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(54) METHODS AND APPARATUS FOR IDENTIFYING PATIENTS AT RISK FOR LIFE THREATENING ARRHYTHMIAS

(76) Inventors: **Orhan Soykan**, Shoreview, MN (US); **Timothy H. Robinson**, Savage, MN (US); **Walter H. Olson**, North Oaks, MN (US); **Vinod Sharma**, Blaine, MN (US); **Amy C. Dearking**, Rochester, MN (US)

Correspondence Address:
MEDTRONIC, INC.
710 MEDTRONIC PARKWAY NE
MS-LC340
MINNEAPOLIS, MN 55432-5604 (US)

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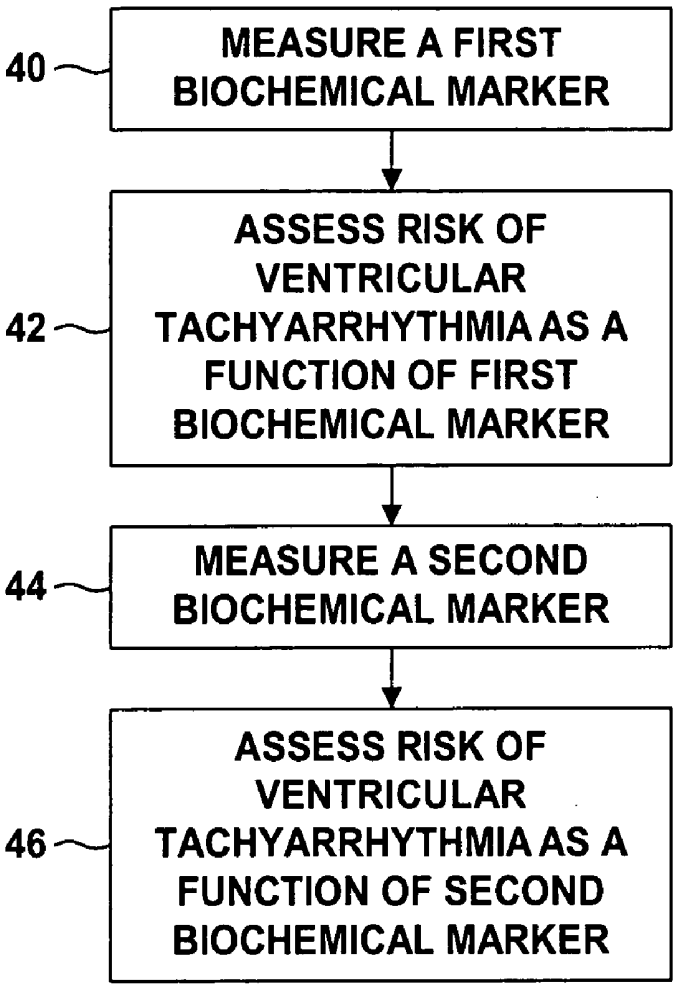
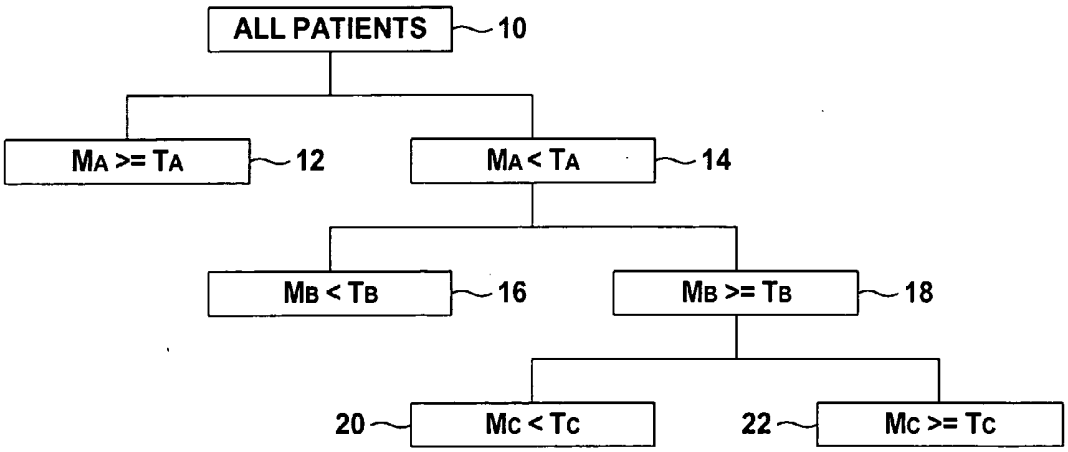
(52) **U.S. Cl.** **607/14**; 607/9

(57) **ABSTRACT**

In general, the invention is directed to systems and techniques for assessing a risk of ventricular tachyarrhythmia in a patient by measuring one or more biochemical markers that reflect the health of a patient. Typically, the patient submits a sample, such as a blood sample, which is tested for one or more biomarkers. Based upon the results of the tests, the patient's risk of ventricular tachyarrhythmia may be assessed. When the patient is found to be at risk, the patient may receive an implantable medical device or drug therapy to address the risk.




ALL PATIENTS
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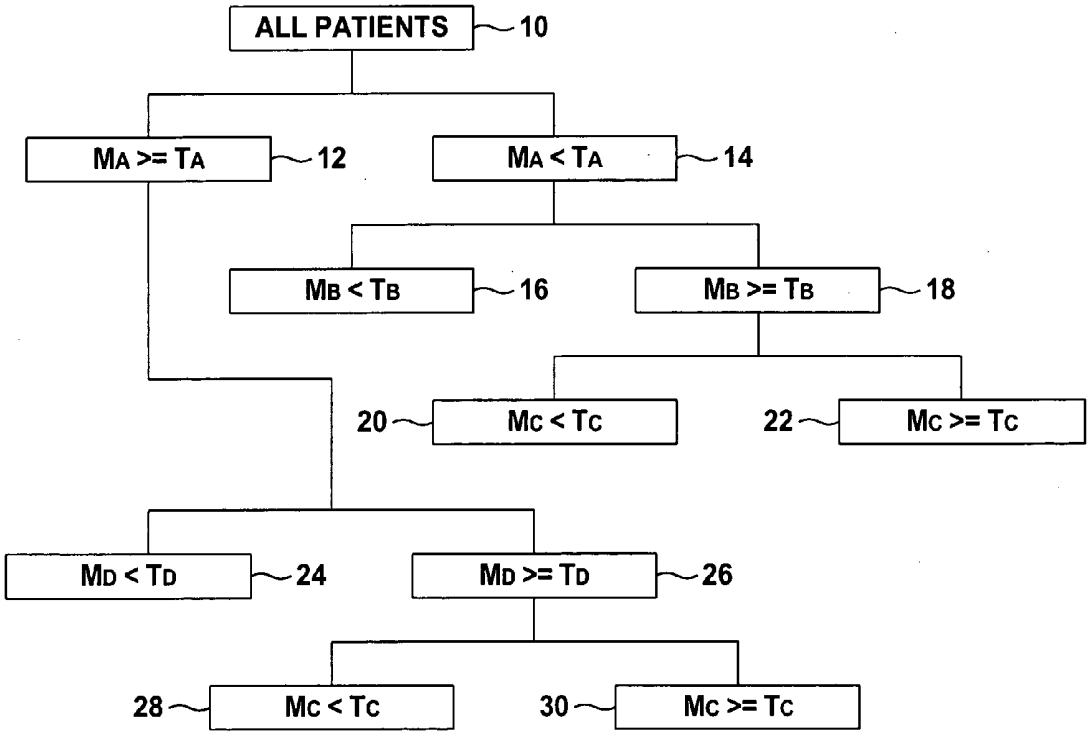
MA >= TA
12
MA < TA
14
MB < TB
16
MB >= TB
18
20
MC < TC
22
MC >= TC

