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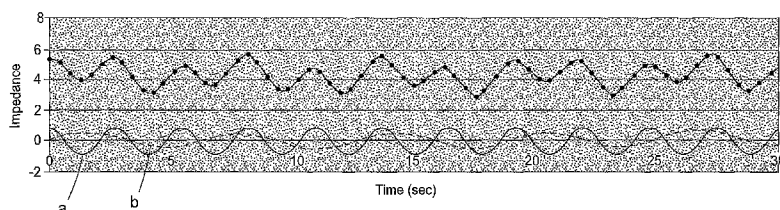


Fig. 4

(57) Abstract: An implantable cardiac device comprises a heart stimulator (10, 12) for electrically stimulating the heart of a patient, detecting means (2, 4) for measuring a physiologic parameter which is affected by the status of a cardiovascular disease associated with sympathetic activation, signal processing means (6) for determining at least one of a low frequency, LF, and a very low frequency, VLF, Mayer wave component in the measured parameter, and an analyzer for analyzing the determined Mayer wave component in relation to a predetermined reference value to determine the status of the cardiovascular disease. The detecting means comprise measuring means (2) arranged to measure, as said physiologic parameter, a mechanical change in at least one of the four chambers of the heart. In a corresponding method for monitoring the status of a cardiovascular disease associated with sympathetic activation of a patient having an implantable electric heart stimulator (10, 12) a physiologic parameter affected by the cardiac disease is measured. At least one of a low frequency, LF, and a very low frequency, VLF, Mayer wave component in the parameter is determined, and the wave component is analysed in relation to a predetermined reference value to determine the status of the cardiovascular disease. A mechanical change in at least one of the four chambers of the heart is measured as the physiologic parameter.

AN IMPLANTABLE CARDIAC DEVICE AND METHOD FOR MONITORING THE STATUS OF A CARDIOVASCULAR DISEASE

Technical Field

5 The present invention relates to an implantable cardiac device comprising a heart stimulator for electrically stimulating the heart of a patient, detecting means for measuring a physiologic parameter which is affected by the status of a cardiovascular disease associated with sympathetic activation, signal processing means for determining at least one of a low frequency, LF, and a very low
10 frequency, VLF, Mayer wave component in the measured parameter, and an analyser for analyzing the determined Mayer wave component in relation to a predetermined reference value to determine the status of the cardiovascular disease, and to a corresponding method for monitoring the status of a cardiovascular disease associated with sympathetic activation of a patient having
15 an implantable electric heart stimulator.

Background

Heart Rate Variability, HRV, has been suggested as a parameter reflecting the activity in the Autonomic Nervous System, ANS. This activity is altered with the
20 health of a patient. The pathophysiologic activation of ANS at heart failure and other diseases reveal the level of stress and unbalance in the body. HRV diminishes during heart disease and can for instance be used to detect and show deterioration of a Heart Failure, HF, and predict sudden cardiac death. Unfortunately HRV can only be measured during sinus rhythm. For patients having
25 their heart rate modulated to a large extent by an Implantable Cardiac Device, such as a pulse generator or ICD, calculation of HRV is not feasible.

Mayer waves are low frequency oscillations in ANS causing a. o. blood pressure variations and HRV. The phenomenon is not well understood but its existence and response to heart disease, and also other circumstances, have
30 been confirmed, see e.g. Cardiovascular Research, 70, 2006, pp. 12-21, Circulation 95, 1997, pp. 1449-54, and J. Hypertens., 17(12 Pt 2), Dec. 1999, pp. 1905-10.

EP 1 151 719 discloses an implantable apparatus for monitoring the condition of a heart failure patient using respiration patterns. The patient's respiratory patterns are monitored to identify periodic breathing or Cheyne-Stokes

respiration. Different parameters are suggested for assessing Cheyne-Stokes respiration, like mechanical changes of thorax due to breathing, changes in blood and tissue pH, CO₂ concentration and the R-R interval, extracted from ECGs.

From R-R interval information measures of HRV are derived and the presence of
5 respiratory fluctuations as well as Mayer waves are tested by examining the variability over specific frequency ranges. The absence of fluctuations in the respiratory fluctuation frequency band as well as in the Mayer waves frequency bands is interpreted as a worsening of the disease status.

In US 5 645 570 an implantable device for detecting the sympatho-vagal
10 balance of a patient is described. From ECGs the variability of the heart rate is evaluated as the number of consecutive R-R intervals, which differ from one another by at least a minimum threshold. If this number satisfies a predetermined intervention criterium a therapeutic device for the patient is triggered.

