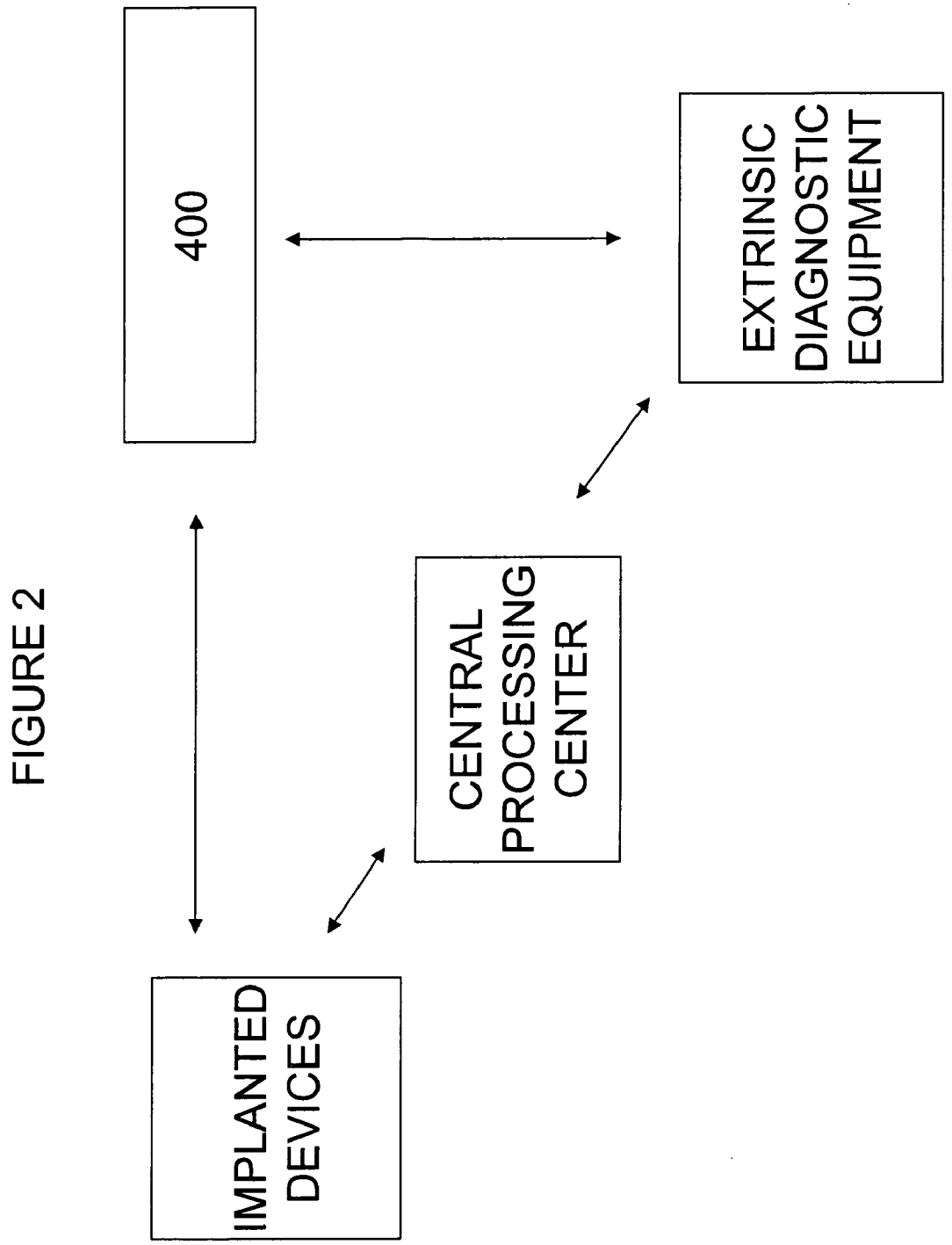

400
EXTRINSIC DIAGNOSTIC EQUIPMENT
CENTRAL PROCESSING CENTER
IMPLANTED DEVICES

FIGURE 2

FIGURE 2a

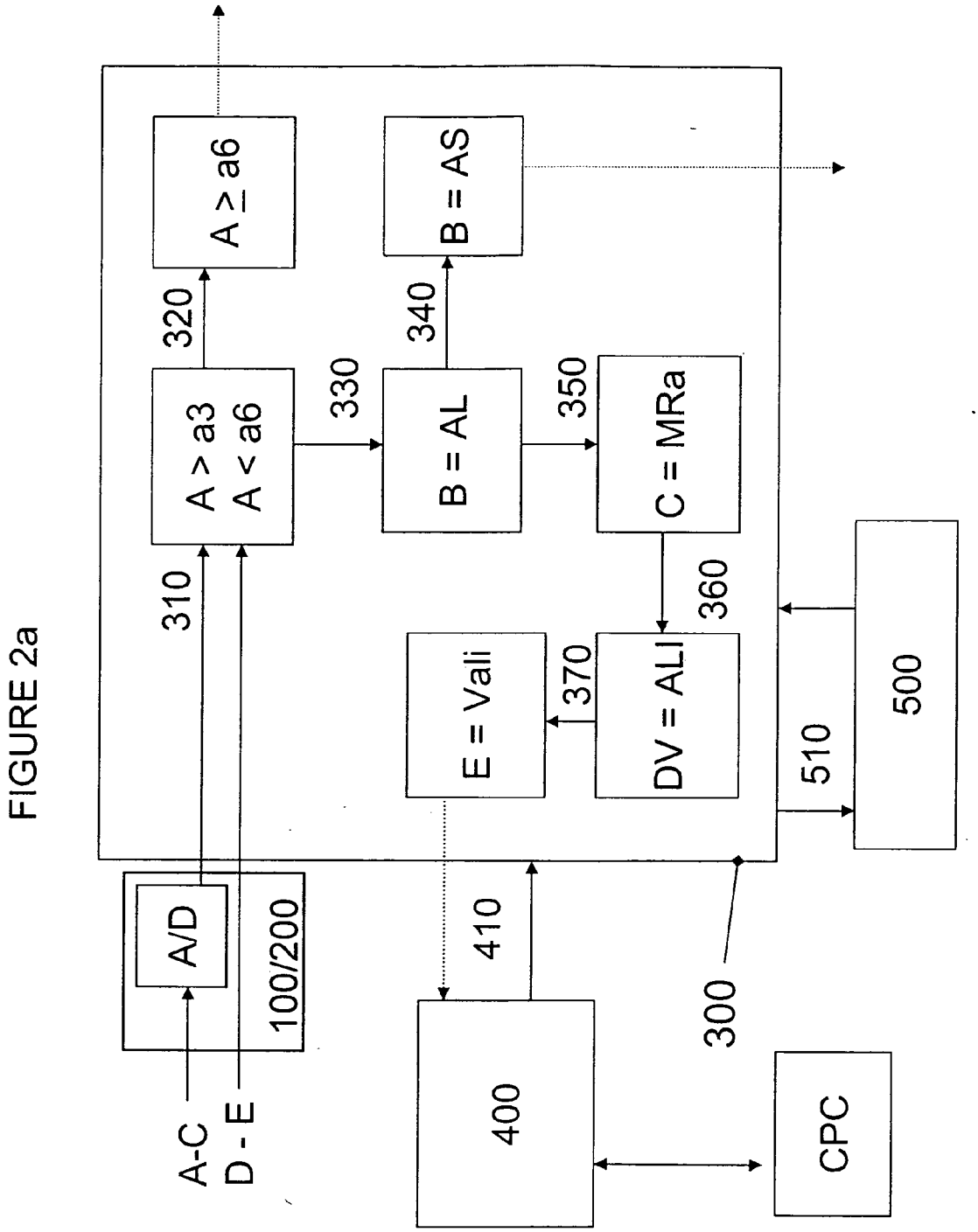

A ≥ a6
B = AS
320
340
A > a3
A < a6
330
B = AL
350
C = MRa
310
360
E = Vali
370
DV = ALI
500
510
A/D
100/200
410
300
A-C
D - E
400
CPC

Figure 3A
CARDIAC PERFORMANCE

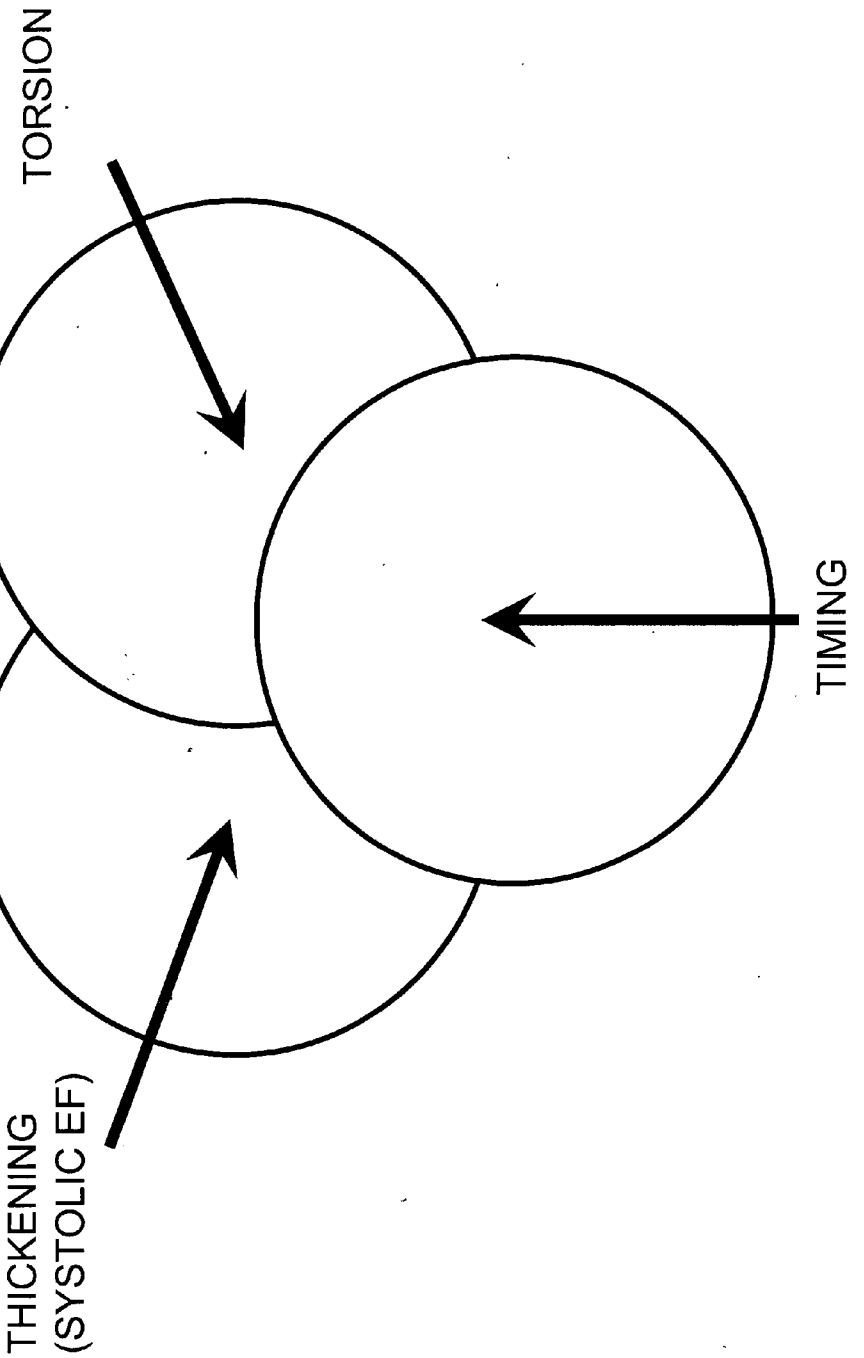
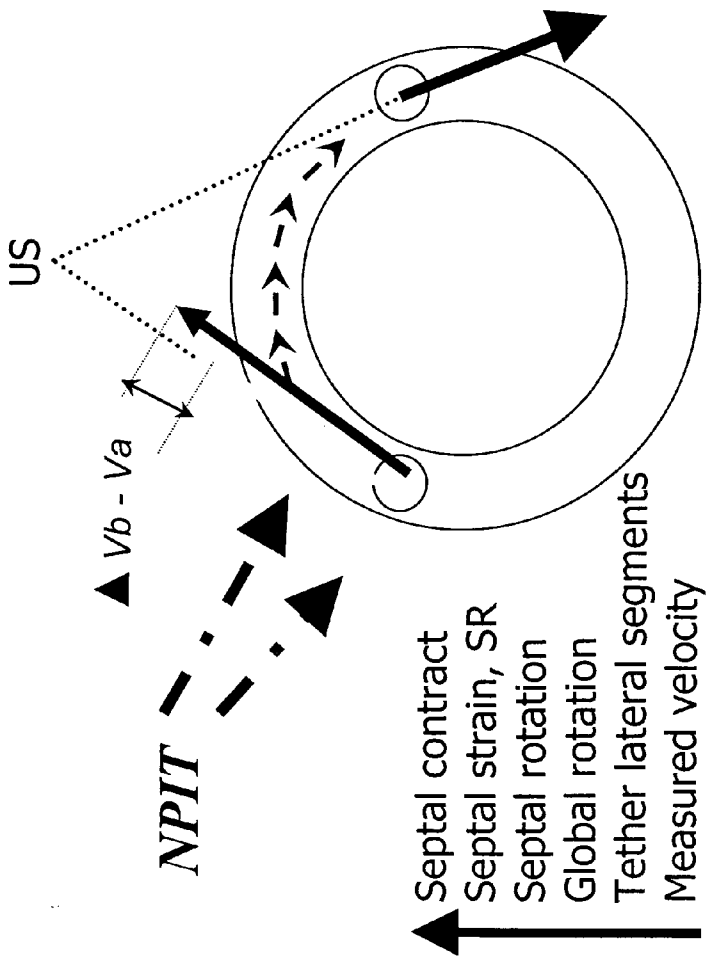


Figure 3B: GLOBAL TETHERING and CARDIAC PERFORMANCE



Strain & SR septum > lateral wall: remove spatial gradient velocity
True Rotational Velocity septal & lateral wall increase similarly