FIG. 1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22
MC >= TC
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24
MD >= TD
26
28
MC < TC
30
MC >= TC

FIG. 2

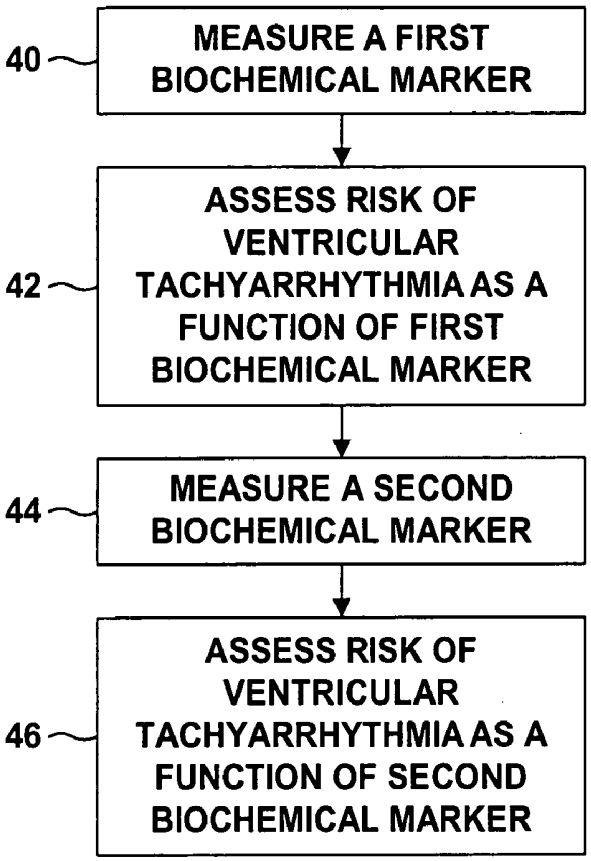
40
MEASURE A FIRST BIOCHEMICAL MARKER
42
ASSESS RISK OF VENTRICULAR TACHYARRHYTHMIA AS A FUNCTION OF FIRST BIOCHEMICAL MARKER
44
MEASURE A SECOND BIOCHEMICAL MARKER
46
ASSESS RISK OF VENTRICULAR TACHYARRHYTHMIA AS A FUNCTION OF SECOND BIOCHEMICAL MARKER

FIG. 3

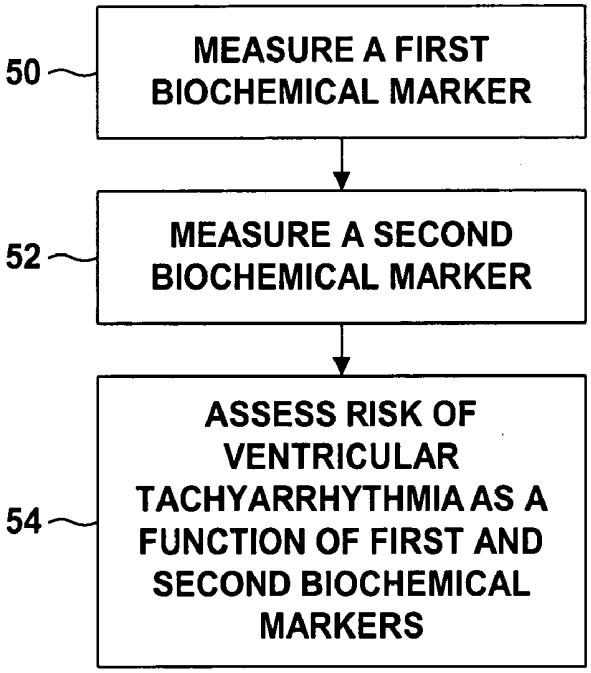
50
MEASURE A FIRST BIOCHEMICAL MARKER
52
MEASURE A SECOND BIOCHEMICAL MARKER
54
ASSESS RISK OF VENTRICULAR TACHYARRHYTHMIA AS A FUNCTION OF FIRST AND SECOND BIOCHEMICAL MARKERS