In Lee A. Fleisher, "Heart Rate Variability as an Assessment of
15 Cardiovascular Status", Journal of Cardiothoracic and Vascular Anesthesia, Vol. 10, No. 5 (August), 1996, pp. 659-671 the usage is described of time intervals between consecutive heart beats, preferably the R-R intervals, for evaluating HRV. The R-R intervals are derived from ECGs. The evaluation can be made in the time domain or in the frequency domain. In the latter case the power spectrum in the
20 Mayer wave frequency range can be used to predict mortality of Congestive Heart Failure, CHF, patients.

The above discussed prior art for HRV analysis, e.g. the use of the R-R interval measurements for assessment of HRV, is applicable only to patients in sinus rhythm, cf. e.g. the above mentioned article Lee A. Fleisher, "Heart Rate
25 Variability as an Assessment of Cardiovascular Status", Journal of Cardiothoracic and Vascular Anesthesia, Vol. 10, No. 5 (August), 1996, p. 662, left column, third paragraph. For patients having their heart rate modulated or controlled by a heart stimulator it is, however, not possible to use the traditional HRV analysis.

It has, however, appeared that e.g. variability of blood pressure and blood
30 flow are possible markers for studying pathophysiologic activation of ANS at heart failure and other diseases. The strength of the arterial blood pressure oscillations, for instance, is highly affected at some cardiovascular diseases associated with sympathetic activation, e.g. congestive heart failure, CHF. There are also other physiologic parameters than the blood pressure which are affected during

sympathetic activation. Thus the left ventricular tension and the left ventricular contraction pattern are also indicators of sympathetic activation as well as the mechanical AR-interval and pre-ejection time.

The purpose of the present invention is to provide a device and propose a
5 method for monitoring the status of a cardiovascular disease associated with sympathetic activation which can be used also for patients having their heart rate modulated by a heart stimulator.

Disclosure of the Invention

10 This purpose is obtained by a device and a method of the kind defined in the introductory portion which have the characterizing features of claims 1 and 21 respectively.

Thus, according to the invention a mechanical change in at least one of the four chambers of the heart is measured. The corresponding signal is
15 processed for determining at least one of the low frequency, LF, and the very low frequency, VLF, Mayer wave components in the measured parameter. This Mayer wave component is then analysed for determining the status of the cardiovascular disease of the patient. In this way it is possible to monitor the status of a cardiovascular disease of a patient having a heart stimulator, and not only monitor
20 the present status of a disease but also to predict incipient heart events. An early detection of a change in the patient's status is thus possible, and a flag can then be set indicating that the patient should visit his doctor for a health control and possible change in drug administration. Normally it is wanted to foresee Acute Decompensated Heart Failure, ADHF, in an early state. 80% of these cases
25 involve patients having previously diagnosed or chronic heart failure. Each episode of ADHF carries a higher mortality. Being able to prevent episodes of ADHF before they occur by studying Mayer waves would therefore benefit the prognosis and save lives.

According to advantageous embodiments of the device according to the
30 invention the measuring means are adapted to measure the electric transcardiac bio-impedance. The measuring means are preferably adapted to measure the electric bio-impedance quadropolarly between right atrium and right ventricle, or bipolarly in the right ventricle. Signals measured in this way are more stable and predictable and seems to mirror the left ventricular contractions as well. The

electric bio-impedance can, however, also be measured over the left ventricle, LV. The measuring means then can comprise two electrodes, one adapted for positioning in the right ventricle and the other adapted for positioning in a coronary vein on the left ventricle. The impedance measured between these electrodes
5 mirrors the left ventricular volume. Other positionings of the electrodes are also possible. The electrodes can e.g. be adapted for epicardial location. As mentioned above the pathophysiologic activation of ANS at heart failure reveals the level of stress and unbalance in the body, and the variety of blood pressure and blood flow are possible markers that can be studied for this purpose. The left ventricular
10 contraction pattern can be monitored by the above mentioned measurements of the electric bio-impedance over LV. Oscillations in LV pressure are indicated by stroke volume variations measured by the electric bio-impedance over LV.

Respiration modulation of the ANS signal can be a problem. The respiration frequency is, however, normally higher than the physiologic oscillations
15 generated by ANS, viz. Mayer waves. Since the Mayer waves are low, 3-140 mHz, compared to the respiration component, ~200mHz, the respiration component can be eliminated by appropriate filtering of the peak to peak amplitude, the time integrated area of the measured impedance signal, or the contraction strength obtained from the measured dynamic impedance signal. Both respiration and
20 heart rhythm can be measured separately, e.g. by bio-impedance measurements or electric signal detection, which also facilitates discrimination of respiration components from Mayer waves components.