FIGURE 4

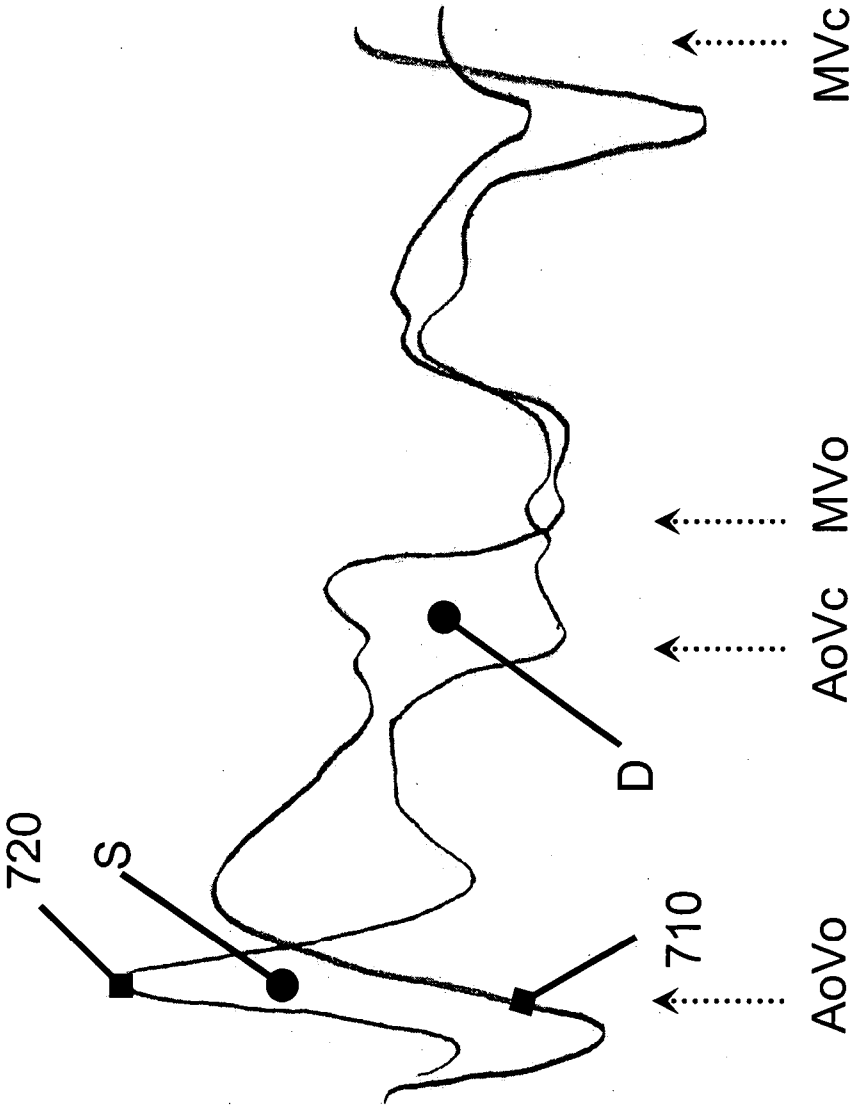


FIGURE 5

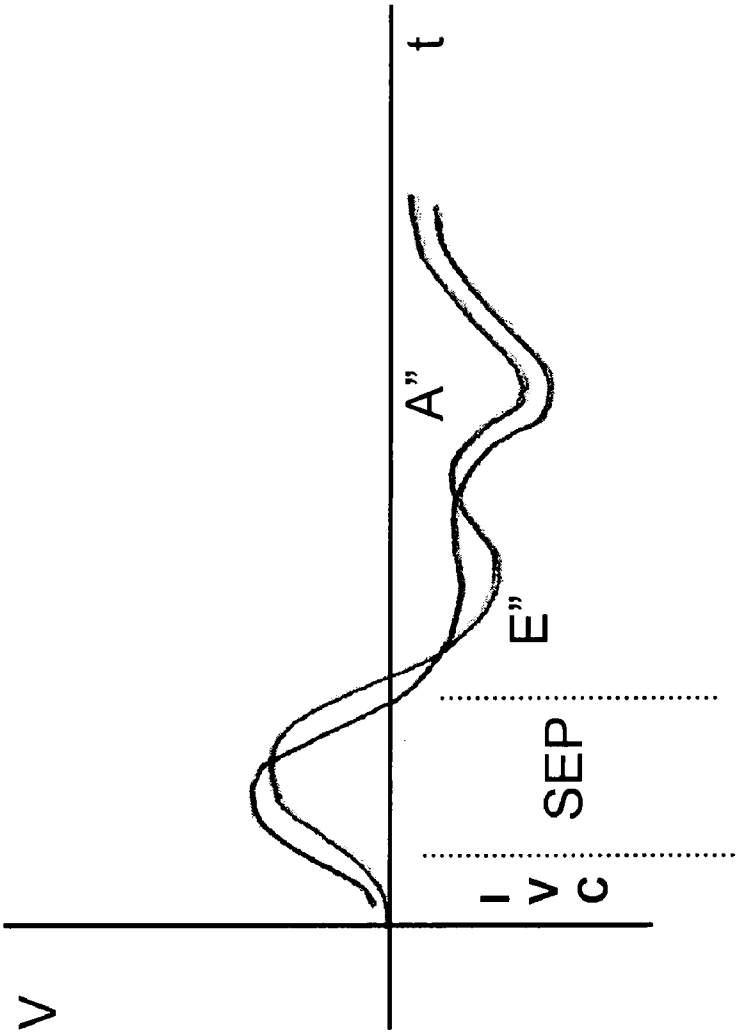


FIGURE 6

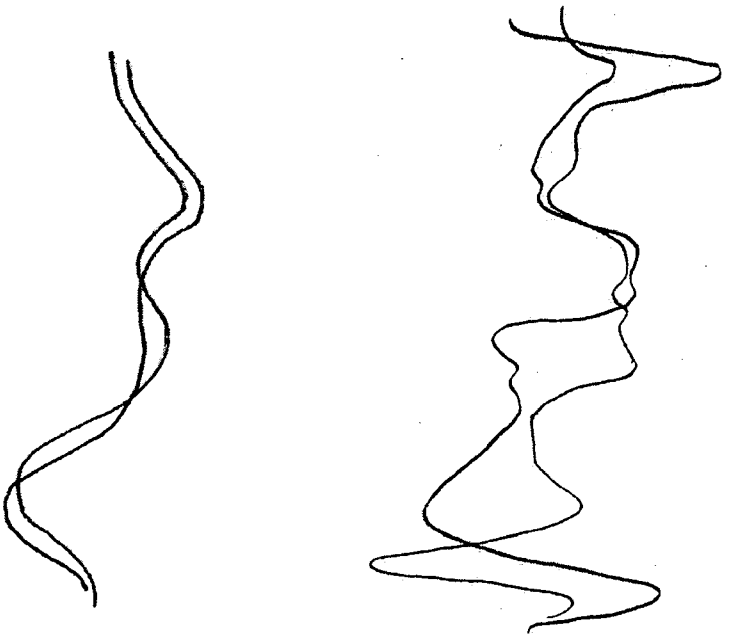


FIGURE 7

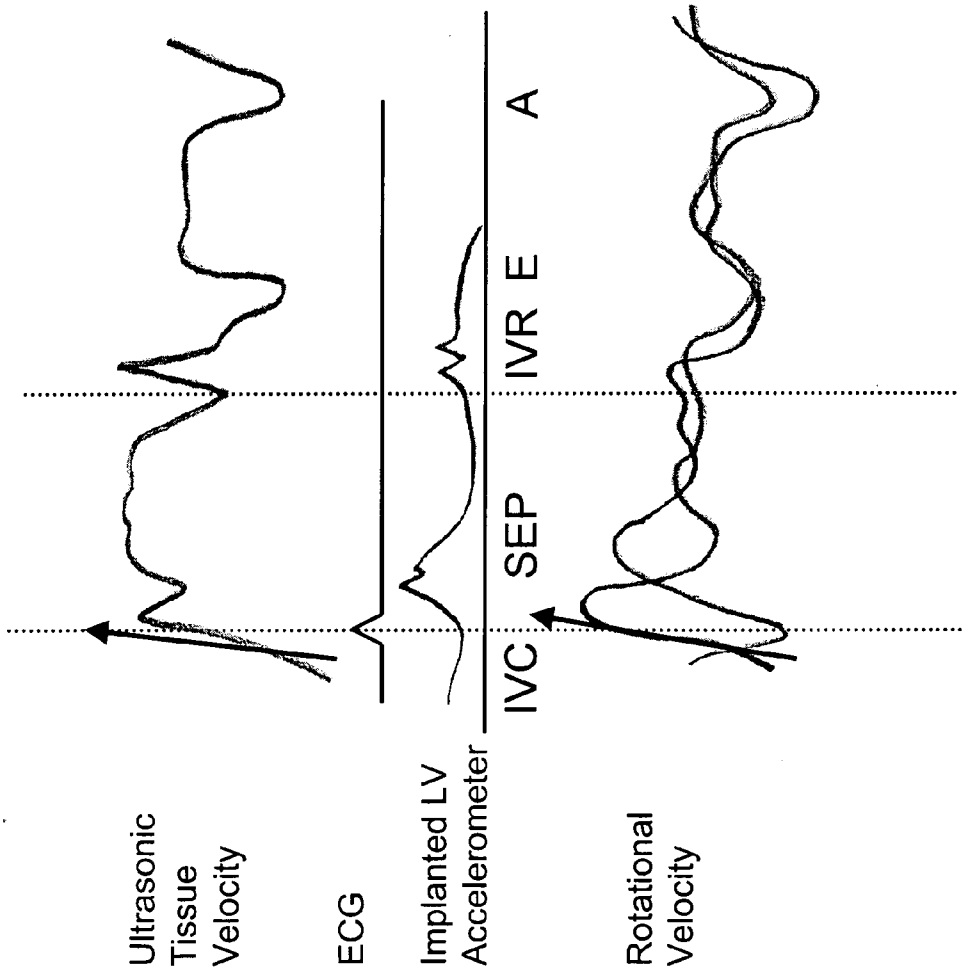

Ultrasonic Tissue Velocity
ECG
Implanted LV Accelerometer
Rotational Velocity
IVC
SEP
IVR
E
A

FIGURE 8

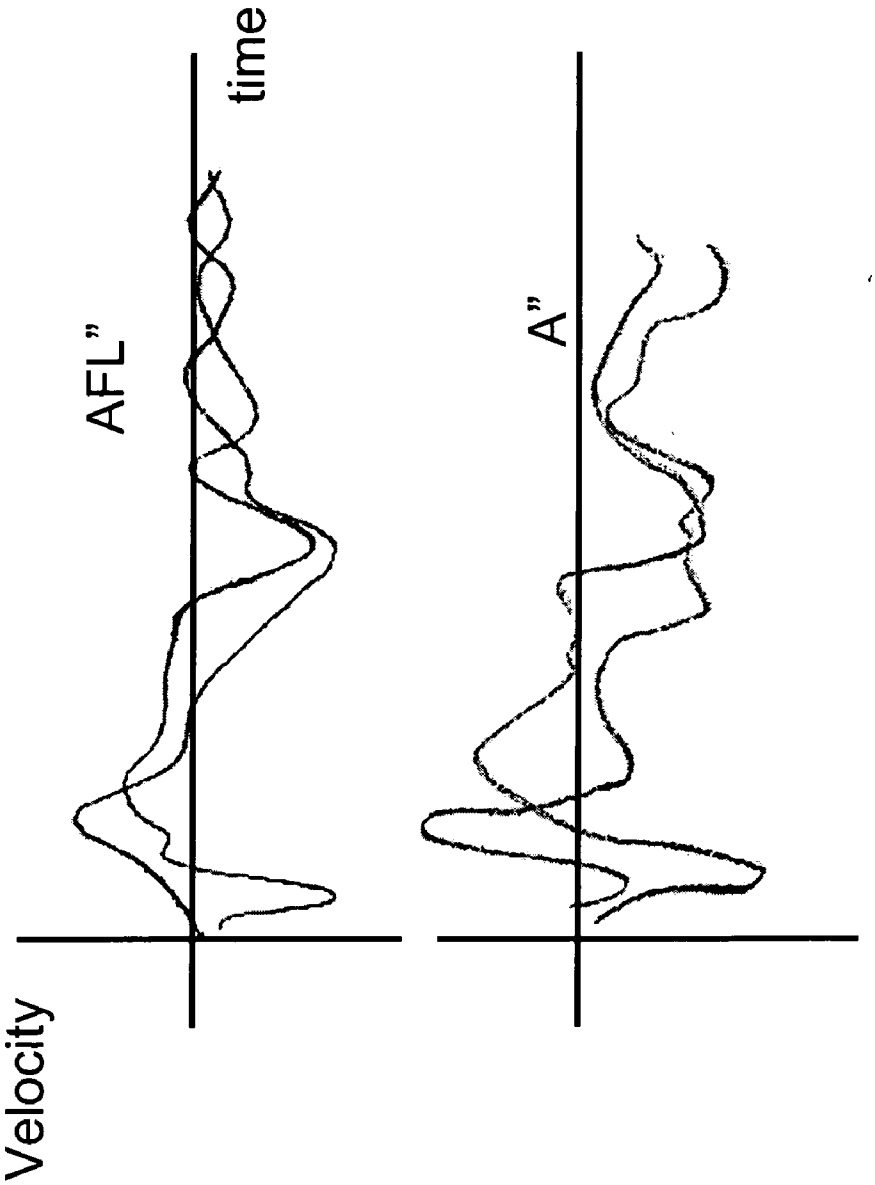
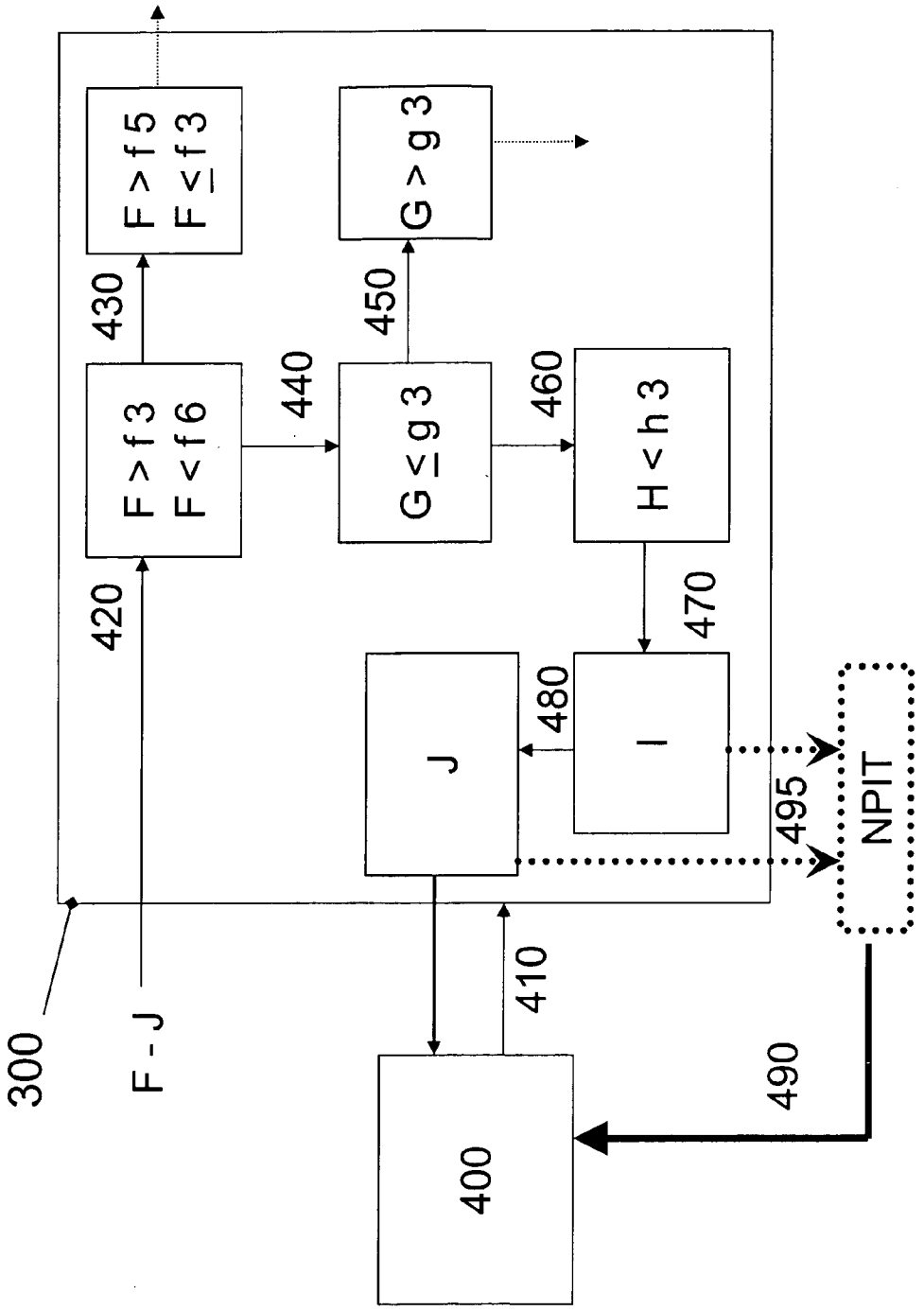


FIGURE 9


F > f 5
F <= f 3
G > g 3
430
450
F > f 3
F < f 6
440
G <= g 3
460
H < h 3
420
470
J
480
I
495
NPIT
300
F - J
410
490
400