FIG. 4

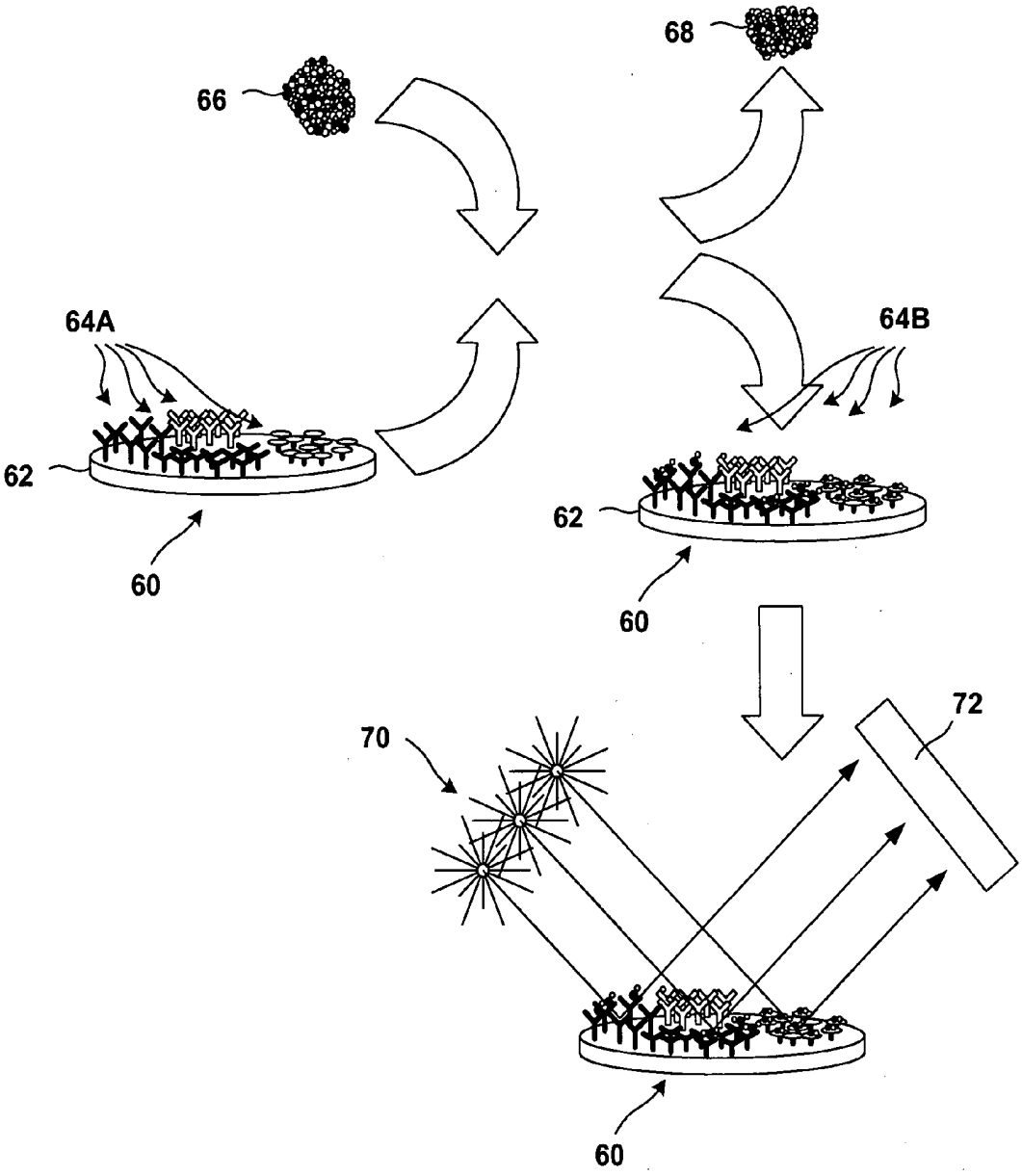

FIG. 5

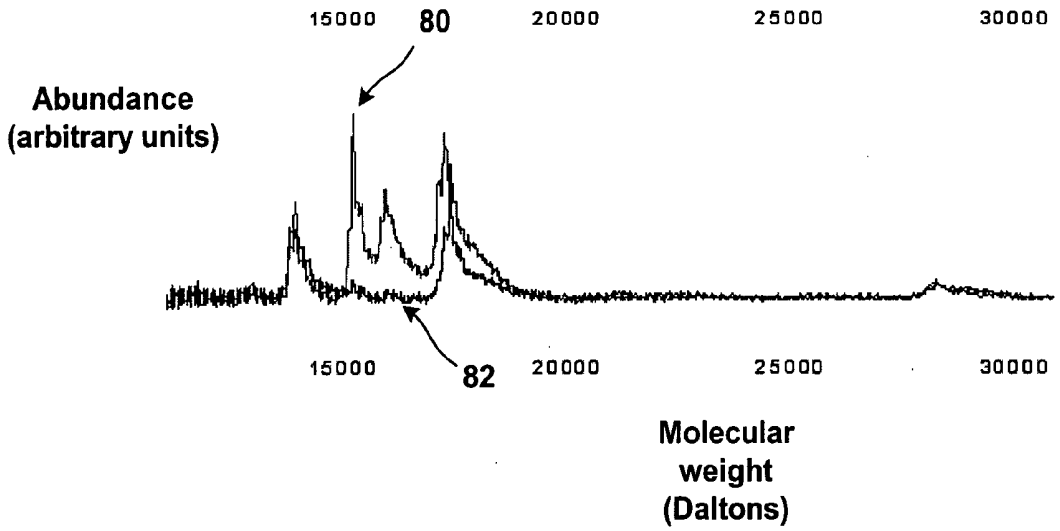
15000
80
20000
25000
30000
Abundance
(arbitrary units)
15000
82
20000
25000
30000
Molecular
weight
(Daltons)

FIG. 6

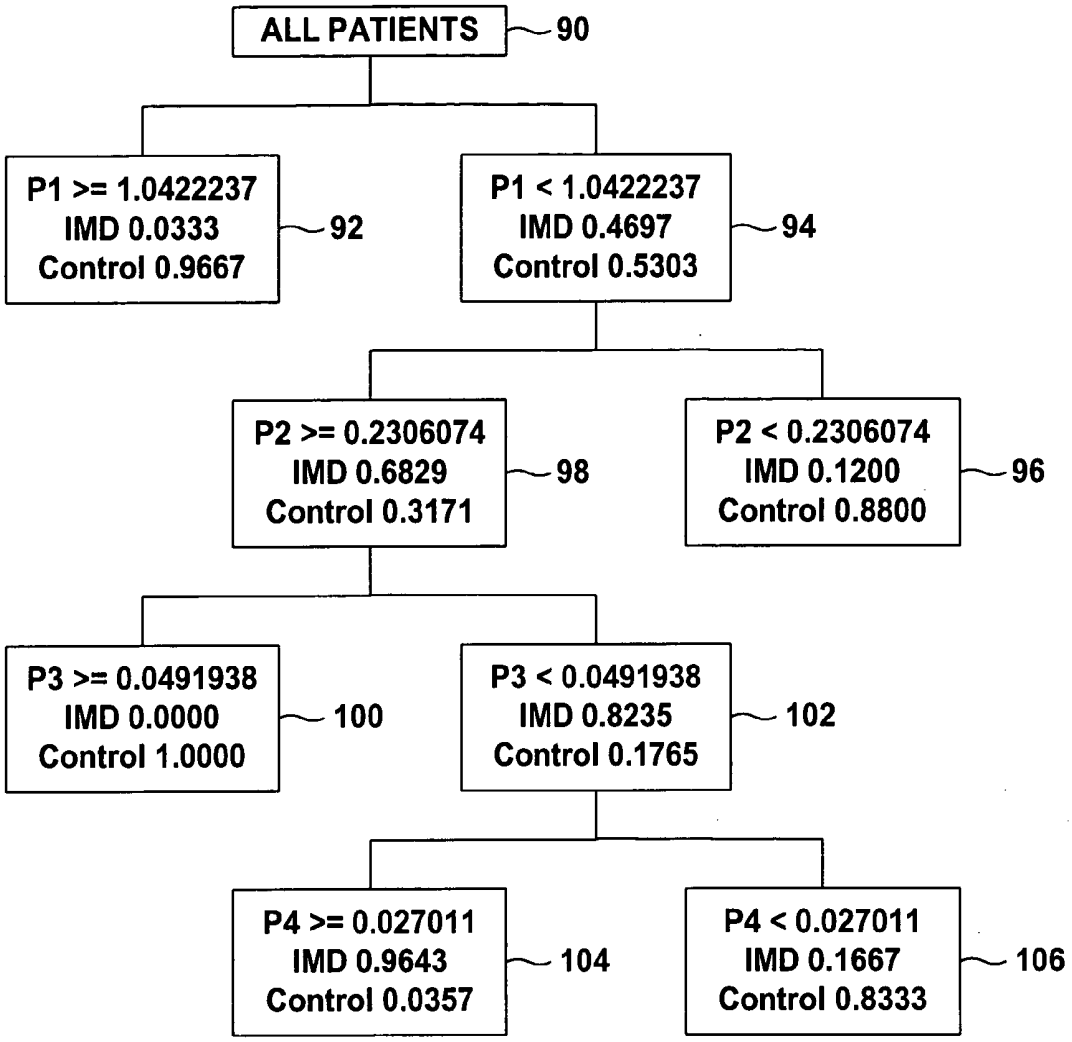
ALL PATIENTS
90
P1 >= 1.0422237
IMD 0.0333
Control 0.9667
92
P1 < 1.0422237
IMD 0.4697
Control 0.5303
94
P2 >= 0.2306074
IMD 0.6829
Control 0.3171
98
P2 < 0.2306074
IMD 0.1200
Control 0.8800
96
P3 >= 0.0491938
IMD 0.0000
Control 1.0000
100
P3 < 0.0491938
IMD 0.8235
Control 0.1765
102
P4 >= 0.027011
IMD 0.9643
Control 0.0357
104
P4 < 0.027011
IMD 0.1667
Control 0.8333
106