According to other advantageous embodiments of the device according to the invention the measuring means comprise a pressure sensor for measuring
25 blood pressure variations in one of the four chambers of the heart. The pressure sensor can then comprise a piezoelectric sensor or a membrane sensor.

The myocardial contractility is also affected during sympathetic activation. The left ventricular contraction pattern can be monitored by measurements of the bio-impedance over LV, as discussed above. The left ventricular muscular tension
30 is an indicator of sympathetic activation which can be monitored by a sensor too. According to still other advantageous embodiments of the invention the left ventricular contractility is therefore measured. The slope of a predetermined portion of the signal, corresponding to the measured bio-impedance, is determined as a measure of the left ventricular contractility according to an advantageous

embodiment of the method according to the invention. The measuring means of the device according to the invention can comprise a sound sensor for picking up heart sound amplitudes indicating mitral and/or aortic valve closures as measures of ventricular contractility. The measuring means can also comprise a tension
5 sensor adapted for positioning on the epicardium, or in the epicardial space.

According to yet another advantageous embodiment of the device according to the invention the measuring means are arranged to measure mechanical changes in at least one of the quantities the mechanical atrioventricular conduction time, i. e. the mechanical AR-interval, and pre-ejection
10 period as the physiologic parameter affected by the status of a cardiovascular disease associated with sympathetic activation and thus useful for studying sympathetic activation.

According to other advantageous embodiments of the device according to the invention the detecting means is arranged to measure the physiologic
15 parameter for a period of at least several minutes, and the signal processing means are arranged to calculate at least one corresponding data sample per heartbeat. A memory is provided for storing the data samples and a filter is provided for filtering the stored data and determining the amplitudes of LF and/or VLF Mayer wave components. Fourier transforming means can alternatively be
20 provided for determining LF and/or VLF Mayer wave components of the measured physiologic parameter as well as the amplitudes of these components. Data are preferably measured continuously, with a frequency of e.g. 128 Hz, and at least one parameter data sample is calculated for every heartbeat as mentioned above. To be able to find the very low frequency Mayer oscillations, typically of 40 mHz,
25 the recording of data must be performed during at least several minutes, such that a data string of at least a few hundred data are obtained for storage and further analysis.

According to another advantageous embodiment of the device according to the invention the signal processing means are adapted to determine the
30 spectrogram of at least one of the Mayer wave components, and the analyser is adapted to analyze the determined spectrogram in relation to a predetermined template spectrogram to determine the status of the cardiovascular disease. Continuous recording of such a Mayer wave spectrogram can be used for early detection of a changed cardiac status of the patient.

According to still another advantageous embodiment of the device according to the invention an alerting means is provided to alert the patient to contact a medical doctor, if the deviation of the determined Mayer wave component from the reference value exceeds a predetermined threshold. If the Mayer wave oscillations decrease compared to the reference value or a normal template the risk of a coming cardiac event is increasing.

According to yet another advantageous embodiment of the device according to the invention its heart stimulator comprises controlling means for controlling the heart stimulation therapy depending on detected status of the patient's heart disease. A timing of the electric stimulation or pacing therapy which is not optimized will create an increased sympathetic tonus. This will stress the autonomic regulation and reduce the variability of physiologic signals and Mayer wave oscillations. With an optimal pacing therapy, viz. optimal stimulation rate, and optimal AV- and VV-delays, the oscillation amplitude will be at its maximum.

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Brief Description of the Drawings.

To further explain the invention an embodiment of the device according to the invention will be described in greater details with reference to the accompanying drawings on which figures 1 and 2 show dynamic blood pressures measured non-invasively on two different patients, figure 3 shows heart rates, HR, measured on patients of various NYHA, New York Heart Association, classes, figure 4 shows a physiologic parameter calculated from a measured impedance signal together with respiration and Mayer wave oscillations, figure 5 is a block diagram illustrating an embodiment of the device according to the invention, and figures 6 and 7 show qualitatively frequency spectra of a measured physiologic parameter having VLF and LF Mayer wave components as well as a respiration frequency component for two patients with different health status.

Detailed Description of a Preferred Embodiment

Figures 1 and 2 show dynamic blood pressures measured non-invasively on two different patients as a function of time.

Figure 1 shows pressure variations measured on a female, Congestive Heart Failure, CHF, patient of 64 years, NYHA class 2, i.e. class 2 according to the New York Heart Association classification, and suffering from Left Bundle Branch

Block, LBBB. The time scale of the shown diagram is 8 sec/division. As appears the systolic pressure varies with a Mayer wave frequency of 20-30 mHz and the average systolic pressure amounts to 115.59 mmHg.