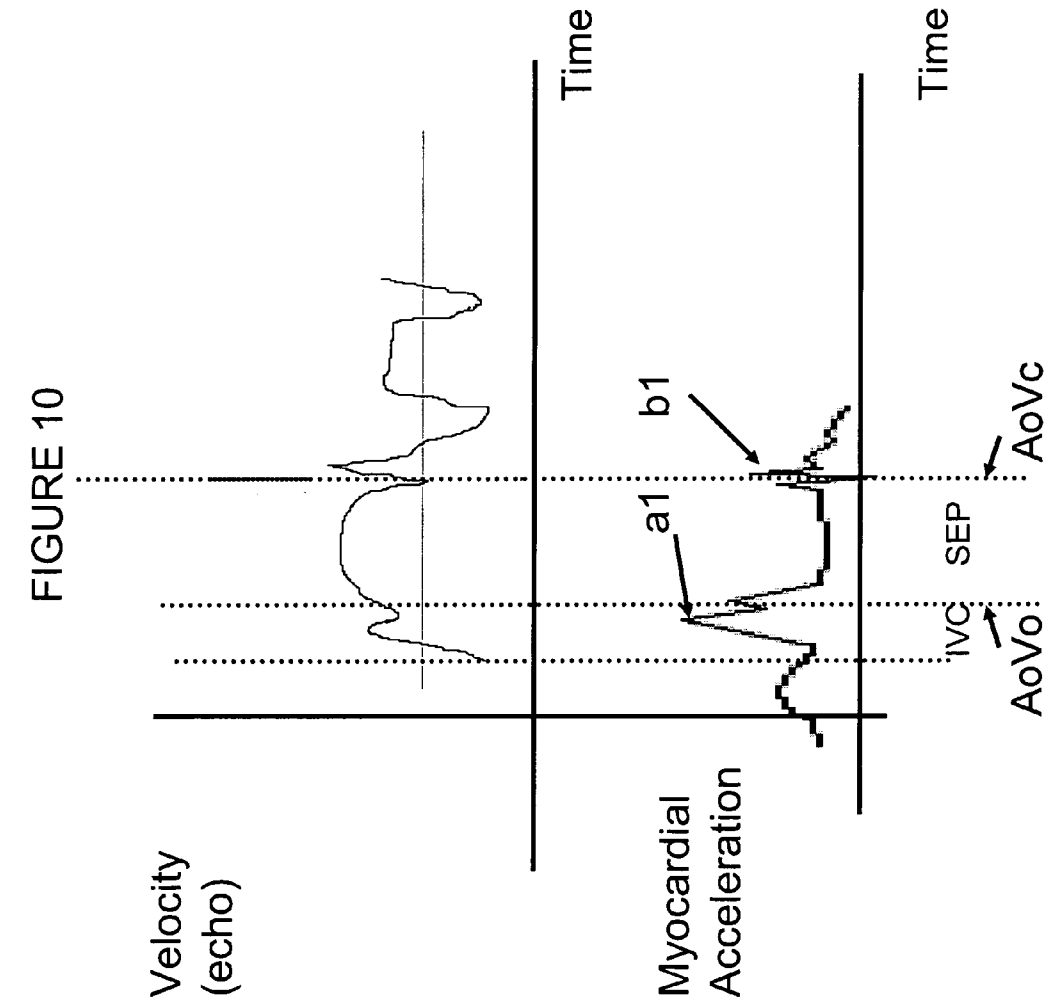

Velocity
(echo)
Time
Myocardial
Acceleration
Time
a1
b1
AoVo
IVC
SEP
AoVc

FIGURE 10

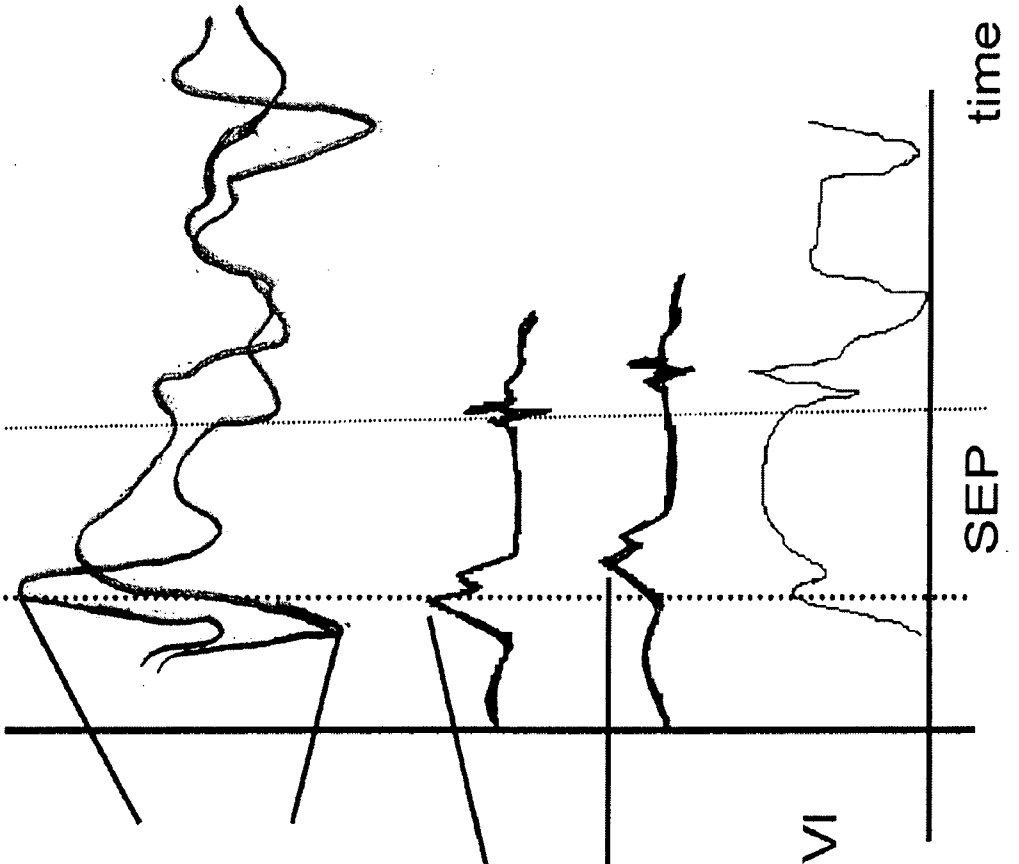


FIGURE 11

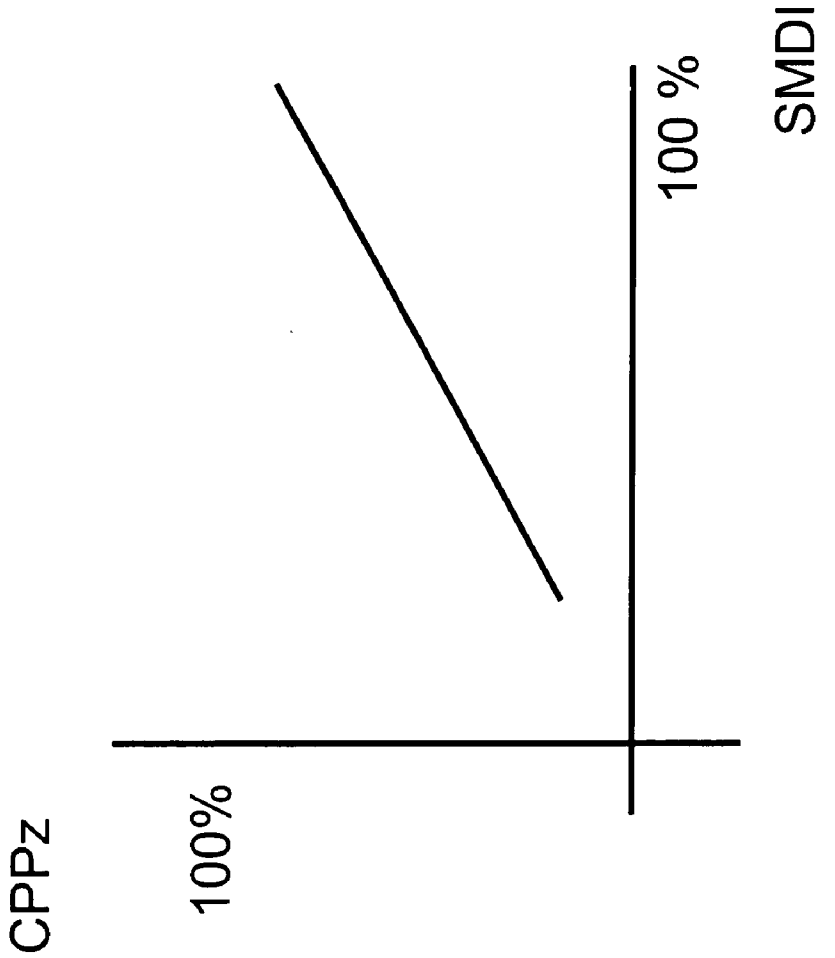


FIGURE 12

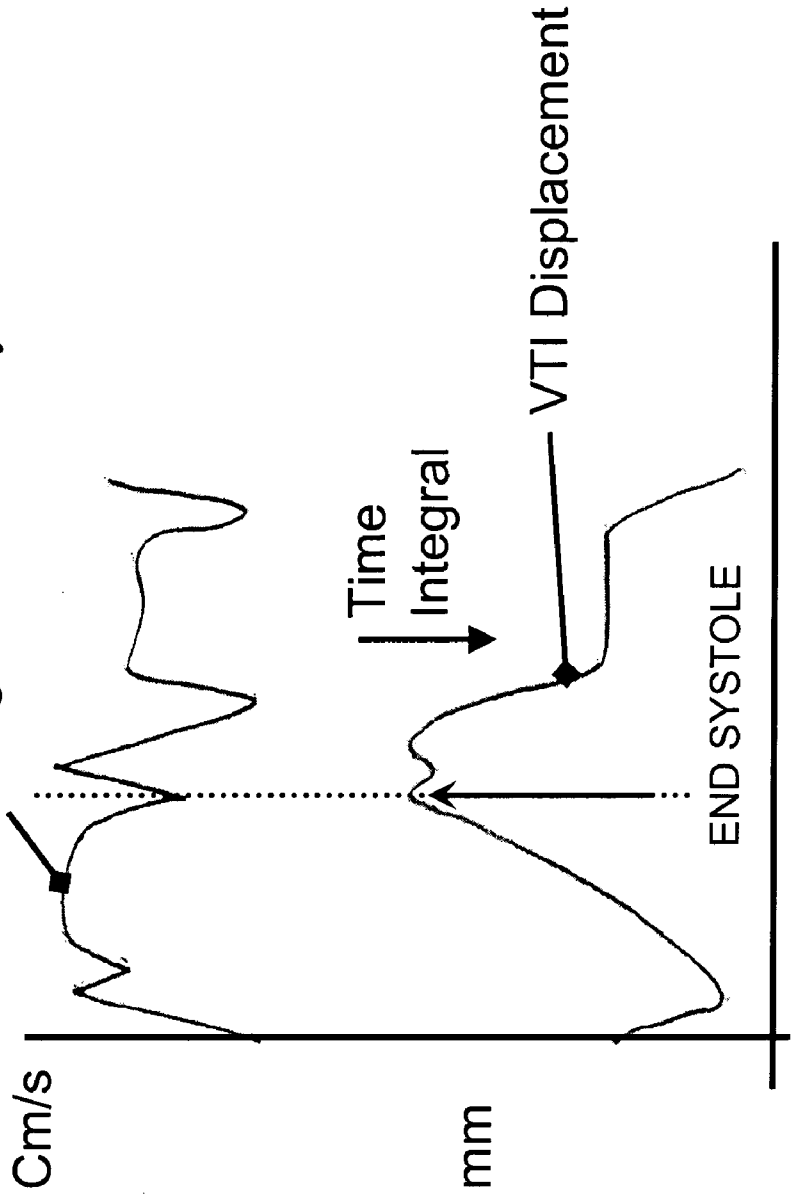

Longitudinal velocity
Time
Integral
VTI Displacement
END SYSTOLE
Cm/s
mm

FIGURE 13

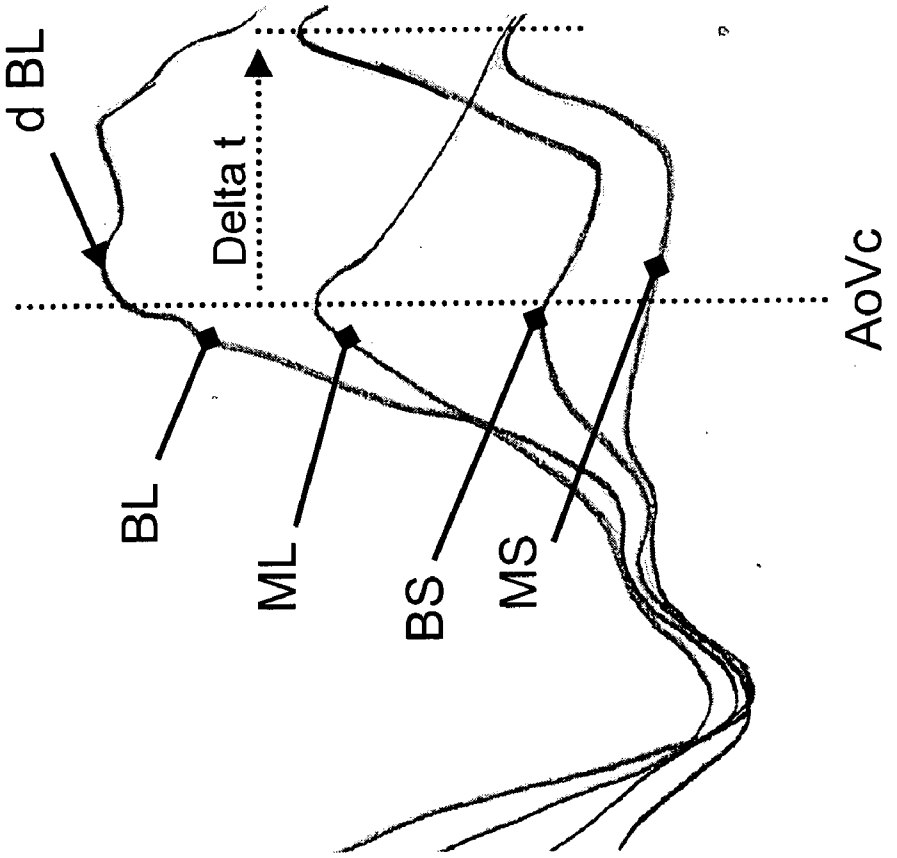


FIGURE 14

FIGURE 15

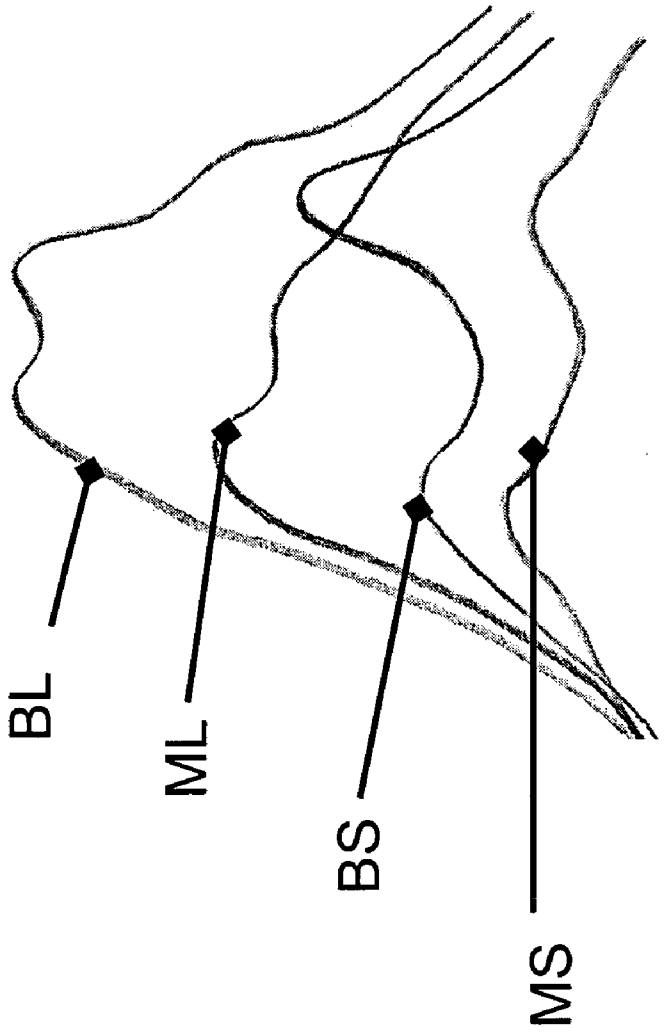
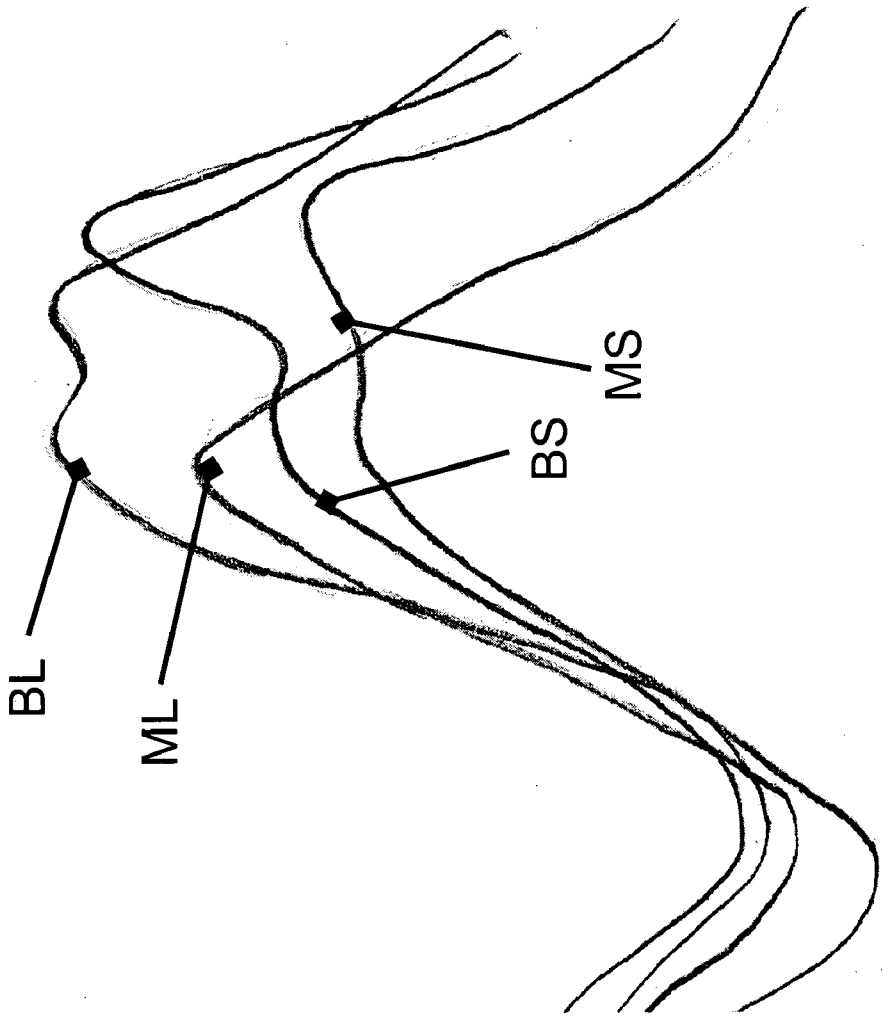