FIG. 7

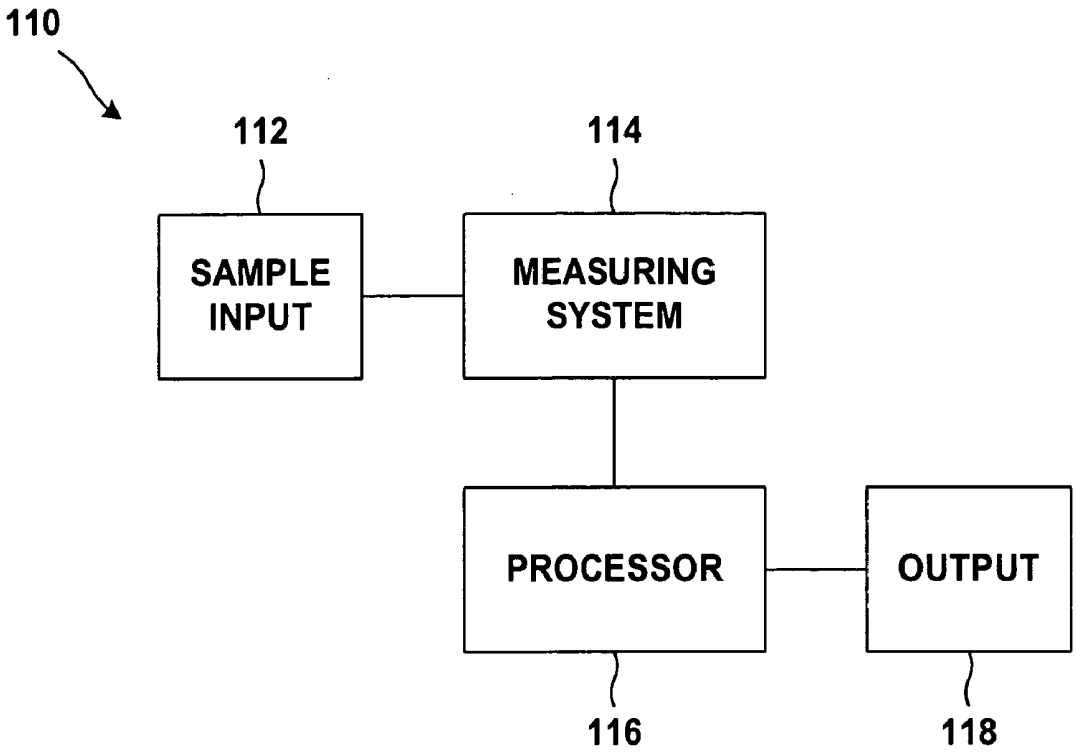
110
112
114
SAMPLE INPUT
MEASURING SYSTEM
PROCESSOR
OUTPUT
116
118

FIG. 8

METHODS AND APPARATUS FOR IDENTIFYING PATIENTS AT RISK FOR LIFE THREATENING ARRHYTHMIAS

PRIORITY INFORMATION

[0001] The present invention claims priority from U.S. provisional Application No. 60/542,004, filed Feb. 5, 2004.

TECHNICAL FIELD

[0002] The present invention relates to a system and method for identifying candidates for receiving cardiac therapy based on biochemical markers associated with propensity for arrhythmias.

BACKGROUND

[0003] Sudden cardiac death (SCD), or cardiac arrest, is the sudden, abrupt loss of heart function in a person who may or may not have diagnosed heart disease. Sudden cardiac death may be caused by almost all known heart diseases. Most cardiac arrests occur when the diseased heart begins to exhibit rapid and/or chaotic activity—ventricular tachycardia or fibrillation. Some are due to extreme slowing of the heart. All these events are called life-threatening arrhythmias. Patient's implanted with an implantable medical device, such as an implantable cardioverter defibrillator (ICD), greatly increase their chances of preventing sudden cardiac death caused by sustained ventricular arrhythmias. However, there are a significant number of patients with an increased propensity for suffering sudden cardiac death who have not experienced and survived previous cardiac episodes and therefore who are not already implanted with an implantable medical device. Consequently, there is a need for techniques and apparatus that can identify individuals at risk for sudden cardiac death prior to the onset of identifiable symptoms in order to provide those patients with an appropriate preventative therapy, such as drug therapy and/or an IMD that provides electrical stimulation therapy.

SUMMARY

[0004] In general, the invention is directed to systems and techniques for assessing a risk of ventricular tachyarrhythmia in a patient. In some medical conditions, including but not limited to ventricular tachyarrhythmia, certain biochemical factors in the body of the patient reflect the health of a patient. A patient that experiences ventricular tachyarrhythmia, for example, experiences an increased concentration of identifiable proteins in his blood, even the patient is symptom free. By measurement of the concentration of these biochemical markers or "biomarkers" in the patient, an assessment of a risk of ventricular tachyarrhythmia for the patient can be made, based upon the measurements.

[0005] In a typical embodiment, the patient submits a sample, such as a blood sample. The sample is tested for one or more biomarkers. Based upon the results of the tests, the patient's risk of ventricular tachyarrhythmia may be assessed.

[0006] When a patient has been identified as being at risk of ventricular tachyarrhythmia, the patient may receive therapy to address the risk. The patient may receive drug therapy, for example, or may receive an IMD that provides electrical stimulation therapy. In general, drug therapy prevents a spontaneous induction of a VT or VF episode. An IMD that provides electrical stimulation therapy, by contrast, terminates VT or VF episodes. Patients who receive therapy generally have improved survival rates.

[0007] In one embodiment, the invention is directed to a method comprising measuring a biochemical marker in a patient, and assessing a risk of ventricular tachyarrhythmia in the patient as a function of the measurement. This method supports the measurement of any number of biochemical markers and combinations of biochemical markers, and further supports a variety of measurement techniques.

[0008] In another embodiment, the invention is directed to a method comprising measuring a biochemical marker in a patient, and assessing a benefit of implanting an electronic cardiac stimulation device in the patient as a function of the measurement. In a further embodiment, the invention is directed to a method comprising measuring one or more biochemical markers in a patient, and assessing a benefit of administering an antiarrhythmic drug to the patient as a function of the measurement.

[0009] The invention also includes embodiments in which a computer-readable medium includes instructions for causing a programmable processor to carry out any of the methods of the invention.

[0010] In an additional embodiment, the invention presents a system that includes a measuring system configured to measure a biochemical marker in a patient and a processor configured to assess a risk of ventricular tachyarrhythmia in the patient as a function of the measurement. The measuring system may comprise, for example, a mass spectrometer, ELISA tests or any other biochemical assays.