Figure 2 shows corresponding pressure variations measured on a male
5 CHF patient of 69 years, NYHA class III and suffering from LBBB. The time scale of the shown diagram is 20 sec/division. The systolic pressure varies with a Mayer wave frequency of 15-20 mHz and the average systolic pressure amounts to 97.20 mmHg.

A periodic Mayer wave variability appears clearly in the measured blood
10 pressures of both these CHF patients.

Figure 3 illustrates results of heart rates, HR, measurements on two NYHA class 2 patients, three NYHA class 3 patients and one NYHA class 4 patient. For each patient mean value, standard error, SE, and $\pm 1.96 \cdot SE$ are indicated for the measured HR. The diagrams in figure 3 show that SE decreases with increasing
15 NYHA class number, viz. HRV decreases with increasing NYHA class or with increasing severity of the cardiac disease.

The upper curve in figure 4 shows qualitatively a physiologic parameter as a function of time, calculated from an impedance signal measured over LV. Each dot of the curve represents a calculated parameter value for each heartbeat.

20 The parameter values could be calculated from another measured physiologic signal as well.

The lower curve a in figure 4 represents a Mayer wave and the lower curve b the respiration. Both the Mayer wave and the respiration are influencing the measured parameter depending on the physiologic state of the patient.

25 The measurements illustrated in figure 4 are performed continuously. The measurements could, however, alternatively be performed periodically, e. g. once per hour.

Figure 5 is a block diagram of an embodiment of the device according to the invention. The device comprises a sensor 2 for measuring a physiologic
30 parameter which is affected by the status of a cardiovascular disease associated with sympathetic activation. A signal recorder 4 is provided for recording the parameter data. Data are measured continuously, e.g. with a frequency of 128 Hz, and at least one parameter data value is calculated for each heartbeat. To be able to find VLF Mayer oscillations, of typically 40 mHz, the recording must be

performed during several minutes. The data are processed in a data processor 6 and a string of a few hundred data points are stored in a memory 8. In the signal processor 8 the data string is digitally filtered to separate the Mayer wave components and the respiration component and to determine their amplitudes.

5 The spectrogram thus determined is also stored in the memory 8.

As an alternative the data processor 6 can comprise a Fourier transforming means for localising the mentioned frequency components and determining their amplitudes.

The data processor 6 also comprises an analyser for analyzing the
10 determined Mayer wave components in relation to a predetermined reference value to determine the status of the cardiovascular disease. In practice the analyser is preferably adapted to analyze the determined Mayer wave spectrogram in relation to a predetermined template spectrogram to determine the status of the cardiovascular disease.

15 The embodiment in figure 5 also comprises a heart stimulator in the form of a pacemaker 10 for delivering electric stimulation pulses to a patient's heart. A control unit 12 is provided to receive from the data processor 6 the result of the above described analysis for controlling the pacemaker therapy depending on the detected status of the patient's cardiovascular disease.

20 A continuous recording of the Mayer wave spectrogram can be used for making an early detection of a changed cardiac status, as discussed above. The device shown in figure 5 thus also comprises a notifier 14 connected to the data processor 6 for setting a flag indicating that the patient should visit his medical doctor for a health control or change in drug administration, if the analysis shows
25 that the determined Mayer wave component deviates from a predetermined reference value with more than a predetermined threshold.

As disclosed above a physiologic parameter which is affected by the status of a cardiovascular disease associated with sympathetic activation is measured e.g. by the electric bio-impedance. Appropriate filtering of the peak to
30 peak amplitude, or the integrated area of the systolic contraction strength in the dynamic impedance signal is made. By this filtering the Mayer waves can be discriminated from the respiration rhythm, because the Mayer wave oscillations have a significantly lower frequency the respiration signal. This is illustrated in figures 6 and 7 and also by curves a and b in figure 4. Both respiration and the

heart rhythm can be measured separately, which facilitates distinguishing the two types of waves.

Figures 6 and 7 thus qualitatively illustrate frequency spectra of a physiologic parameter, e.g. the systolic blood pressure, with strong VLF and LF Mayer waves present in figure 6 and with weak Mayer waves present in figure 7. The amplitude of the respiration component, Resp, is substantially constant in the two figures.

The strong Mayer wave oscillations in figure 6 may be a good sign for the status of the patient's health. In the situation illustrated in figure 7, on the other hand, the amplitude of the Mayer wave oscillations has decreased compared to a normal template, which means an increased risk for a preceding heart event.