FIGURE 16



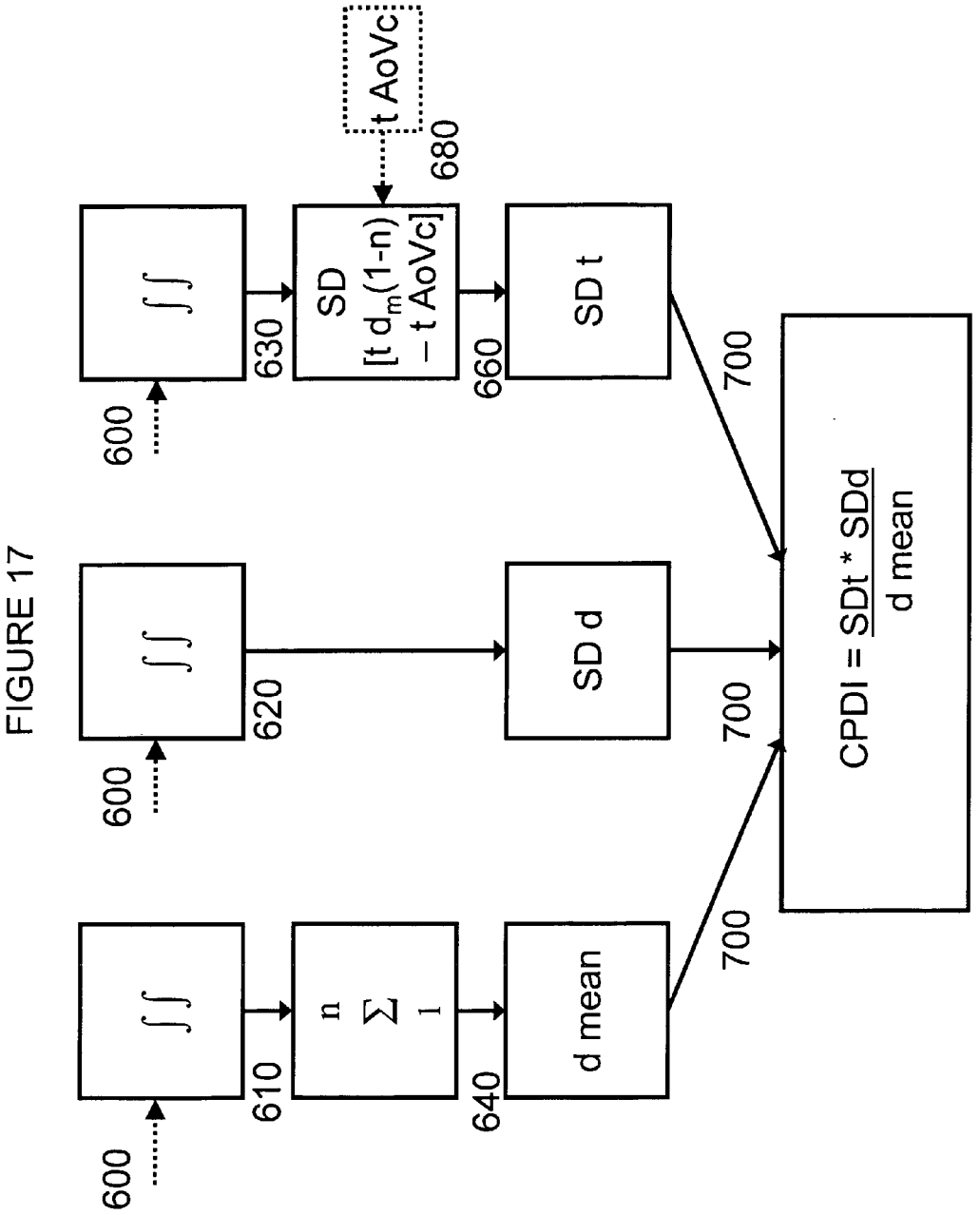
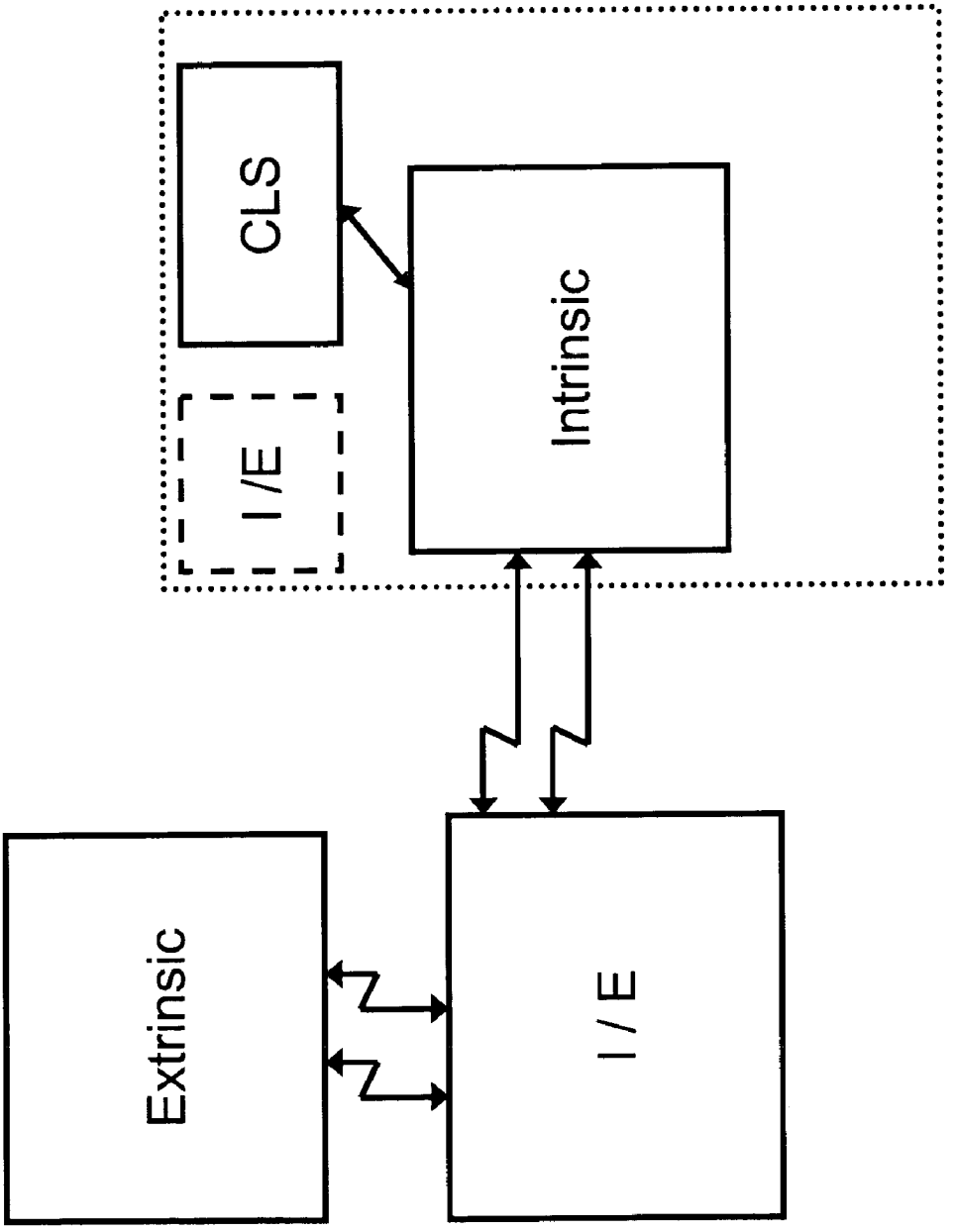

t AoVc
680
∫∫
600
630
SD
[t d_m(1-n) – t AoVc]
660
SD t
700
∫∫
600
620
SD d
700
∫∫
600
610
Σ n 1
640
d mean
700
CPDI = SDt * SDd / d mean

FIGURE 17

FIGURE 18



METHOD AND ALGORITHM FOR DEFINING THE PATHOLOGIC STATE FROM A PLURALITY OF INTRINSICALLY AND EXTRINSICALLY DERIVED SIGNALS

RELATED APPLICATIONS

[0001] This patent application claims priority to provisional patent applications No. 60/647,102 filed Jan. 26, 2005; and 60/660,101 filed Mar. 9, 2005, incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0002] 1. Field of the Invention

[0003] This application pertains to a system and apparatus for determining the status of a patient and more particularly to a system and apparatus wherein measurements from the patient are combined with external information such as statistical information collected from other patients and results of diagnostic testing to obtain a diagnosis, treatment options and prognostic information for the patient quickly and accurately using evidence based medicine.

[0004] 2. Description of the Prior Art

[0005] Major advances are occurring in the development of imaging modalities and implantable technologies capable of diagnosing and treating a variety of pathophysiology. Thus, the clinician has numerous diagnostic tests at his or her disposal and an option of therapeutic regimens. Coupled with the wealth information from these tests, there is a need to expeditiously evaluate the results of a plethora of diagnostic tests, and compare the data to historical data sets. Treatment algorithms designed to assess such informational data sets provide better direct therapy (evidence-based medicine).

[0006] To a large extent, practice decisions based on anecdotal data and individual studies have dictated medical practice to date. However, large scale population studies and the development of registries along with digitization of acquired diagnostic data obtained from these studies provide more powerful statistical analyses of patient outcome by comparing differing therapeutic modalities. The availability of such data will depend on a means for device-device communication and the evolution of wide range digitization of medical records and of data derived from different diagnostic equipment. Though the majority of the algorithms and examples described herein are in reference to advances in cardiovascular medicine and genetics, the inventions described have broad range application to any medical field.

[0007] The advent of digital signal processing (DSP) in evolving technologies (e.g. implantable pacemaker/defibrillators) will allow for informational data sets to be available in discrete numeric format, processed by high-speed microprocessors, and incorporated into device-based software algorithms. Such processing will allow a user to relate, in a complementary fashion, clinically relevant data obtained from both an imaging apparatus and implanted device as to derive a composite of information for diagnostic purposes and for optimizing patient management. The application of DSP will enable calculation algorithms to perform several processing operations simultaneously.

[0008] By way of example, software algorithms for readily evaluating a number of variables descriptive of cardiac performance and electromechanical dysynchrony (physiological properties) are assimilated within an implanted device or downloaded between an implanted device and a separate apparatus/extrinsic diagnostic equipment (e.g. echocardiography machine, cardiac MRI). A composite of physiological properties obtained from the implanted device is digitized (if necessary) and compared to normal and pathologic values as to generate physiological descriptors that have a numerical score. Models constructed to predict probability of outcome from the data obtained are implemented for such comparisons (Selker et al. Patient specific predictions of outcomes in myocardial infarction for real-time emergency use: a thrombolytic predictive instrument. Ann Intern med 1997; 127: 538-56). These physiologic descriptors are then input into software algorithms as to produce an informational data set of clinical and technical relevance. This informational data set (IDS) is output in form of an easily interpretable set of recommendations or prognostic data for the clinician. In one embodiment, such IDS can be downloaded into removable digital storage media or other media compatible with implanted device software and incorporated into an electronic medical record (EMR). In a preferred embodiment, the IDS is available to closed loop control systems that direct device based therapies (e.g. Cardiac Resynchronization Therapy, CRT).

[0009] The following references provide background information for the present application and illustrate the state of the art. All these references are incorporated by reference.

U.S. Pat. Nos. 6,804,559, 6,795,732, 6,792,308, 6,816,301, 6,572,560, 6,070,100, 6,725,091, 6,628,988, 6,740,033, 5,971,931, 5,833,623, 6,826,509, 6,805,667, 6,574,511, 6,418,346, 5,549,650

Published US patent applications: 20040176810, 20030083702, 20020026103, 20040111127, 20020072784, 20030216620, 20040167587, 20050182447, 20050043895

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[0018] Pappone C, Rosanio S, Burkoff D, et al. Cardiac Contractility Modulation by Electric Currents Applied During the Refractory Period in Patients with Heart Failure Secondary to Ischemic or Idiopathic Dilated Cardiomyopathy. Am J Cardiol 2002; 90: 1307-1313.

[0019] Willems R, Sipido K R. Nonexcitatory Stimulation as a novel treatment for heart failure: cause for excitement? European Heart Journal 2004. 25: 626-628.

[0020] Padeletti L, Barold S S. Digital Technology for Cardiac Pacing. Am J Cardiolo 2005; 95: 479-482.

[0021] Thomas J D, Greenberg N L, Garcia M J. Digital echocardiography 2002: now is the time. J Am Soc Echocardiograpy 2002; 15: 831-8.

[0022] Feignebaum H. Digital echocardiography [review]. Am J Cardiology 2000; 86: 2G-3G.

SUMMARY OF THE INVENTION

[0023] The present invention relates to acquiring a plurality of diagnostic information based on intrinsic properties of a given patient and extrinsic information derived from diagnostic testing performed on the patient, and combining the available data to derive prognostic information about a specific pathologic state using evidence based medicine. Recommendations for therapy delivered intrinsically via an implanted device or extrinsically via various therapeutic modalities are made with such analysis algorithms. Some of the examples used herein are focused mainly on implantable cardiac rhythm management (CRM) devices and other similar devices for diagnosing or treating heart failure. These types of devices generate a multitude of measurements diagnostic of a specific pathologic state, based on software algorithms incorporated into device-based platforms to obtain a composite of relevant physiological data from implanted sensors/transducers. The algorithms generate informational data sets for diagnostic/monitoring purposes with the object of guiding physician management and/or programming of an implanted device via a closed loop control system. Such informational data sets may be used, for example, to guide titration of pharmaceutical therapies, diagnose myocardial ischemia or determine a patient's candidacy for coronary revascularization or valve replacement surgery. This technology is also capable of incorporating downloadable indices/data from extrinsic diagnostic equipment into implanted devices/programmers and vice versa at periodic intervals via removable digital media (e.g. removable hard drive, magnetic-optical disc) or wireless telemetry (e.g. Bluetooth). Bi-directional communication of this data is used to confirm adequate functioning of an implanted device and verify diagnoses made with extrinsic equipment (cross-verification). This data can be examined to confirm response to specific therapeutic modalities such as cardiac resynchronization therapy (CRT), cardiac contractility modulation (CCM) or alternate Non-Pharmacologic Inotropic Therapy (NPIT).