[0011] The details of one or more embodiments of the invention are set forth in the accompanying drawings and the description below. Other features, objects, and advantages of the invention will be apparent from the description and drawings, and from the examples.

BRIEF DESCRIPTION OF DRAWINGS

[0012] **FIG. 1** is a conceptual logical diagram illustrating an embodiment of the invention.

[0013] **FIG. 2** is a conceptual logical diagram illustrating a variation of the embodiment of the invention shown in **FIG. 1**.

[0014] **FIGS. 3 and 4** are flow diagrams illustrating techniques for assessment of risk of ventricular tachyarrhythmia.

[0015] **FIG. 5** is a conceptual diagram illustrating a technique for mass analysis of a sample for biochemical markers.

[0016] **FIG. 6** is a graph showing differences in biochemical marker abundance for a patient at risk of ventricular tachyarrhythmia, compared to a patient in a control group.

[0017] **FIG. 7** is a logical diagram illustrating a technique for sorting patients at risk of ventricular tachyarrhythmia from a control group.

[0018] **FIG. 8** is a block diagram of a system configured to carry out an embodiment of the invention.

DETAILED DESCRIPTION

[0019] **FIG. 1** is a conceptual logical diagram illustrating an embodiment of the invention. Based upon measuring one

or more biochemical markers in a group of patients **10**, the invention provides for assessing a risk of ventricular tachyarrhythmia in each patient as a function of the measurement.

[**0020**] In the illustration shown in **FIG. 1**, a "tree analysis" sorts the patients into groups according to measurements of three biochemical markers. The biochemical markers are identified by the letters "A,""B,""C" and "D." Typical biochemical markers include proteins, lipids, genes and peptides or any combination thereof, but the illustration shown in **FIG. 1** is not limited to any particular biochemical marker or set of biochemical markers. Specific examples of biochemical markers are discussed below.

[**0021**] For each patient, a measure of a first biochemical marker (denoted M_A) is determined. Determining the measure of biochemical marker "A" for a particular patient may include, for example, determining the concentration or mass of biochemical marker "A" in a standard sample of bodily fluid taken from that patient. For each patient, the measure of the first biochemical marker is compared to a threshold value (denoted T_A). Those patients for whom M_A is greater than or equal to T_A are deemed to be a group **12** that is not at significant risk of ventricular tachyarrhythmia, and no further testing need be done for the members of group **12**. Those patients for whom M_A is less than T_A are deemed to be a group **14** that may be, or may not be, at risk of ventricular tachyarrhythmia. In **FIG. 1**, the members of group **14** undergo further testing to determine the individual members' risks of ventricular tachyarrhythmia.

[**0022**] For each patient in group **14**, a measure of a second biochemical marker "B" (denoted M_B) is determined. For each patient in group **14**, the measure of the second biochemical marker is compared to a second threshold value (denoted T_B). Those patients for whom M_B is less than T_B are deemed to be a group **16** that is not at significant risk of ventricular tachyarrhythmia, and no further testing need be done for the members of group **16**. Those patients for whom M_B is greater than or equal to T_B are deemed to be a group **18** that may be, or may not be, at risk of ventricular tachyarrhythmia.

[**0023**] The members of group **18** undergo further testing with respect to a measure of a third biochemical marker "C" (denoted M_C). For each patient in group **18**, the measure of the third biochemical marker is compared to a third threshold value (denoted T_C). On the basis of the comparison, the patients are divided into a group **20** that is not at significant risk of ventricular tachyarrhythmia, and a group **22** that is at significant risk of ventricular tachyarrhythmia.

[**0024**] In other words, **FIG. 1** illustrates assessing a risk of ventricular tachyarrhythmia for a patient as a function of the measurement of three biochemical markers. Unless a patient meets the threshold criteria for all three biochemical markers, the patient will not be deemed to be at significant risk of ventricular tachyarrhythmia.

[**0025**] The thresholds T_A, T_B and T_C are determined empirically. Clinical studies and experience may be used to determine thresholds for each biochemical marker. The thresholds may differ from marker to marker. For some biochemical markers, a patient may be at higher risk when the measure of the biochemical marker is above the threshold, and for other biochemical markers, the patient may be at higher risk when the measure of the biochemical marker is below the threshold.

[**0026**] **FIG. 2** is a conceptual logical diagram illustrating an embodiment of the invention that is a variation of the technique illustrated in **FIG. 1**. Unlike **FIG. 1**, patients sorted into group **12** are subjected to further testing. For each patient in group **12**, a measure of a fourth biochemical marker "D" (denoted M_D) is determined, and the measure is compared to a fourth threshold value (denoted T_D). On the basis of this comparison, patients in group **12** are sorted into groups **24** and **26**. Those patients in group **24** are deemed to be not at significant risk of ventricular tachyarrhythmia, and no further testing need be done for the members of group **24**.

[**0027**] Those patients in group **26**, however, are subjected to further testing. The members of group **26** undergo further testing with respect to the third biochemical marker "C," just like the members of group **18**. On the basis of a comparison of the measure of the third biochemical marker to the third threshold, the patients in group **26** are divided into a group **28** that is not at significant risk of ventricular tachyarrhythmia, and a group **30** that is at significant risk of ventricular tachyarrhythmia.

[**0028**] In other words, **FIG. 2** illustrates assessing a risk of ventricular tachyarrhythmia for a patient as a function of the measurement of four biochemical markers. A patient may be deemed to be at significant risk of ventricular tachyarrhythmia according to more than one testing path.

[**0029**] **FIG. 3** is a flow diagram illustrating logical sorting embodiments such as are depicted in **FIGS. 1 and 2**. An apparatus, such as apparatus illustrated in **FIGS. 5 and 6**, or a technician measures a first biological marker (**40**) and assesses a risk of ventricular tachyarrhythmia in the patient as a function of the measurement (**42**). The apparatus or technician measures a second biological marker (**44**) and assesses the risk of ventricular tachyarrhythmia in the patient as a function of that measurement (**46**).

[**0030**] In the procedure outlined in **FIG. 4**, the apparatus or technician measures a first biological marker (**50**) and measures a second biological marker (**52**), and assesses the risk of ventricular tachyarrhythmia in the patient as a function of both measurements (**54**). The techniques shown in **FIGS. 3 and 4** may achieve the same result, that is, a patient may be sorted according to risk of ventricular tachyarrhythmia using either technique. When a patient is deemed to be at risk, an appropriate therapy may be applied. Therapy for a patient may include, for example, implanting an electronic cardiac stimulation device in the patient that terminates episodes of ventricular tachyarrhythmia or administering an antiarrhythmic drug that prevents induction of such episodes.

[**0031**] **FIG. 5** is a conceptual diagram illustrating a technique for measuring a plurality of biological markers. A biochip **60** comprises a substrate **62** and one or more sensing elements **64**A. In **FIG. 5**, four distinct sensing elements are coupled to substrate **62**, but the invention encompasses use of any number of sensing elements.