[0024] In an alternate application, these algorithms are used in the field of genetic medicine through a similar means, combining data reflective of properties intrinsic to an individual in conjunction with environmentally based or extrinsic characteristics of that individual in context of known predictors of a given disease state derived from large population studies.

[0025] Diagnostic imaging modalities are moving toward digitization with standardization of storage format adherent to standard models (Digital Imaging and Communication in Medicine). Thus, there is a need to formulate composite indices which can be digitally processed and input into fast software algorithms for processing. Extrinsically derived composite indices can be evaluated from time to time and compared to similar indices generated from an implanted device (intrinsic), assimilated into an implanted device's existing diagnostic data. Translation of mathematical indices derived from signals acquired by implanted device sensors into conventional indices commonly used with external imaging modalities will facilitate device-device communication.

[0026] Through the utilization of this invention, a means of translation between analogous intrinsic/extrinsic indices is developed from the acquired pooled data after significant numbers of patients gain access to these technologies. The concepts underlying this invention are extended to imaging technologies including, but not limited to, echocardiography, magnetic resonance imaging, PET scans, nuclear imaging or computed tomography, and other diagnostic/laboratory tests. The extrinsically derived composite data can be downloaded into an implanted device for storage (e.g. medical record keeping) and available to the clinician in combination with similarly derived device based indices. The combined informational data set (intrinsic and extrinsic) can then more accurately provide prognostic information and generate recommendations for various therapies (e.g. using neural networks). Comparisons between extrinsic and intrinsic diagnostic data can be used to confirm diagnoses (e.g. presence of myocardial ischemia). A method and means for correlating intrinsically and extrinsically derived data with a translation function is developed once large numbers of patients have access to these technologies and patient outcome under varying clinical circumstances is determined. Digitization and standardization of storage formats will facilitate the application of such a translation function for derivation of analogous intrinsic and extrinsic indices using a universal mathematical language that will provide the clinician with prognostic information and treatment suggestions.

[0027] By way of example, this technology is generally described in relation to its application to implanted devices in patients with congestive heart failure as this particular field is in a state of rapid technologic evolution. Such implanted devices can be expected to have lead based and non-lead based sensors and transducers capable of acquiring data that is analogous to the diagnostic information obtained from extrinsic imaging modalities. A brief review and examples of such technologies are included herein along with related references. This review serves to familiarize the reader with the mechanical and physiological principles helpful for understanding this invention by correlating device based sensor data to analogous data acquired with echocardiography.

[0028] Patients referred for consideration of CRT implantation undergo echocardiographic or other imaging analysis. Current ultrasound technologies allow for a means of evaluating changes in regional volume, differential myocardial motion and contractility. Temporal frame rates for evaluating such subtle differences in timing are currently under 10 milliseconds. Available equipment manufactured by a number of companies such as General Electric, Philips, TomTec and Siemens are capable of measuring changes in both global and regional volumes within the cardiac chambers during the cardiac cycle. Analysis of tissue Doppler data allows for calculation of tissue velocities, myocardial strain and strain rate derived from the spatial gradient of tissue velocity (strain rate equation). This can also be performed by defining relative locations of ultrasound reflectors in two or three dimensional space over time using a technique referred to as speckle tracking (GE). Such data is currently processed at fast enough rates as to generate real time parametric imaging. As improvements in processing and microprocessor robustness occur (Moore's law), one can expect a number of analyses (unique and redundant) will be performed simultaneously in digital format and be able to be compiled into informational data sets that can be used for diagnostic purposes. This also holds true for implantable CRM and heart failure devices.

[0029] Recent advances in cardiac MRI have allowed temporal frame rates that approach the level of ultrasound imaging. These frame rates are adequate enough to allow for regional strain analyses that define degree and location of electromechanical dysynchrony during two cardiac cycles. Magnetic resonance tagging, phase contrast MRI, and stimulated MRI (DENSE techniques) are MR methodologies capable of characterizing myocardial motion and strain. Newer techniques such as use of harmonic phase analysis (HARP) vastly improve upon imaging and processing time and allow for more rapid strain analysis. In the Fourier domain, spatial modulation of magnetization (SPAMM) tagged MR data will have multiple spectral peaks. Any off-origin spectral peak will relate to tissue motion. Spatial derivatives of harmonic phase can be computed for any pixels as to derive strain measurements. Such techniques allow for acquisition of a number of cardiac performance parameters and measurements of electromechanical timing (dysynchrony). The details of such innovations are described in the cardiac MRI literature.

[0030] An index of dysynchrony or dysynchrony index, DI, and cardiac performance parameters, CP, may be derived by any and all of these imaging modalities as well as within an implanted device. The DIs and CPs allow for a means of quantifying and localizing electromechanical dysynchrony and quantifying systolic and diastolic cardiac performance. A number of DIs and CPs have been defined in the literature and these, as well as, several novel DIs and CPs developed by the inventor (see below and cited references) may be used for such analysis. The user can implement fast software algorithms using DSP to compile informational data sets (IDS) descriptive of cardiac performance (CP) and electromechanical dysynchrony.

[0031] The present invention provides for a rapid interpretation of physiological properties (DI, CP) as to generate relevant information, IDS, to the physician who is considering delivering a specific therapy to the patient (e.g. programming a CRT device, altering medical therapies, ordering diagnostic tests). Any available index or index to be defined may be incorporated into algorithms for performing such tasks and those mentioned in this application are by way of example. Demographic information and genotype can also be input into these algorithms.

Non-Pharmacologic Inotropic Therapy—Cardiac Contractility Modulation

[0032] CRT devices are well known in the field and to those experienced in the art. Non-excitatory stimulation, NES, is an evolving technology that holds promise to improve heart failure symptoms and may be less well known to the reader. Thus, a description of this technology and references are incorporated herein for the sake of completeness.

[0033] Devices capable of delivering non-excitatory stimulation to myocardium during absolute refractory periods (Impulse Dynamics) have been demonstrated to improve cardiac contractility by a mechanism termed cardiac contractility modulation (CCM). Initial experience with CCM devices suggests patients with congestive heart failure have improvements in symptoms and may be expected to have an improved outcome but such technology is expensive and the battery longevity of the device is often less than 6 months. These devices function by augmenting intracellular calcium concentration in regions of stimulated myocardium. This results in improvements in global cardiac performance for reasons that are currently not well understood. References that relate to this technology are cited below and can be reviewed if necessary. The inventor describes novel indices related to global tethering effects illustrative of how CCM affects cardiac performance and explains theories and potential mechanisms by which CCM improves global cardiac function with only local current delivery. Indices related to global tethering can be derived using this technology and evaluated by a physician to determine which patients may benefit from such expensive technology. The same indices can be monitored as part of a closed loop system within an implanted device as to confirm benefit and direct how often such therapy should be delivered as to reduce battery expenditure.

Application to Digital Devices—Interfacing/Telemetry

[0034] Currently implanted pacemakers/defibrillators which rely on analog technology will be evolving into devices that universally transform all analog signals into digital format. This will allow data compression and storage of extensive amounts of information in digital libraries within the device. Transfer of relevant clinical data (infor-

mational data set) between imaging equipment and implanted devices through digital technology can then be easily accomplished. This transfer may be by direct connection or wireless telemetry sent to implanted devices and device programmers. Security measures to ensure compliance with HIPAA regulations may require the use of fixed network addresses that place restrictions on access to such data. The clinical utility of the methods and algorithms described herein will be best realized when digital processing operations occurring within implanted devices and extrinsic diagnostic equipment can occur expeditiously and in a standardized format.

BRIEF DESCRIPTION OF THE DRAWINGS

[0035] **FIG. 1** shows a block diagram for handling information in accordance with this invention;

[0036] **FIG. 2** demonstrates wireless bi-directional communication between a central processing center, CPC, and implanted devices/external diagnostic equipment. Periodic updates of monitored indices/data and patient therapies/outcome are sent to the central processing center from individual patients and such pooled data is then transmitted and incorporated back into an internal processing center, **400**, contained within the implanted device and/or extrinsic diagnostic equipment.

[0037] **FIG. 2***a* shows an algorithm implemented within the within the Characterization Apparatus **300** of **FIG. 1** in accordance with this invention. Dotted arrows indicate specific examples of information data sets/clinical recommendations that are available to the following physician after further processing (e.g. with neural networks) in a processing center, **400**, located within the implanted device or extrinsic imaging equipment. Communication and processing of data between **300** and **400** is bi-directional, **410**.

[0038] **FIG. 3***a* shows schematically how three different cardiac parameters are combined by the present invention using a three tiered approach for evaluation of systolic and diastolic cardiac performance, assessment of contractility (thickening), electromechanical activation (timing), and rotation (torsion).

[0039] **FIG. 3***b* illustrates how Non-Pharmacologic Inotropic Therapy (NPIT) such as Cardiac Contractility Modulation may improve global cardiac performance via global tethering despite local current delivery.

[0040] **FIG. 4** depicts tissue velocity curves during the cardiac cycle that demonstrate normal left ventricular systolic, S, (counter-clockwise) rotation during isovolumic contraction and diastolic, D, clockwise rotation during isovolumic relaxation. Sampled regions of interest are septal and lateral segments from a parasternal short-axis view. Motion is relative to an anteriorly located external ultrasound transducer emitting a Doppler signal.

[0041] **FIG. 5** depicts the same data acquired from a patient with advanced heart failure symptoms. As septal and lateral regions of interest have the same velocity time curves relative to the transducer only translation is present without rotation. Such patients lack LV torsion that is an important component of systolic and diastolic cardiac performance.

[0042] **FIG. 6** is a side by side comparison of the velocity time graphs from **FIG. 5**.

[0043] **FIG. 7** depicts velocity (myocardial acceleration—arrows) as a function of time as detected by an implanted lead based accelerometer (middle) and with tissue Doppler imaging (longitudinal—top; rotational—bottom).

[0044] **FIG. 8** illustrates how atrial tachyarrhythmias can affect LV rotation via global tethering affects.

[0045] **FIG. 9** details an algorithm written in pseudo-code within the Characterization Apparatus **300** for a block diagram of a closed loop control system in a device capable of Non-Pharmacologic Inotropic Therapy. Dotted arrows indicate specific examples of information data sets that are available to the following physician. These data sets can be sent via wireless telemetry to central processing centers along with outcome information in all patients who have access to this technology.

[0046] **FIG. 10** depicts the temporal relationship between tissue Doppler derived velocity time graph on top and implanted lead based accelerometer derived myocardial acceleration time graph on the bottom. One cardiac cycle is illustrated, wherein AoVo=aortic valve opening, AoVc=aortic valve closure.

[0047] **FIG. 11** depicts Doppler derived tissue velocity time graph in the longitudinal and circumferential planes (bottom and top, respectively) and analogous data acquired from lead based accelerometers (middle). This illustrates how temporal relationships from extrinsic and intrinsically derived data can be used to derive complementary data sets.

[0048] **FIG. 12** shows a linear relationship between an intrinsically derived parameter of cardiac performance based on impedance and one derived extrinsically using tissue Doppler imaging. The mathematical relationships of analogous intrinsic and extrinsic data is used to derive equations that serve to mathematically translate analogous intrinsically derived and extrinsically derived indices that are representative of prognosis and patient response to differing therapies. Regression analysis or other statistical techniques are utilized to define such relationships along a graduated numerical scale.

[0049] **FIG. 13** illustrates longitudinal velocity time graph, top left; integration of velocity time graph for derivation of displacement, bottom left; sampled region of interest in the basal anteroseptum, top right; tissue tracking parametric imaging depicting relative amounts of displacement for various regions of interest; bottom right. Similar parametric imaging techniques can be used to illustrate intrinsically derived data such as time of peak impedance or impedance derived indices of cardiac performance.

[0050] **FIG. 14** illustrates longitudinal displacement curves for basal lateral (BS), mid-lateral (ML), basal septal (BS), and mid-septal (MS) regions. The derived curves are during biventricular pacing with programmed parameters set as: DDDBiV rate **70**, AV delay 250 msecs, VrVI offset =+40 msecs with NPIT turned off. Basal lateral regions (and mid lateral) reach peak displacement, d BL, at the ideal time of AoVc, while septal regions reach peak displacement time Delta after AoVc.

[0051] **FIG. 15** illustrates longitudinal displacement curves for basal lateral (BS), mid-lateral (ML), basal septal (BS), and mid-septal (MS) regions. The derived curves are

during biventricular pacing with programmed parameters set as: DDDBiV rate 70, AV delay 250 msecs, VIVr offset=+40 msecs with NPIT turned off.

[0052] **FIG. 16** illustrates longitudinal displacement curves for basal lateral (BS), mid-lateral (ML), basal septal (BS), and mid-septal (MS) regions. The derived curves are during biventricular pacing with programmed parameters set as: DDDBiV rate 70, AV delay 250 msecs, VrVI offset=0 msecs, with NPIT turned on, applied to leads located on the inter-ventricular septum. Synchronization of time to peak displacement and increased septal displacement is noted with these parameters programmed.

[0053] **FIG. 17** is a flow diagram that depicts how a simplified algorithm that analyzes single sensor displacement data derived from implanted lead based accelerometers can be used to derive a cardiac performance/dysynchrony index, CPDI. CPDI can, in turn, be used to direct programming of interval timing and NPIT as part of a closed loop control system. (II is a double integral of displacement= acceleration).

[0054] **FIG. 18** illustrates how an intrinsic/extrinsic comparison apparatus functions.

DETAILED DESCRIPTION OF THE INVENTION

[0055] By way of example, the algorithms described herein serve to guide programming of a CRT device and program the frequency of NPIT as part of a closed loop system, as well as, identify the presence of myocardial ischemia. The dysynchrony indices will be generally referred to as DI and any cardiac performance parameter as CP. These physiological properties are well known in the art as established in the above-referenced published U.S. patent applications. The examples described are included as to illustrate how the inventive algorithms function, though the application of such algorithms are by no means limited to these clinical scenarios. The DI's and CP's can be either intrinsically acquired or extrinsically derived (Dix, CPx) as denoted in **FIG. 1**. The input data also includes demographic information or relevant historical information as is described in more detail below.

[0056] Referring to **FIG. 1**, physiological properties, DI, DIx and CP, CPx are collected and digitized by the Detection Apparatus, **100**. Apparatus **100** may be an external unit, part of a device programmer or in a preferred embodiment contained within the implanted device itself. Any number of DIs and/or CPs may be input to **100**. By way of example, CP may be an impedance based determination of cardiac performance, severity of mitral regurgitant (MR) based on echocardiography, lead based accelerometer derived indices of myocardial motion, accelerometer based determination of left ventricular rotational velocity/torsion or any other parameter that reflects cardiac function. The DIs include but are not limited to regional differences in time of peak impedance, relative times of peak myocardial acceleration, differentials in regional myocardial motion (e.g. septal and lateral LV) determined by lead based accelerometers, tissue Doppler echocardiographic indices. Specific demographic information even including prognostically relevant genotypic characteristics may be entered into **100** as well. These may be analyzed and compared to extrinsically derived physiological properties that are input into **100**, as described in more detail below.

[0057] Analysis of physiological properties obtained from large-scale clinical trials with a variety of imaging technologies (e.g. ultrasound, MRI) defines specific characteristics. For purposes of explanation, most of the explanations in this application will focus on properties that distinguish heart failure patients with varying forms of electromechanical dysynchrony and differences in cardiac performance and genetic markers for disease. A number of ongoing studies are examining these characteristics and how they relate to patient outcome and response to varying therapies.

[0058] In one application of the invention, these characteristics can be defined using monitoring technologies within implanted cardiac devices. These characteristics are compiled from numerous patients and evaluated as pooled data to correlate clinical outcome/prognosis based on various CPs, DIs, genotypes, relevant demographics and patient diagnostic information.

[0059] By way of example, these characteristics can determine how to program interval timing in a CRT. These characteristics can also direct the duration and frequency of activation of novel pacing modalities such as CCM or alternate NPIT. Characteristics derived from external monitoring equipment, (e.g. CPx and DIx), can be incorporated into reference/template data in digital format for comparison to real time acquired DIx, CPx, using predictor algorithms in the Analysis Apparatus, **200** along with intrinsically derived indices obtained from the implanted device itself (e.g. CP and DI). These physiological properties are assigned a numerical value along a graduated scale and output from **200** as physiological descriptors, **210**.

[0060] In a preferred embodiment, the range of the numerical scale is based on similarly acquired data gathered from population studies, preferably using monitoring techniques capable of transmitting such information via wireless telemetry to a central processing center/data bank and back to the specific monitoring equipment (e.g. implanted device, echocardiography machine). The resulting numerically scored data, **210**, is input to the Characterization Apparatus, **300**, in **FIG. 1**, where comparisons are made and algorithms employed to generate an informational data set that relays the relevant information to the user and/or directs programming of an implanted device as part of a closed loop system.

[0061] At step **110** the data is compiled, and if in analog form, is digitized in **100** and then input to **200** where the physiological descriptors are scored as to characterize the detected pathophysiological features of the patient using multivariate statistical techniques such as Discriminant Analysis. Other statistical techniques may be used to perform an analysis of these physiological descriptors. By way of example, Discriminant Analysis will compare measured DI. DIx and CP, CPx values related to regional and global systolic/diastolic function and attributes or assigns a binary numerical value to a range of characteristics based on comparisons to normal template data acquired from population studies. As an example, an arbitrary characteristic A may be defined as a function of three-impedance based measurements; variation in the integral under regionally derived dynamic impedance waveforms, Z (t) dt, during the systolic ejection phase, (Discriminant characteristic X), the standard deviation in peak regional impedance from multiple electrode combinations (Discriminant characteristic Y) and the standard deviation of peak positive dZ/dt during

systole in multiple vectors (Discriminant characteristic Z). These characteristics are automatically obtained by device based sensors, accrued and digitized within the Detection Apparatus, **100**. In one embodiment, an operator can have the option to review any automatically obtained characteristic (e.g. impedance waveform) before entry into **200**, to confirm that an adequate signal is present for data processing. Analysis apparatus **200** assigns to characteristic A a specific value as described below. The values of A reflect a composite of findings that are weighted based on level of relevance to characteristic A and results of pooled data (i.e., known results of extrinsic diagnostic tests and intrinsic sensor based data) obtained from patients implanted with devices with this capability (this data will have been telemetered to the central processing center and then telemetered back to the implanted device). Thus, characteristic A may equal a1 when Discriminant characteristics X, Y and Z fall into a specific range of values. The relative importance of Discriminant characteristics X, Y and Z for Characteristic A is represented by values x, y and z. In this example x may be weighted at 50 percent (x=0.50), y and z at 25 percent, and

A=a1 when Discriminant value L<=xX+yY+zZ

[0062] By way of example, A equal to a2 or a3 is found when the morphology of regionally derived impedance waveforms (X) septal and lateral peak Z (Y) and regional comparisons of dZ/dt in more than one vector (Z) are consistent with dilated, non-coronary CM, and values in excess of a5 are found when values are consistent with multiple infarctions (more heterogeneous properties). Values of a4 and a5 are seen under circumstances consistent with a single infarct zone. The higher the number following a, the more likely the cardiomyopathy (CM) is a result of multiple regional infarctions rather than non-coronary CM (a1). Changes in any or all of these characteristics over time or at increased heart rates can indicate a new myocardial infarction or myocardial ischemia, respectively, and prompt a clinician to perform angiography.

[0063] Referring to **FIG. 2***a*, characteristics A through E which have been detected/acquired and if needed digitized in **100** are organized and scored based on comparisons to template data in **200** and then entered into Characterization Apparatus **300**. For purposes of explanation, we will denote physiological properties A through C as CPs and D and E as DIs. In this circumstance, A-C are analog signals and D-E are digital. In the example shown in **FIG. 2** Apparatus **200** and **300** are integrated. These physiological properties are digitized (A/D) if needed and the resulting data is input to A at step **310**. Characteristics A through E are a numerical value along a graduated scale or reflect the absence or presence of a specific condition (0 or 1). More specifically, A is a deformation geometry index based on comparisons of regional impedance waveforms, Z (t) dt and a number of CPs derived from Z (t) dt. In this particular example, the findings are consistent with ischemic cardiomyopathy (ICM) rather than dilated CM as septal and lateral peak impedance values, Z (p), differ by a pre-specified amount and other anisotropic features in Z (t) dt are found to be consistent with a single infarct zone. Thus, the derived deformation geometry index, A, will fall within a preset range of values, a4-a5. As described above, values less than a3 are ascribed when Z data is consistent with dilated, non-coronary CM, and values become in excess of a5 when values are consistent with multiple infarctions. At periodic intervals this evaluation is performed and the resulting data is stored and available for review at follow up visits or in a preferred embodiment by wireless telemetry. The frequency of such periodic evaluations can be a default value or programmable time interval (e.g. every day). Likewise, the pooled data from the central processing center can be communicated back to the implanted device or external diagnostic equipment at periodic intervals (e.g. every month), and is thus updated as more data is entered from patients/equipment with access to this technology. In this case example, the patient has had a change in condition. The system which had previously labeled this patient as having a single infarct zone (e.g. anterolateral) at query box A no longer applies (step **330**), and as new conditions have arisen, the algorithm proceeds to step **320** as the value of A has increased. Under these circumstances more than one infarct zone is found and major changes have occurred suggesting the patient has suffered a new myocardial infarction with multi-segmental wall motion abnormalities (A>=6). This would prompt the clinician to perform an echocardiogram and/or pursue an ischemia work-up (dotted arrow). The range of values for A are determined from pooled data acquired from numerous patients who have access to this technology as mentioned above. Characteristic B relates more specifically to location of infarct zone (rather than global deformation characteristics) and is based on data acquired from extrinsic echocardiographic assessment of wall motion or an analogous assessment from implanted device based lead sensors/transducers. In query box B, the infarct is denoted to involve only the anterolateral wall based on the assigned value of B and step **350** ensues to the next step as to evaluate valvular function, C. Other characteristics of B may indicate an anteroseptal infarction, **340**, (e.g. reduced values of peak endocardial acceleration measured from a lead based accelerometer placed on the interventricular septum). If this is a new finding it would be flagged (as in **320** above) and the physician can be prompted to perform more diagnostic testing (dotted arrow). In a preferred embodiment, an alarm can be triggered that is audible or palpable (e.g. vibration) to the patient and/or sent to a central processing center via wireless telemetry. Determination of infarct location at query box B, can be based on a number of variables subject to Discriminant Analysis techniques in **200**. Such variables may also be used for defining any number of additional characteristics as described below.

[0064] In this case example, C is equal to MRa (step **360** ensues) when Discriminant Analysis of echocardiographic data demonstrate that the MR flow exceeds a certain value. The direction of MR can be detected based on extrinisic echocardiographic imaging and noted to be eccentric rather than central. Such a finding is consistent with electromechanical dysynchrony and when taken in context of other variables at step **370**, suggests that such a patient will respond to CRT therapy and LV pacing can be activated if available in the implanted device. C=MRx indicates that mitral valve surgery should be considered. Other complementary data (intrinsic or extrinsic) can be evaluated before such a recommendation is made. Some examples include; larger effective regurgitant orifice areas determined by ultrasonic color Doppler, and increases in LV end-diastolic dimensions or assessment of MR from implanted device based sensors.

[0065] Again the value of C is assigned in Analysis Apparatus **200**. In **200** the degree of MR is given a numerical value based on comparisons of MR severity derived from normal and abnormal patients along a graduated scale. Thus, in this particular patient, echocardiographic assessment of MR determines that it is severe (e.g. EROA value near maximal) and the value of MR is graded numerically as 9 out of 10, where 10 is most severe and 0 being normal with no MR present). Peak endocardial acceleration, Acceleration index, at query box DV, has characteristics that are consistent with multiple myocardial segments reaching peak myocardial acceleration at significantly different times during the cardiac cycle (septal and lateral regions). In fact, the delays in peak myocardial acceleration are more pronounced and values of peak myocardial acceleration are lower at increased heart rates, suggesting that these territories have viable, dysynchronous myocardium. Such a patient would benefit from revascularization. Step **370** then ensues, and at query box E, the patient is labeled as someone with multisegmental abnormalities in anterior, lateral and inferior walls based on a composite of echocardiographic and acceleration indices. As conditions DV=ALI and E=Vali are met, the Characterization Apparatus will define the patient as having significant dysynchrony in anterior, lateral and inferior territories with impaired wall motion but viable myocardium. The composite of this data is communicated to the clinician in any format. By way of example, when the values of A, B, C, DV, E fall within a specific range, a message is communicated in display box **500**: "this patient has been identified as one who will have a positive outcome from revascularization and mitral valve replacement, based on patients with similar clinical findings this patients' prognosis will improve with revascularization and mitral valve surgery if other factors do not increase operative risk. Individual outcomes may vary."

[0066] The ability of the system to generate such data is dependent on existing data sets/statistical probabilities of outcome (prognostic information) with different permutations of parameters (e.g. A-E) that are compared in **400** to findings in other patients who's outcome has been determined and stored in the CPC. Neural networks or other techniques are applied in **400** to update and 'teach' the system at periodic intervals from data made available from the CPC.

[0067] After revascularization (e.g. coronary artery bypass surgery), changes in the parameters may or may not still indicate that the patient would benefit from CRT. Postoperative assessment of intrinsic device based indices in conjunction with extrinsic imaging techniques such as tissue Doppler echocardiography can be used to determine further management. In a preferred embodiment, the extrinsic and intrinsic data acquired can be analyzed in a complementary fashion, compared to previous case examples with similar findings in the central processing center and the system can provide the clinician with statistical data detailing expected response rates and prognosis with and without CRT.

[0068] Though future generation pacing systems may include LV pacing capabilities, activation of resynchronization therapy may only appropriate at specific times (e.g. exercise induced conduction abnormalities, changes in electromechanical properties with remodeling/reverse remodeling) and thus, CRT activation can be implemented when needed. This will save costs to the system and battery longevity. When activated, the system can make real time recommendations about programming of interval timing or perform these automatically as part of a closed loop system. Similarly, activation of regionally delivered NPIT will occur at the appropriate times and to the appropriate leads when directed by such a closed loop system as described in more detail below. Activation of NPIT will occur when any cardiac performance index or indices indicate(s) impairments in cardiac performance. By way of example, if measurements of inotropy using implanted lead based accelerometer data showed a reduction in systolic cardiac performance the system will activate NPIT. In a preferred embodiment, activation of NPIT is based on assessment of a plurality of parameters as denoted in **FIG. 9**. These parameters can be intrinsically derived and/or extrinsically derived (echocardiographic assessment of stroke volume).

[0069] The apparatus predictor algorithms need not rely on a single index but will incorporate redundancy techniques as to improve specificity much in the same way an operator may define hypokinetic myocardium if such findings are found in more than one imaging plane on a conventional 2 dimensional echocardiogram. This is also important as inadequate signal to noise ratios or the lack of specific sensors may compromise the systems ability to define certain characteristics. Thus, the system can rely on a plurality of signals, intrinsic and/or extrinsic in its analysis. This case is by way of an example and illustrates how any number of redundant or repetitive steps occurs with fast software algorithms.

[0070] In the example described herein this patient will be defined as someone likely to respond to revascularization surgery and possibly mitral valve replacement and CRT. This result can be output in any format (digital or analog), numeric or as written language. Neural networks or comparable means can analyze the available data, draw comparisons between the individual case and a library/data bank of other cases stored in the central processing center with outcome information prior to reporting any observations and before making recommendations in **400**. The apparatus/algorithms may specifically report such characteristics via a graphical display and/or printed out by monitor/printer **500** as described above. This will allow an operator to review and manually input data based on subjective assessment of the acquired data (step **510**) before final processing in **300** (**FIG. 2**). Such data may be transmitted by removable media such as hard drives or magnetic-optical discs or via wireless telemetry.

[0071] As the current invention allows for acquisition of data acquired from large population studies with entry of the data into a central data bank, the algorithms employed and recommendations generated (IDS) apply evidence-based medicine. Initially, such technology will be used for monitoring purposes. As more patients have access to equipment with such technologic capability, the more predictive the IDS will be for determining prognosis. Once validated with large scale clinical trials, formal recommendations can be relayed to the practitioner based on the predictor algorithms described herein. When possible, the device can perform automatic programming with closed loop control systems. Though the device based algorithms have the capacity to perform these functions, such sequential, advancements in the application of such technology can be achieved by

software downloads (device upgrades) at the appropriate times (comprehensive central data bank, FDA approval).

[0072] It is readily apparent that such a technologic advancement holds promise to reduce health care costs and improve patient outcome as patients most likely to benefit from specific therapies will have access to such treatment and those patients unlikely to benefit from specific therapies will avoid the potential risks/health care costs of such treatment.

[0073] Outcome analysis performed within the device and/or a central processing center gathers and processes such data via wireless telemetry from extrinsic diagnostic equipment and/or implanted devices with such capability. Thus, at pre-programmed intervals such intrinsically and extrinsically derived data sends acquired data in numeric format (e.g. characteristics A-E) to the central processing center (**FIG. 2**) and from the central processing center back to **400** within the implanted devices/device programmers and extrinsic diagnostic equipment (double headed arrows in **FIG. 2**).

[0074] Any and all data received by the central processing center (CPC) is stored in a data bank, and tracked for all patients who have such data entered. The data can be from implanted devices (intrinsic) or external diagnostic equipment (extrinsic). Patient specific therapies and outcome are input to the CPC. The outcome data can be in the form of any index of cardiac performance or hard endpoints such as morbidity or mortality data. The data is processed via neural networks or other technique in **400** with the output data being any recommendations for patient treatment communicated to the user in **500** (e.g. recommendation for valve replacement) or activation of CRT or NPIT in an implanted device.

[0075] In this fashion, predictor algorithms in the CPC or within the implanted device/extrinsic diagnostic equipment can generate prognostic data for individual patients based on population studies using evidence based medicine. The pooled data is used to help predict outcome and guide treatment. The centrally processed pooled data can be made available to expert panels elected by the American Heart Association, various regulatory committees such as the Food and Drug Administration, and Centers for Medicare and Medicaid Services (CMS).

Non-Excitatory Stimulation and Global Tethering/Left Ventricular Torsion

[0076] The normal heart contracts and relaxes as a helix. Embryologic development of the heart is in a helical fashion. Viewing the heart from apex to base, this rotation is counterclockwise during systole and clockwise during diastole. Such helical rotational properties/torsion significantly contribute to cardiac performance, though this is currently not recognized in both academic and clinical circles. Such properties are lost in patients with dysynchronous contractile patterns and cardiomyopathy. Diastolic uncoiling and systolic coiling of the heart results in a suction effect for diastolic inflow and a twisting, wringing effect for systolic output. Pathologic myocardium and/or conduction abnormalities alter this pattern and lead to diastolic and systolic dysfunction.

[0077] The relative contribution of LV torsion to cardiac performance is significantly underestimated. Patients with severe impairments in contractility but absent heart failure symptoms may have retained cardiac performance as LV torsion is preserved. Likewise, patients who appear to have preserved contractility and advanced heart failure symptoms might be expected to have impairments in LV torsion. Electromechanical activation patterns are a third factor contributing to overall cardiac performance. Thus, the inventor recognized that three major mechanical factors, myocardial thickening, electromechanical timing and left ventricular torsion contribute to cardiac performance, patient symptomatology, and clinical outcome (**FIG. 3**). Such pathologic states can be rectified by appropriate temporal and spatial stimulation of the cardiac chambers and with non-pharmacologic inotropic therapy using novel pacing modalities (e.g. CCM).

[0078] As mentioned above, initial studies in patients with systolic heart failure who have implanted devices capable of delivering non-excitatory electrical current have demonstrated improved systolic performance and reductions in heart failure symptomatology.

[0079] The inventor believes that CCM or other NPIT function by increasing regional contractility, and thus, increasing local systolic strain and peak strain rate but not necessarily in remote myocardial segments. NPIT increases systolic longitudinal displacement of regional (e.g. septal) segments but properties of distant territories (e.g. lateral) are effected as well. This occurs as a result of global tethering; tethering effects that affect far-field tissue velocity/motion despite regional current delivery (e.g. only in the interventricular septum). By augmenting strain and motion of the interventricular septum, NPIT will in turn increase the systolic rotation of the left ventricle and augment diastolic recoil/counter-rotation. These effects will increase LV torsion and improve both systolic and diastolic cardiac performance (**FIG. 3B**). In particular, increases in LV torsion as a result of global tethering significantly contribute to the beneficial affect of NPIT on cardiac performance over and beyond the affect of NPIT on local contractility.