[**0032**] Biochip **60** is a set of miniaturized test sites, or microarrays, arranged on a solid substrate **62** made from a material such as silicone or glass. Each test site includes a set of sensing elements **64**A. In general, sensing elements include one or more components that change conformation in the presence of an analyte of interest. Typical sensing elements include antibody molecules that change conforma-

tion in the presence of a specific biomarker, but that do not change conformation in the presence of any other biomarker. The invention encompasses any sensing element, however, and is not restricted to antibodies. The sensing elements of biochip **60** may have general properties such as high affinity toward hydrophilic or hydrophobic molecules, or anionic or cationic proteins, for example.

[**0033**] Substrate **62** may have a surface area of about one square centimeter, but the invention encompasses biochips that are larger or smaller. Substrate **62** may be formed in any shape, may include any number of test sites, and may include any combination of sensing elements. The invention is not limited to any particular biochip.

[**0034**] Biochip **60** is exposed to sample **66**. Sample **66** may include any biological sample from a patient, such as a blood sample. Biomarkers present in sample **66** react with sensing elements on biochip **60**. Exposed sensing elements **64**B typically react with biomarkers in sample **66** by undergoing a conformational change, or by forming ionic, covalent or hydrogen bonds. The unreacted or unbound portion of sample **68** is washed away.

[**0035**] The concentrations of biomarkers in sample **66** are a function of the extent of the reaction between exposed sensing elements **64** and sample **66**. The extent of the reaction is determinable by, for example, mass spectrometry. The Surface Enhanced Laser Desorption/Ionization (SELDI) process is an example of a mass spectrometry technique for determining the concentrations of biomarkers.

[**0036**] In general, the SELDI process directs light generated by one or more light sources **70** at biochip **60**. A mass analyzer **72** measures the molecular weight of the biomarkers. In particular, biomarkers on biochip **60** are ionized and separated, and molecular ions are measured according to their mass-to-charge ratio (m/z). Ions are generated in the ionization source by inducing either the loss or the gain of a charge (e.g. electron ejection, protonation, or deprotonation). Once the ions are formed in the gas phase they can be electrostatically directed into mass analyzer **72**, separated according to their mass and finally detected.

[**0037**] Proteins bound to sensing elements **64**B, for example, can be ionized and separated based on molecular properties, such as being hydrophilic versus hydrophobic. Proteins captured by sensing elements **64**B are freed by the energy provided by a weak laser pulse, and charged positively by the removal of a second electron as a result of illumination by a second laser pulse. Time of flight though a vacuum tube following acceleration in an electric field allows the measurement of the mass-to-charge ratio.

[**0038**] The invention supports other techniques for determining the concentrations of biomarkers, and is not limited to the SELDI process. In one embodiment, for example, the techniques of the invention could be carried out by using conventional assays for individual biomarkers, such as an Enzyme Linked ImmunoSorbent Assay (ELISA tests). An advantage of using a biochip is that a biochip saves time and effort in comparison to individual assays when multiple markers are to be measured.

[**0039**] Many protein markers are generally accepted as being indicative of cardiac conditions. C-Reactive Protein (CRP) is associated with sudden cardiac death, Fatty Acid Binding Protein is a plasma marker associated with acute myocardial infarction, Cardiac Troponin is associated with myocardial infarction, Myosin Light and Heavy Chains are associated with heart failure, brain natriuretic peptide (BNP) is associated with left ventricular heart failure, and so on.

[**0040**] Other markers may be associated with other cardiac conditions of interest. The markers may be identified by their name, or by other characteristics, such as molecular weight.

[**0041**] In an example clinical study, patients with coronary artery disease were divided into two groups: a test group that had coronary artery disease, and an implantable medical device (with one sustained VT/VF episode with cycle length less than or equal to 400 ms); and a control group having coronary artery disease but no implantable medical device, and no known history of VT/VF. In the study, sixteen patients had an IMD and thirty-two were in the control group. Certain patients were excluded from the study, including non-Caucasians, females, patients outside of age limit of 45-80, and patients having certain health problems or cardiac conditions. Patients meeting the inclusion criteria were enrolled in the study. Upon enrollment, an extensive questionnaire, including medical history was filled.

[**0042**] Three blood samples were drawn from each patient. At least one sample comprised 8.5 mL blood drawn from the patients for serum separation. Serum is the cell free portion of the blood containing proteins and lipids. At least one other sample of an additional 12 mL blood was drawn and kept as whole blood for eventual genetic analysis. The samples were analyzed using proteomic and lipidomic techniques.

[**0043**] During processing, proteins in the serum were fractionated into 4 distinct groups based on the pH (acidity) of the protein. Later on, these proteins were spotted onto three surfaces of one or more biochips. The surfaces had different chemical affinities. A surface designated "CM10" was responsive to weak cation exchange surface. A surface designated "H50" was a hydrophobic surface. A surface designated "IMAC" was an immobilized metal affinity surface. The SELDI time-of-flight technique was used to measure the molecular weight of the proteins on each surface.

[**0044**] **FIG. 6** shows the results of sample proteomic spectra of two patients, one having an IMD (**80**) and one in the control (**82**). These results indicate that some of the protein markers in the blood were expressed differently in two groups. Data produced by processing of all of patients followed similar patterns, i.e., the data indicated that some of the protein markers in the blood obtained from patients were expressed differently in two groups. The differences in markers may form a basis for distinguishing the patients that would benefit from an IMD from the patients that would not benefit.

[**0045**] **FIG. 7** shows a tree analysis applied to these results to identify potential biomarkers that differentiate patients who have a higher propensity for fatal ventricular arrhythmias from the others. As a result of the tree analysis, four protein markers could be used to classify the 48 patients correctly. Specifics of these protein markers are shown in table below:

Protein Number	Molecular Weight (Da)	Isoelectric pH (pl)	Capture Surface
P1	10,146.5	9+	CM10 weak cation exchange)
P2	15,006	9+	CM10 weak cation exchange)
P3	166,582	5–7	CM10 weak cation exchange)
P4	10,948	9+	IMAC (Immobilized Ion Affinity Surface)
P5	11,991	5–7	Immobilized Metal Affinity Surface
P6	10,552.4	9	Weak Cation Exchange Surface
P7	43,529.4	9	Weak Cation Exchange Surface
P8	13,806.8	9	Hydrophobic Surface

[0046] In the above table, proteins are identified by a number and are characterized by a molecular weight in Daltons and an Isoelectric pH (pl). The molecular weight in Daltons is not necessarily unique to any particular protein, but proteins are often distinguishable by molecular weight. It is not necessary to the invention that the protein having that molecular weight and/or pi be specifically identified by name or by amino-acid sequence.

[0047] As shown in **FIG. 7**, the amount of protein P1 in the serum was tested for all patients **90**. Patients **92** having an abundance of P1 greater than or equal to 1.0422237 (measured in arbitrary units) were not at significant risk of ventricular tachyarrhythmia were therefore not candidates for an IMD. Patients **94** having an abundance of P1 less than 1.0422237, however, could not be classified by abundance of P1 alone.