[0080] Development of multi-site pacing systems capable of NPIT promises to further enhance the benefits of such technology and avoid any potential for increases in dysynchrony resulting from regional non-excitatory stimulation. In patients with electromechanical dysynchrony, CRT-NPIT pacing systems can improve cardiac performance and synchronize myocardial activation. Because of the anisotropic properties of the myopathic heart, an individuals needs for resynchronization therapy and non-pharmacologic inotropic therapy may vary from myocardial segment to segment, patient to patient and time to time. In order to maximize a given patient's response to such device based therapies, specific algorithms and control systems will be necessary.

[0081] Multiple novel rotational/torsion parameters can be derived that describe the helical properties of the heart during the cardiac cycle and are ideal for analysis of the effects of NPIT. For illustrative purposes, **FIG. 4** depicts physiological rotational properties derived from tissue velocity curves obtained in a person without structural heart disease. The tissue Doppler derived velocity time curves are generated by insonification of regions of interest placed at 10 o'clock and 2 o'clock of the LV imaged in the mid-papillary parasternal short axis view relative to an anteriorly located ultrasound transducer. Inspection of curves **710** and

720, respectively, demonstrates septal and lateral wall rotational velocity as a function of time. The velocity vectors of the septum, **710**, and lateral, **720**, segments are in a counterclockwise direction during isovolumic contraction (IVC) and the SEP and a clockwise direction during diastolic filling. Diastolic translational motion is denoted by E" and A". During this time frame no rotation is seen. E" occurs during early diastolic filling and A" during atrial kick. Patients with CM and congestive heart failure lack normal LV rotation/torsion. These properties have been demonstrated in the MRI literature through ultrasound techniques (speckle tracking), as well as, using tissue Doppler imaging will facilitate such an analysis. **FIG. 5** depicts septal and lateral wall rotational tissue velocity as a function of time in a patient with Class IV CHF despite biventricular pacemaker implantation (**FIG. 6** also illustrates the curves for comparative purposes). No rotation is seen in this circumstance and only a translational effect is noted as both septal and lateral segment velocities have the same amplitude and velocity vector relative to the transducer. In **FIG. 7**, the arrows (top, bottom) represent myocardial acceleration, the first derivative of tissue velocity, in longitudinal and rotational (circumferential) vectors. Such measurements can be related to intrinsic measurements derived from implanted accelerometers (middle) as explained in more detail below. This technology is known in the art and has recently been incorporated into device based control systems that program CRT device interval timing. Such devices are available in Europe (Sorin) but device based measurement or myocardial motion/acceleration have not be used to control NPIT.

[**0082**] Patients with organized atrial tachyarrhythmias (e.g. atrial flutter) lack the normal A" (**FIG. 8** bottom) and may be seen to have oscillatory rotational properties, AFL", (**FIG. 8** top) during this time frame (Schecter S. et al. The Effects of Atrial Flutter on Left Ventricular Rotation: A Tissue Doppler Study. Heart Rhythm 2005). Thus, LV rotational properties can be affected by changes in LV function, electromechanical dysynchrony, as well as regionally distant phenomenon related to atrial arrhythmias as a result of global tethering effects. In **FIG. 8** the rotational velocity time graph on the top is from a patient with preserved LV rotation and atrial flutter is depicted. The rotational velocity time graph on the bottom is from a patient with no structural heart disease. The amplitude of rotational velocity is similar in both patients in systolic and diastolic time frames. The patient with a-flutter (top) has only mild heart failure symptoms despite marked impairments in contractility (EF 15%). Patients with advanced heart failure may have impairments in LV rotational properties with better contractility than patients with no heart failure symptoms and severe hypocontractility. LV rotation and torsion as well as the relationship of regional electromechanical activation times to the systolic ejection phase (i.e. dysynchrony) play a significant, underestimated role in clinical symptoms of heart failure. Thus, a plurality of factors should be weighed appropriately when evaluating cardiac performance and response to device based therapies (**FIG. 3A**).

[**0083**] In the extrinsic apparatus designed to evaluate a plurality of signals, algorithms for identifying patients likely to respond to NPIT can utilize input physiological properties including septal contractility, septal and distal segmental longitudinal displacement, regional and global strain analyses and LV torsion into Analysis Apparatus **200** for numerical scoring (step **110** in **FIG. 1**). The digitized physiological descriptors are then output and entered into Characterization Apparatus **300** (step **210** in **FIG. 1**) for derivation of a relevant informational data set. These measurements can be repeated at regular intervals after implantation of a NPIT device in an effort to define the lowest frequency that such a high energy pacing modality should be implemented as to maximize battery longevity (the effects of CCM may last for prolonged time periods after current delivery is terminated). Such data can be compared to analogous data acquired by an implanted device (e.g. peak endocardial acceleration) as to provide the clinician with more robust informational data sets.

[**0084**] For explanatory purposes, we will describe the method and means by which such an algorithm functions using non-invasive imaging echocardiographic techniques and then illustrate how these methodologies are applied to be intrinsic to device based software. By way of example, referring to **FIG. 8**, physiological descriptors F-J are input to Characterization Apparatus **300**. F is a measurement of torsion which can be based on tissue velocity and 2D strain data (e.g. speckle tracking), G relates to septal performance/motion (e.g. septal strain, septal regional volume dV/dt, longitudinal displacement derived from tissue tracking), H describes chamber geometry (LVEDV, sphericity), I relates to lateral wall performance/motion, and J, changes in parameters F-I with NPIT turned on or off or relative to baseline measurements (pre-activation). At F, after input step **420**, LV torsion measurements are evaluated. Patients with moderately decreased torsion (f4-f5) are likely to respond to NPIT. Those with severe impairments ($<f4$) will be non-responders and as such NPIT is not activated, step **430**. Patients with minor or no impairments in torsion will not reap significant enough benefit for NPIT activation given the costs to the system (e.g. battery longevity) and thus at step **430**, NPIT is not recommended. At step **440** those patients with moderately impaired LV torsion have septal performance characterized in G. This can be based on measurements of strain, strain rate, regional dV/dt, cyclic variation of integrated backscatter (CVIB). If the findings confirm septal contractile abnormalities with contractile reserve/viability ($g1<G\leqq g3$), step **460** occurs, else NPIT is inactivated (step **450**). Note that for $G=g1$, septal contractility can not be increased and as such NES will not be advantageous. Next, LV chamber geometry is evaluated. This may be done by measurements of LVEDV and sphericity. Patients with markedly dilated, globular hearts who are non-responders to NPIT ($H\geqq h3$) do not have NPIT activated. Those with LV geometry appropriate for NPIT proceed to step **470**. Next, lateral or non-septal segmental performance is evaluated, physiological descriptor I. In patients with effective NPIT, increases in longitudinal displacement or non-septal regional tissue velocity/acceleration will be expected. Thus this assessment can serve as an integral part of an open loop feedback system (unless an interface or closed loop system is in place, see below). If the findings at this step are consistent with global tethering effects on non-septal segments this information is utilized in decision-making algorithms that decide the frequency and duration of current stimulation (ideally as part of a closed loop system). (Importantly, though some of the effects of NPIT occur with active stimulation, these effects may last for variable time frames and as such this type of feedback loop is useful.) At I, the frequency of NPIT stimulation is decided upon and such data can be made available either with removable media, via interface, or

wireless telemetry communicating with the implanted device/device programmer. If I is incorporated within the device itself as part of a closed loop feedback system described in more detail below, (intrinsic physiological descriptors), this data may be directly communicated (dotted arrow, step **495**) to the impulse delivery system, NPIT, within the implanted unit. The NPIT determines the nature of non-excitatory stimulation. If I determines that NPIT should continue the algorithm proceeds to step **480**. At J an analysis and scoring of a composite of physiological descriptors (e.g., F-I) occurs and also functions to provide the system with feedback about the affect of NPIT on F-I. This composite of intrinsic physiological descriptors is communicated to NPIT and serves to direct the frequency and duration of non-excitatory stimulation in conjunction with the data determined at I. A bin counter system or other algorithm can be utilized to translate I and J into frequency and duration of NPIT. This data is made available to **400** via step **490** for physician review as part of an IDS. Any algorithm can be employed to serve the function of evaluating the need for and properties of non-excitatory stimulation or alternate Non-Pharmacologic Inotropic Therapy (NPIT) device without departing from the scope and spirit of this invention.

[**0085**] In the current invention, the algorithms described above, are employed within a CRT and/or NPIT device in an analogous manner. Regional trans-myocardial changes in impedance are surrogate to strain measurements reflective of contractility and lead-based accelerometers/piezoelectric transducers are surrogate to measurements of rotation/torsion, longitudinal displacement. Referring to **FIG. 10**, Doppler derived tissue velocity of a normal myocardial segment is depicted on top. The corresponding myocardial acceleration time graph is illustrated on the bottom. As is evident from this figure, the tissue velocity and accelerometer based measurements are temporally related. A multi-site CS lead with accelerometers located along the lead body is ideal for such an assessment as the CS courses along the circumference of the basal LV cavity in a plane parallel to the AV annulus. The accrued data from multiple accelerometers along a lead body can be processed in the device itself or, in a preferred embodiment, summated via circuitry within the lead body itself. The latter will not necessitate use of additional connectors. The acquired data from such transducers can be used to estimate LV rotation/torsion during the cardiac cycle and compared to other data acquired (**FIG. 11**). The temporal relationship of extrinsically derived LV rotation (top), intrinsic myocardial acceleration (middle) and extrinsic tissue velocity (bottom) is depicted in this figure. This figure also illustrates that during IVC, a differential between peak RV septal (Srot) and LV lateral rotation (Lrot) and peak RV septal (Sacc) and LV lateral acceleration (Lacc) may exist. These temporal relationships allow for acquisition of data related to event timing and assessment of electromechanical dysynchrony. The data acquired by implanted accelerometers can be processed to derive measurements related to LV rotation/motion/displacement consistent with tissue velocity data described above and can be evaluated via device-device communication either with removable media or an interface. Methods for deriving velocity or displacement data from accelerometers using integrator circuits are known in the art and described in detail in referenced U.S. Pat. No. 5,549,650 (Bornzin et al.). Physiological properties that are input to the Analysis Apparatus may be both extrinsically derived or derived from a plurality of signals within the implanted device and used for comparative purposes. The use of accelerometers and other lead based sensor measurements (e.g. impedance data) described herein are merely exemplary and any sensor or transducer which is part of an implanted device can acquire data that is incorporated into these algorithms.

[**0086**] The algorithms detailed herein are described using physiological indices derived from implanted cardiac devices and extrinsic imaging modalities as this field is in a state of rapid evolution. The principles underlying this invention can be applied to other fields that are similarly evolving at a rapid pace. Identification of genetic markers for predicting disease/outcome is one such field.

[**0087**] In an alternate embodiment, the concepts herein are extended to algorithms that incorporate data intrinsic to the body such as chromosomal properties related to genetic markers of disease (e.g. coronary artery disease, cardiomyopathy, long QT syndrome, oncogenes), circulating lipoproteins, serum markers; and extrinsic to the body such as results of various diagnostic tests (demographic data, phenotype, results of imaging modalities, pathologic findings from biopsies). This data can be input to **100** along with CP and DI and is relevant as an increasing number of genetic mutations have been identified that are predictive of disease states (e.g. progressive cardiomyopathy) and sudden cardiac death (Villard E, Duboscq-Bidot L, Charron P, et al. Eur Heart J 2005; 26:794-803). Treatment options including device based therapies, pharmacologic treatment and delivery of genetic material into pathologic tissue may be more appropriately chosen when the invention herein is widely available.

[**0088**] By way of example, analysis algorithms are being developed for detection of genomic properties in human cancer cell lines. These methods are currently employed using intrinsic or extrinsic markers for disease. Greater predictive power can be expected by combining both intrinsic and extrinsic data/signals.

[**0089**] Daruwala et al. has developed a versatile statistical algorithm to detect genome copy number variation (Daruwala R S, Rudra A, Ostrer H, et al. A versatile statistical analysis algorithm to detect genome copy number variation: Proceedings of the National Academy of Sciences of the United States of America, 2004. November 16; 101 (46): 16292-7). This algorithm analyzes genomic data obtained from a variety of array technologies allowing for detection of regions of the genome with altered copy number. The algorithm combines data from multiple 'intrinsic' sources and thus facilitates the discovery of genes and markers important for predicting risk of developing cancer. It implements a priorless maximum a posteriori estimator and dynamic programming implementation to increase computational robustness. This specific technique and others like it are being utilized to predict or detect cancer.

[**0090**] Algorithms that implement genetic markers for identifying patients prone to developing coronary artery disease are also being developed (Jones, Karen Ann et al., Atherosclerosis-associated Genes; patent application 20020015950). This algorithm is ultimately employed to treat or prevent "a disease associated with the altered expression of a gene that is coexpressed with one or more known atherosclerosis-associated genes in a subject in need, the

method comprising the step of administering to the subject in need the pharmaceutical composition . . . in an amount effective for treating or preventing the disease".

[0091] The health care costs associated with widespread genetic testing and ethical issues associated with using genetic predictors of disease for clinical decision making (e.g. pharmaceutical/genetic therapy, prophylactic surgery) are tremendous. Thus, a more accurate means for predicting outcome will lead to development of guidelines which determine who in the general population should be tested and which treatment options are preferred. This will reduce health care costs, reduce the frequency of and risks of unnecessary therapies/surgeries and prevent the emotional trauma from positive results in patients with an otherwise low risk for developing a specific pathologic state.

[0092] Risk assessment tools exist for predicting probability of developing cancer. One example is the Breast Cancer Risk Assessment Tool (http://brca.nci.nih.gow/brc/). This is a risk stratification tool that relies on extrinsic data and not genetic markers. Certain models/calculation methods have been developed such as the Gail Model and NSABP model (http://www.halls.md/breast/riskcom.htm). The construct of these models employed evidence based medicine. Genetic data will have more predictive power and would be weighed more heavily in the algorithm described herein. Nonetheless, combining extrinsic data such as that used in the Gail Model and intrinsic data that relates to genetic markers for disease will result in greater predictive power than either methodology alone.

[0093] Referring to **FIG. 1**, DI can be replaced by Diagnostic Intrinsic data, and CP with Complementary Peripheral or extrinsic data. In **FIG. 2**, the indices input into the system can likewise include specific markers that are associated with development of a specific malignancy (e.g. breast cancer) or even risk of mortality from cancer. Intrinsic properties A-C can be genomic data/features of phenotypic expression and D-F, complementary, peripheral or extrinsic data.

[0094] As described above, several factors can be used to derive a numeric score for properties A-F. A can relate to genomic copy number variation and presence of other genomic traits (e.g. EVI1, MYC genes). B can relate to presence of and type of disease-associated germlne mutations (e.g. BRCA1, BRCA2). C can be a genotypic descriptor related to likelihood of genetic expression.

[0095] Extrinsic data can include demographic data (history of tobacco or alcohol intake), results of imaging studies (e.g. breast sonograms, mammograms, MRI), pathologic findings from biopsies and family history of cancer. Extrinsic physiological descriptors can represent, D, family history, E, results of breast MRI, and F, biopsy findings. By way of example, D can be scored based on heritage (e.g. Ashknenazi descent), number of immediate (first-degree) and second-degree relatives that have been diagnosed with specific cancer types, the life-expectancy of such relatives, response of familial cancer to therapy in a weighted fashion (e.g. Discriminant Analysis). E can relate to MRI properties such as the anisotropy of breast tissue density, presence of specific findings associated with increased risk of breast cancer. F can relate to pre-malignant findings (e.g. dysplasia, papillomatous tissue, ductal carcinoma in situ) on breast biopsies performed on a given individual or even an individual's family members.

[0096] Specific physiological indices are entered into the algorithm using a discrete numeric format along a graduated scale as described above. Physiological descriptors such as presence of BRCA mutations (descriptor B) and biopsy pathology data (descriptor F) will be weighed more heavily than other less predictive descriptors (e.g. using Discriminant analysis). The output informational data set provided to the physician will guide decision-making by providing an estimation of probable outcome (e.g. percent risk of developing invasive breast cancer, percent risk of dying from breast cancer) and the effect of various therapeutic regimens (e.g. increased surveillance, treatment with Tamoxifen, future genetic therapies, prophylactic mastectomy/oophorectomy) for modifying such an outcome. The central processing center, CPC, and pooled data bank would ideally be located where chromosomal analysis is performed (i.e. Myriad laboratories) as few centers are currently available for such genetic testing. It would be mandatory for any patients having such testing to have all demographic data, family history and other descriptors sent to the CPC. This data in turn would be communicated into **400** for processing. In this example, apparatus **300** is an separate apparatus or contained within extrinsic diagnostic equipment such as a breast MRI machine or mammography unit.

[0097] Thus, the spirit and scope of this invention relates to a variety of pathologic states and not just those related to the field of cardiology.

Translation Function

[0098] When this invention is applied to implanted cardiac device technology, mathematical methods for correlating the various indices can be used as to allow translation of device based data to imaging based data and vice versa. Novel mathematical units that are assigned a value along a graduated scale can apply to both intrinsically and extrinsically derived data. These units can be derived as to develop a universal mathematical language that is applicable to both device-based and non-device based sensors/transducers. By way of example, a number of patients who have had an impedance based dysynchrony parameter, CPPz, acquired/derived from an implanted device, and a multi-dimensional echocardiographic measurements of dysynchrony, SMDI, derived can be compared (though not necessary for understanding this concept, SMDI represents the Systolic Myocardial Dysynchrony Integral, a triple integration in polar coordinates of the Curved Anatomic M-mode myocardial dimension, coursing around a 360 arc about the heart, between base to apex, endocardial to epicardial surfaces, where the limits of integration are between the time of aortic valve opening and time of end diastolic motion of all myocardial segments; the derivation of SMDI can be found in the published patent application Ser. No. 10/779,162). Such a comparison can include patient demographic data, clinical variables and patient outcome. Regression or other statistical analysis of extrinsic and intrinsic parameters is used to correlate intrinsic and extrinsic parameters. The relationship need not be linear but may be exponential, curvilinear, determined by a derived differential equation or otherwise correlated in some other fashion. By way of example, SMDI and CPPz can have a linear relationship. Thus, SMDI and CPPz are directly proportional along a graduated scale between normal and pathologic values (**FIG. 12**). We can define normalcy as greater than or equal to 80 percent (chance of not having a specific outcome) and

the most pathologic state with the worst prognosis as less than 20 percent. Thus, in the universal mathematical language, the clinician can evaluate a given patient not by a specific value (e.g. EF=30%), but by the percentage likelihood of poor outcome (e.g. heart failure decompensation, death) based on evidence based medicine. Input of multiple indices derived from multiple sensors/transducers and even genotype will increase the predictive power of algorithms that incorporate varying sensor data. The resulting information is 'translated' and communicated to the practitioner in terms of prognosis (e.g. percent likelihood of specific outcome) and is dependent on evidence based medicine.

[0099] A translation function can, in a more simplified approach, be used to translate mathematical units derived from one type of implanted sensor into conventionally recognized units. For example, displacement data derived from lead based accelerometers to indices used with tissue Doppler or speckle tracking techniques (e.g. longitudinal mm distance, radians rotated). This can be defined for an individual patient based on simultaneously acquired data with, for example, an ultrasonic interface connected ('162) or by using a look up table developed from pooled data (registry) derived from numerous patients who have had both intrinsic and extrinsic data derived. Regression analysis or other technique can be used to correlate any intrinsically and extrinsically derived index (**FIG. 12**) and derive functions/equations that translate an intrinsic index to an extrinsic index and vice versa. Those described herein are merely exemplary.

Referring to **FIG. 12**:

$$(CPPZ)=m*(SMDI)$$

[0100] A linear relationship between intrinsic impedance parameter CPPz and extrinsic ultrasound parameter SMDI is present. Slope m relates how CPPz and SMDI changes as a function of one another.

[0101] This relationship can be derived as a function of time during the cardiac cycle and in this example SMDI becomes an instantaneous measurement of cardiac dysynchrony, MDI, and CPPz an instantaneous impedance based measurement of dysynchrony which may be directly proportionate to each other. (Cardiac motion/deformation can be symmetric and synchronous at one point during the cardiac cycle (e.g. end diastole) and not at another time frame (e.g. end-systole)).

integral Z(t) dt α MDI(t) dt

[0102] To further elaborate on the concepts described, the reader is referred to **FIG. 13** through **16**. **FIG. 13** illustrates how myocardial displacement is derived from evaluation of Doppler derived tissue velocity as a function of time (integration of curve). This data can be obtained from lead based accelerometer signals in an analogous fashion with displacement data derived with two integrator circuits (Bornzin et al., U.S. Pat. No. 5,549,650). Use of one integrator circuit to derive velocity data and relative times of peak velocity from more than one lead based accelerometer will yield an intrinsically derived index analogous to the tissue Doppler derived Yu's index—standard deviation of time of peak velocity for multiple insonified regions of interest. This temporal information can be input along with pure displacement data (cardiac performance data) into the software algorithms described in this invention. Thus, in this simplified embodiment, the plurality of signals may be related to varying data derived from only one type of sensor/transducer. Ideally, such lead based accelerometers are located on the mid-basal portion of the interventricular septum and LV lateral wall. More basally located accelerometers are optimal as degree of displacement is greatest at basal locations (**FIG. 13**).

[0103] In **FIG. 14-16**, a patient with a CRT device has changes in interval timing programmed and activation of NPIT. Septal and lateral (mid and basal) regional displacement is depicted. When a lateral LV lead is pre-activated 40 msecs before an RV interventricular lead, (**FIG. 14**) without lateral or septal NPIT, dysynchronous conditions are found and average longitudinal displacement is less (basal and mid-septal displacement less than lateral). In **FIG. 15**, NPIT is delivered to lateral and septal leads and dysynchronous activation and impaired septal displacement is seen. In **FIG. 16**, the same patient has NPIT delivered to septal electrodes with no offset in interval timing between RV and LV leads. An optimal temporal relationship and comparable degrees of displacement of septal and lateral segments are found under these circumstances. Changes in interval timing alone might accomplish the same and avoid the costs to the system from delivering NPIT.

[0104] In these examples, the peak displacement seen at end-systole is noted to vary under different circumstances. If the same patient has NPIT delivered to lateral leads, the resulting curves may become more disparate. Simultaneous delivery of NPIT to septal and lateral electrodes in this patient may also lead to less congruence in displacement curves (**FIG. 15**) as only septal activation is needed with a zero msec offset in VV interval timing. If such a patient has a system only capable of delivering lateral NES, a device based control system would terminate NPIT as to preserve battery longevity and improve clinical outcome. On the other hand, if global tethering resulted in improvements in septal displacement with only laterally delivered NPIT, the control system would enable NPIT.

[0105] Circumferentially located lead based accelerometers placed about a CS lead will enable an implanted system to derive rotational indices (e.g. peak systolic radial displacement, time of peak rotational velocity) and thus the system will be capable of evaluating all three elements of cardiac performance, The Three T's; thickening, timing and torsion (**FIG. 3A**).

[0106] Referring to **FIG. 17**, at step **600** raw accelerometer data is input into 2 integration circuits to generate displacement data for all implanted lead based accelerometers 1–n. At step **610** the displacement data for accelerometers 1–n is averaged to generate cardiac performance parameter d mean at step **640**. At step **620**, the doubly integrated accelerometer data is input into a standard deviation calculator which calculates the standard deviation of displacement values 1–n, SDd. Ideal conditions exist when there is homogeneous displacement in multiple regions. Thus, SDd will have a minimal value during optimal conditions of synchrony. (Step **620** would be most clinically applicable when accelerometers 1–n are along the same vector (e.g. longitudinal displacement). Thus, one would not necessarily want to combine accelerometer data derived from a circumferentially oriented accelerometer positioned along the coronary sinus with data derived from a longitu-

dinally positioned accelerometer, though timing information for differing vectors of displacement could be utilized as in step **630**. At step **630**, the time of maximal displacement of all accelerometer displacement data, t d_m, is determined from displacement time graphs similar to those shown in **FIG. 14**. In **FIG. 14**, a displacement time graph for tissue Doppler derived values is illustrated with an optimal time of peak displacement for basal lateral, d BL, region of interest, while septal regions of interest dysynchronously reach peak displacement at time Delta after AoVc. A similar displacement time graph can be generated for doubly integrated lead based accelerometer data and temporally referenced to the cardiac cycle using an intracardiac electrogram, cardiac acoustic data reflecting valvular events or other time cycle. If a preferred embodiment, the algorithms employ a plurality of signals, and determine the difference in time between aortic valve closure (tAoVc) as determined by a sensor (e.g. cardiac acoustical transducer) at step **680** as to calculate the SD in time of peak displacement relative to time of AoVc for all lead based accelerometers. Alternatively, we can calculate the SD in time of peak displacement for accelerometer signals 1−n disregarding any relationship to the cardiac cycle. The advantage of relating time of peak displacement to tAoVc is that ideal conditions of synchrony and cardiac performance exist when peak displacement occurs at the end of the systolic ejection phase. In either case, the SD of time of peak displacement parameter, SD t, is calculated at step **660**. At step **700**, all parameters are input into the blended cardiac performance/dysynchrony index, CPDI, calculator. This CPDI represents a blend of accelerometer data that possesses properties of timing and cardiac performance. The units of expression are in time (milliseconds) and a minimal value is ideal as the numerator is the product of SDt and SDd and the denominator is d mean. The denominator contains cardiac performance data, while the numerator contains timing and displacement data representative of electromechanical synchrony. The better the cardiac performance and synchrony, the lower the value in milliseconds. Thus, we have derived a novel mathematical index using accelerometer data. The units of expression can be converted or translated to analogous values if this data were to be simultaneously acquired using tissue Doppler indices and comparisons are made (e.g. using an echo-device interface as described in '162). (Information generated as a result of data transfer is used to construct a universal language of mathematical indices applicable to intrinsic (device-based) and extrinsic software algorithms.) Analysis of this CPDI for various permutations in interval timing can be accomplished by any method including, but not limited to, the matrix optimization method (MOM) described in '162. A three dimensional MOM can be utilized for this case example. The three dimensions would include AV interval timing, VV interval timing, and type of NPIT being delivered.

[**0107**] In the latter algorithms described, a plurality of signals is derived from one transducer/sensor type without need for multiple sensor technology. The accrued data represents more specific information and translation between intrinsic and extrinsic indices will be relatively simple. Translation can be performed by comparing external monitoring data and device based data acquired from a single individual (e.g. manually downloaded, via an interface or wireless telemetry). Translation can also be performed for large samples of patients (from a centralized database/registry) in a more generalized fashion. When multiple sensor technology is implemented, as detailed in the algorithms described previously, the resulting informational data set has broader application and prognostic information and clinical recommendations can be made using neural network techniques, for example. Thus, mathematical indices derived using multiple sensor technology can be incorporated into algorithms that generate prognostic information. The resulting informational data sets will have more widespread ramifications than the specific information provided by an individual index (e.g. displacement) which is best suited for optimizing device function through closed loop control systems. Device software algorithms can implement more complex, device-based, closed loop control systems using multiple sensor technology if the costs to the system and processing times are not excessive.

[**0108**] Closed Loop System Function Confirmation

[**0109**] In an alternate embodiment, this technology can confirm the appropriate functioning of closed loop systems within implanted devices from time to time. Similar physiological descriptors may be acquired by implanted devices and external diagnostic equipment and constitute multiple complementary data sets. As an example, myocardial acceleration can be derived using tissue Doppler techniques or implanted lead-based accelerometers (**FIG. 7**). Determination of myocardial acceleration can relate information about cardiac performance during isovolumic contraction, systole, S, left ventricular rotation/torsion and diastolic, D, counter-rotation/torsion (**FIG. 4**). This data, in turn, may be used for monitoring purposes or titration of device based therapy. By way of example, and in a preferred embodiment, externally derived measurements of degree and timing of myocardial acceleration (e.g. tissue Doppler measurements of myocardial rotational, longitudinal or omnidirectional velocity/acceleration) can be used to confirm appropriate function of a closed loop system that automatically makes such determinations within an implanted device. An intrinsic/extrinsic comparison apparatus (I/E) functions to translate and compare analogous indices derived from an implanted device and any external diagnostic equipment thereby performing checks and balances for closed loop systems, CLS, contained within the implanted device (**FIG. 18**). I/E can be incorporated into a separate apparatus, part of the extrinsic imaging device or preferably part of the implanted device (dashed box in Figure). Outcome analysis can be used to confirm appropriate function of such a closed loop system using conventional measurements of quality of life when the technology is applied to heart failure devices that deliver NPIT and CRT. Quality of life can be determined by simply inputting data in numeric format based on a patient completed quality of life questionnaire. Optimally, quality of life can be determined via the implanted device itself based on a plurality of signals. Such signals can include measurements of patient activity based on accelerometers within a device can, measurements of thoracic fluid content based on transthoracic impedance data or a variety of indices of cardiac performance. Similar algorithms have been described in the field of neurology using implanted devices for treating and preventing seizures (Echauz, Javier Ramon et al. Unified probabilistic framework for predicting and detecting seizure onsets in the brain and multitherapeutic device patent application number 20040068199).

[**0110**] Data acquired by any imaging modality can be made available for entry into an apparatus that performs

such complex algorithms in an efficacious manner. In this fashion, a physician can render diagnoses and make management decisions based on a number of indices simultaneously rather than relying on independent physiological properties. Digital signal processing allows for imaging data derived from alternate imaging modalities to be compiled in a central processing unit and analyzed in context of similarly derived parameters acquired from implanted devices. Wireless data transfer can be via a number of means such as the Internet, removable digital media or telecommunication. The gathering of voluminous data banks/libraries/registries of data acquired from external monitoring equipment, implanted devices/sensors coupled with patient demographic data and clinical outcomes will lead us to practice evidence based medicine. The derived data will be used to develop treatment guidelines and clinical recommendations appropriate for each patient as an individual. In turn, this technology will reduce health care costs and benefit society as a whole.

[0111] The spirit and scope of the concepts described herein are applicable to a variety of diagnostic modalities, monitoring systems, disciplines, implanted devices and a variety of indices derived by external and internal means. This information can be communicated to a physician any number of ways and sent via wireless telemetry to an electronic medical record. Derivation of universal mathematical indices/units of expression will facilitate translation and bi-directional communication of diagnostic data between an implanted device and external diagnostic equipment and confirm functionality of closed loop control systems and extrinsic diagnostic imaging modalities (cross-verification).

Data Communication

[0112] Parametric imaging techniques can be used to illustrate intrinsically derived data such as time of peak impedance/acceleration/displacement or device based indices of cardiac performance. In a preferred embodiment, intrinsically derived indices that are analogous to extrinsically derived data are displayed using color encoded pixels superimposed on images of the heart generated, for example, by echocardiography. By way of example, regional differences in time of peak impedance or time of peak displacement derived from implanted sensors can be displayed in similar fashion to tissue Doppler derived indices portrayed on state of the art echocardiography machines.

[0113] Many other modifications may be made to the invention without departing from its scope as defined in the appended claims.

I claim:

1. A method of generating cardiac information comprising:

comparing pooled diagnostic data stored in a centralized data bank with data collected from a plurality of similarly acquired data from individual patients including sensor-derived data from within the patients' implanted cardiac rhythm management device; and

deriving information from said comparison, said information being representative of the pathologic state of the individual patient.

2. The method of claim 1 further comprising the providing of one or more of a prognosis, recommended treatment options and programming of said cardiac rhythm management device.

3. The method of claim 1 wherein said comparing and deriving is performed in stand-alone equipment.

4. The method of claim 1 wherein said comparing and deriving is performed in a patient's cardiac management system.

5. The method of claim 1 further comprising using said information to confirm appropriate functioning of cardiac rhythm management devices at periodic intervals.

6. A method of generating programming parameters for implantable devices comprising:

combining a plurality of one or more of patient demographic information, genetic characteristics and results of diagnostic testing from any given patient to generate patient specific prognostic information based on statistical comparisons to similar data acquired from patients whose outcome under varying treatments is stored in a central processing center.

7. A method of generating programming parameters for cardiac rhythm management devices comprising:

collecting analogous data from cardiac rhythm management device-based sensors and external diagnostic equipment; and

using said data to obtain said parameters, said parameters being selected to control the frequency and duration of pacing modalities selected to increase cardiac contractility.

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