[0048] For patients **94**, the amount of protein P2 in the serum was tested. Patients **96** having an abundance of P2 less than 0.2306074 were not candidates for an IMD. Patients **98** having an abundance of P2 greater than or equal to 0.2306074 were tested for protein P3. Patients **100** having an abundance of P3 greater than or equal to 0.0491938 were not candidates for an IMD, while patients **102** having an abundance of P3 less than 0.0491938 were tested for protein P4. Patients **104** having an abundance of P4 greater than 0.027011 were considered to be candidates for an IMD, while the remaining patients **106** were not considered to be candidates for an IMD.

[0049] The arbitrary units may be normalized to an abundant protein, such as albumin, which is generally consistent in relative abundance among a group of patients. The invention supports the use of other benchmarks as well, such as the total ion current in the mass spectrometer used to measure the protein abundance.

[0050] In addition, the invention supports a range of measurement standards. In some cases, it is not feasible to perform measurements that have one hundred percent sensitivity and specificity, and some standards may be applied to determine whether a patient is at significant risk of ventricular tachyarrhythmia or not. The tree analysis depicted in **FIG. 7**, for example, is generally more sensitive and specific than conventional patient sorting techniques (such as a signal averaged electrocardiogram), even though it may result in some false positives and false negatives.

[0051] The tree shown in **FIG. 7** may be generated using Classification and Regression Tree (CART) analysis. The tree analysis depicted in **FIG. 7** is an example of an approach for assessing a risk of ventricular tachyarrhythmia in one or more patients as a function of a measurement of one or more biochemical markers. The assessment may be performed in other ways as well. The test may be expressed as logical test such as an IF-THEN test, which can be implemented in software:

[0052] IF

[0053] ((P1<1.0422237) AND (P2≧20.2306074) AND (P3<0.0491928) AND (P4>0.027011))

[0054] THEN

[0055] PATIENT IS AN IMD CANDIDATE

[0056] This IF-THEN test gave the following results when applied to the clinical data where two samples from each patient were processed:

	VT/VF	NORMAL
TEST (+)	27	1
TEST (−)	5	63

Sensitivity: 27/(27 + 5) = 84%
Specificity: 63/(63 + 1) = 98%
False Positives: 1/(1 + 27) = 4%
False Negatives: 5/(5 + 63) = 7%

[0057] Using conventional sorting techniques, sensitivity and specificity tend to be around 55 to 75 percent. This clinical data demonstrates an improvement in sensitivity and specificity in comparison to conventional techniques.

[0058] Another technique for assessing a risk of ventricular tachyarrhythmia in one or more patients as a function of a measurement of one or more biochemical markers is to use an artificial neural network. In an exemplary application, the clinical data were analyzed using an artificial neural network having four input nodes corresponding to proteins P1, P2, P3 and P4. The network included four hidden nodes and one output. This artificial neural network gave the following results when applied to the clinical data where two samples from each patient was processed:

	VT/VF	NORMAL
TEST (+)	24	1
TEST (−)	8	63

Sensitivity: 24/(24 + 8) = 75%
Specificity: 63/(63 + 1) = 98%
False Positives: 1/(1 + 25) = 4%
False Negatives: 8/(8 + 63) = 11%

[0059] The test procedures described above are not unique, nor are they necessarily the most efficient method of sorting patients who are candidates for an IMD from those that are not. Nevertheless, these procedures are illustrations of tests that can be used to screen patients to find out the ones who have a propensity for ventricular tachyarrhythmia, and thus may be at increased risk of sudden cardiac death.

[0060] Depending upon the biochemical markers of interest, measurements of mass, concentration or abundance may be less important than determination of whether the marker is present or absent. The invention encompasses embodiments in which measurement of a biochemical marker in a patient includes determining whether the marker is present or not. For example, animal experimentation may establish that animals suffering sudden cardiac death exhibit an absence of a set of proteins and peptides having particular molecular weights. Similarly, animal experimentation may establish that animals suffering sudden cardiac death exhibit proteins or peptides that are otherwise not present. Detection of the presence or absence of such proteins or peptides in a human sample may have clinical significance, as the presence or absence proteins or peptides may be indicative of risk of sudden cardiac death.

[0061] In some cases, what is of interest is not the presence or absence of a biochemical marker, or its concentration on a single occasion, but an increase or decrease in the concentration or the rate of change, as demonstrated by two or more measurements separated by a time interval such as two weeks or one month. The invention supports consideration of change as a basis for assessing a risk of ventricular tachyarrhythmia.

[0062] Test procedures such as the exemplary procedures described above can be automated, in whole or in part. **FIG. 8** is an example of a system **110** that can perform an automated analysis of biochemical markers and can assess a risk of ventricular tachyarrhythmia in a patient as a function of the analysis. System **110** includes a sample input module **112**, which receives a sample for analysis, and a measuring system **114**. In one embodiment of the invention, input module **112** may include one or more biochips like those depicted in **FIG. 5**, and measuring system **114** may comprise a SELDI-based mass analyzer. The invention is not limited to such components, however.

[0063] A processor **116** receives the measurements from measuring system **114** and assessing a risk of ventricular tachyarrhythmia in the patient as a function by analyzing the measurements. Processor **116** may apply a tree analysis, such as the analyses depicted in **FIGS. 1, 2** and **7**, to determine whether a patient is at risk of ventricular tachyarrhythmia. Processor **116** may further assess a benefit of implanting a medical device in the patient as a function of the measurements, or administering an antiarrhythmic drug to the patient.

[0064] An output module **118** reports the results of the analysis. Output module **118** may comprise a display screen, printer, or any other device that reports the results of the analysis. A benefit of implanting a medical device in the patient as a function of the measurement is assessed.

[0065] The invention may offer one or more advantages. Clinical data suggest that, in a significant number of cases, sudden cardiac death is the result of VT or VF. Episodes of VT or VF are treatable with an IMD or medication. The invention presents techniques for identifying the patients who are at risk of experiencing ventricular tachyarrhythmia. As a result, there is an improved chance that these patients will receive life-saving therapy, thereby reducing their risk of sudden cardiac death.

[0066] Therapies involving an IMD or medication need not be exclusive of one another. Furthermore, the invention supports therapies in addition to implantation of an IMD or regulation of a regimen of medication. In some circumstances, the biomarkers may be more than symptomatic or indicative of the risk of VT or VF, and may be substantially causally related to the risk of VT or VF. In such circumstances, therapy may be directed to the biomarkers.

[0067] It may be possible, for example, to treat the patient by adjusting the concentration of biomarkers. When a concentration of certain protein biomarkers is found to be lower in a patient with VT or VF, then perhaps the patient can be treated by injecting those proteins into the blood, thereby restoring a more healthful concentration of the biomarkers. Conversely, when a concentration of certain protein biomarkers is found to be higher, then perhaps the patient can be treated by reducing the concentration of the protein biomarkers. A high concentration can be reduced by, for example, injection of enzymes that cleave or inhibit the activity of one or more protein biomarkers. Similarly, gene therapy can be used to alter protein and gene expression levels. Consequently, application of therapy may include determining one or more proteins or one or more genes, or a combination thereof, to be delivered to the patient.

[0068] The techniques of the invention may call for sample from the patient. In many embodiments, the sample is one that is taken as a matter of course in a medical examination, such as a blood sample.

[0069] Further, the invention should reduce the incidents of false positives and false negatives. As a result, there is a better chance that patients that can benefit from an IMD will have a chance to receive an IMD. In addition, the invention includes the capability of being self-improving. As more clinical data are collected, different or more detailed tree analyses or other sorting techniques may be developed. Empirical experience may make tests more sensitive and more specific.

[0070] Various embodiments of the invention have been described. Various modifications can be made to the described embodiments without departing from the scope of the invention. For example, the invention is not limited to consideration of biochemical markers exclusively. The assessment of risk of ventricular tachyarrhythmia in the patient may also be a function of other measurable physiological factors. Electrophysiological measurements, such as an electrocardiogram, and hemodynamic factors, such as a measurement of ejection fraction, may be taken into consideration. System **110** in **FIG. 8** may further include a sensor to measure a physiological factor, and processor **116** may assess a risk of ventricular tachyarrhythmia as a function of the measurement of the physiological factor.

[0071] Although the invention has been described with proteins as biochemical markers, the invention is not limited to proteins. The invention also supports consideration of other markers, such as genetic markers, lipid markers and lipoprotein markers. The markers may be considered alone or in combination. For example, the invention supports risk assessments as a function of combinations of gene and protein markers. Techniques such as nuclear magnetic resonance, gene sequencing, or single nucleotide polymorphism (SNP) may be used to identify these markers. Consideration of markers such as these may result in enhanced sensitivity and specificity.

[0072] Analysis can be done using multiple techniques. In addition to generating a sorting tree, applying a logical

analysis such as an IF-THEN statement, and artificial neural networks, one can assess a risk of ventricular tachyarrhythmia using linear clustering techniques (e.g. proximity, similarity, dissimilarity, weighted proximity, and principle component analysis), non-linear clustering techniques (e.g. artificial neural networks, Kohonen networks, pattern recognizers and empirical curve fitting), as well as logical procedures (e.g. CART, partition and hierarchical clustering algorithms). The invention is not limited to these techniques, however, and encompasses other linear analysis, non-linear analysis, logical analysis and conditional techniques.

[**0073**] Some of the techniques described above may be embodied as a computer-readable medium comprising instructions for a programmable processor such as processor **116** in **FIG. 8**. The programmable processor may include one or more individual processors, which may act independently or in concert. A "computer-readable medium" includes but is not limited to read-only memory, Flash memory and a magnetic or optical storage medium.

We claim:

1. A method comprising:

measuring a biochemical marker in a patient; and

assessing one of a risk of ventricular tachyarrhythmia in the patient as a function of the measurement, a benefit of implanting a medical device in the patient as a function of the measurement, and a benefit of administering a drug to the patient as a function of the measurement.

2. A method according to claim 1, wherein the biochemical marker comprises a first biochemical marker, the method further comprising:

measuring a second biochemical marker in the patient; and

assessing the risk of ventricular tachyarrhythmia in the patient as a function of the measurement of the second biochemical marker.

3. The method according to claim 2, wherein assessing the risk of ventricular tachyarrhythmia comprises one of generating a sorting tree, generating a logical test, generating an artificial neural network, and assessing the risk of at least one of ventricular tachycardia, ventricular fibrillation, and sudden cardiac death.

4. A method according to claim 1, wherein measuring the biochemical marker comprises one of measuring a mass of the biochemical marker, measuring a mass-to-charge ratio of the biochemical marker with a mass spectrometer, and measuring an isoelectric pH of the biochemical marker.

5. A method according to claim 1, wherein the biochemical marker comprises one of a protein, a lipid and a gene.

6. A method according to claim 1, further comprising:

measuring a physiological factor of the patient; and

assessing the risk of ventricular tachyarrhythmia in the patient as a function of the measurement of the physiological factor.

7. A method according to claim 6, wherein the physiological factor comprises at least one of an electrophysiological factor and a hemodynamic factor.

8. A method according to claim 1, further comprising one of assessing a benefit of implanting a medical device in the patient as a function of the measurement, and assessing a benefit of administering an antiarrhythmic drug to the patient as a function of the measurement.

9. A method according to claim 8, wherein the medical device comprises at least one of an electronic cardiac stimulation device and a drug delivery device.

10. A method according to claim 1, further comprising:

exposing a biochip to a biological sample from a patient, the biochip comprising a plurality of sensing elements; and

assessing the risk of ventricular tachyarrhythmia in the patient as a function of a reaction between the sample and the sensing elements.

11. The method of claim 10, wherein assessing the risk of ventricular tachyarrhythmia in the patient as a function of a reaction between the sample and the sensing elements comprises performing mass spectrometry on the biochip.

12. The method of claim 11, wherein performing the mass spectroscopy comprises performing a Surface Enhanced Laser Desorption/Ionization process.

13. The method of claim 1, wherein measuring the biochemical marker comprises one of determining one of the presence and the absence of the biochemical marker, and determining a change of concentration of the biochemical marker.

14. The method of claim 1, further comprising applying a therapy as a function of the assessment.

15. The method of claim 14, wherein applying a therapy comprises one of implanting an electronic cardiac stimulation device in the patient, administering an antiarrhythmic drug to the patient, and determining at least one of a protein and a gene to be delivered to the patient.

16. A computer-readable medium comprising instructions for causing a programmable processor to:

measure a biochemical marker in a patient; and

assess one of a risk of ventricular tachyarrhythmia in the patient as a function of the measurement, a benefit of implanting a medical device in the patient as a function of the measurement, and a benefit of administering a drug to the patient as a function of the measurement.

17. A system for assessing a risk of ventricular tachyarrhythmia in a patient, comprising:

a measuring system configured to measure a biochemical marker in a patient; and

a processor configured to assess a risk of ventricular tachyarrhythmia in the patient as a function of the measurement.

18. The system of claim 17, wherein the measuring system comprises a mass spectrometer.

19. The system of claim 18, wherein the mass spectrometer is configured to apply a Surface Enhanced Laser Desorption/Ionization process.

20. The system of claim 17, wherein the measuring system comprises ELI SA tests.

21. The system of claim 17, wherein the processor is further configured to assess one of a risk of ventricular tachyarrhythmia as a function of a linear analysis of the measurement, a risk of ventricular tachyarrhythmia as a function of a non-linear analysis of the measurement, and a risk of ventricular tachyarrhythmia as a function of a logical analysis of the measurement.

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[标]申请(专利权)人(译)	SOYKAN ORHAN ROBINSON TIMOTHY ^ h 奥尔森WALTER ^ h SHARMA VINOD DEARKING AMYÇ		
申请(专利权)人(译)	SOYKAN ORHAN ROBINSON TIMOTHY H. 奥尔森WALTER H. SHARMA VINOD DEARKING AMY C.		
当前申请(专利权)人(译)	美敦力公司，INC.		
[标]发明人	SOYKAN ORHAN ROBINSON TIMOTHY H OLSON WALTER H SHARMA VINOD DEARKING AMY C		
发明人	SOYKAN, ORHAN ROBINSON, TIMOTHY H. OLSON, WALTER H. SHARMA, VINOD DEARKING, AMY C.		
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