Also, if the timing of the pacing therapy is not optimized an increased sympathetic tonus will be created. This will stress the autonomic regulation and reduce the variability of physiological signals, and consequently reduce the Mayer wave oscillations, as illustrated in figure 7. An optimal pacing therapy will, however, result in a large signal variety and a maximum Mayer wave oscillation amplitude, cf. figure 6.

The LF and VLF Mayer wave oscillations should be measured with the patient at rest, when few other disturbances are present. The blood pressure and the left ventricular volume will vary with the body position and workload, which makes detection of Mayer waves difficult for unstable situations of the patient. It is also important that the patient is awake, i.e. conscious, at the measurement. Activity sensors and body position sensors as well as a real time clock can therefore be used to ensure repetitive and correct measuring conditions.

As mentioned above a reference value or a reference template of normal HRV is used in the analysis of the measured Mayer wave oscillations. Such a reference value or template is preferably created automatically during the first day(s) and stored in the device. This procedure for determining the reference value or template is repeated after a follow-up, when the patient's health status is known.

The low frequency wave oscillations in the ANS, which cause detectable variations in several different physiologic parameters and which are called Mayer waves in this application, are also named in the literature Traube-Hering-Mayer

waves, Hering's waves, Traube's waves, Traube-Hering curves, Traube-Hering waves and Mayer's waves.

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CLAIMS

1. An implantable cardiac device comprising a heart stimulator (10,12) for electrically stimulating the heart of a patient, detecting means (2,4) for measuring a physiologic parameter which is affected by the status of a cardiovascular disease associated with sympathetic activation, signal processing means (6) for determining at least one of a low frequency, LF, and a very low frequency, VLF, Mayer wave component in the measured parameter, and an analyser for analyzing said determined Mayer wave component in relation to a predetermined reference value to determine the status of the cardiovascular disease, **characterized in** that said detecting means (2,4) comprise measuring means (2) arranged to measure, as said physiologic parameter, a mechanical change in at least one of the four chambers of the heart.
2. The device according to claim 1, **characterized in** that said measuring means (2) are adapted to measure the electric transcardiac bio-impedance.
3. The device according to claim 1, **characterized in** that said measuring means (2) are adapted to measure the electric bio-impedance quadropolarly between right atrium and right ventricle.
4. The device according to claim 1, **characterized in** that said measuring means (2) are adapted to measure the electric bio-impedance bipolarly in the right ventricle.
5. The device according to claim 1, **characterized in** that said measuring means (2) are adapted to measure the electric bio-impedance over the left ventricle.
6. The device according to claim 4, **characterized in** that said measuring means (2) comprise two electrodes, one adapted for positioning in the right ventricle and the other adapted for positioning in a coronary vein on the left ventricle.
7. The device according to any one of the claims 4 – 6, **characterized in** that said measuring means (2) comprise electrodes, adapted for epicardial location.

8. The device according to claim 1, **characterized in** that said measuring means (2) comprise a pressure sensor for measuring blood pressure variations in one of the four chambers of the heart.
9. The device according to claim 8, **characterized in** that said pressure
5 sensor comprises a piezoelectric sensor or a membrane sensor.
10. The device according to claim 1, **characterized in** that said measuring means (2) are arranged to measure the left ventricular contractility.
11. The device according to claims 5 and 10, **characterized in** that said
10 analysor is arranged to determine the slope of a predetermined portion of the signal, corresponding to the measured bio-impedance, as a measure of the left ventricular contractility.
12. The device according to claim 10, **characterized in** that said measuring means (2) comprise a sound sensor for picking up heart sound
15 amplitudes indicating mitral and/or aortic valve closures as measures of ventricular contractility.
13. The device according to claim 1, **characterized in** that said measuring means (2) comprise a tension sensor adapted for positioning on the epicardium, or in the epicardial space.
14. The device according to claim 1, **characterized in** that said measuring
20 means (2) are arranged to measure mechanical changes in at least one of the quantities mechanical AR-interval, and pre-ejection period.
15. The device according to claim 1, **characterized in** that said detecting means (2,4) is arranged to measure said physiologic parameter for a period of at least several minutes, and in that said signal processing
25 means (6) are arranged to calculate at least one corresponding data sample per heartbeat.
16. The device according to claim 15, **characterized in** that a memory (8) is provided for storing said data samples and in that a filter is provided for filtering said stored data and determining the amplitudes of LF and/or
30 VLF Mayer wave components.
17. The device according to claim 14, **characterized in** that a memory (8) is provided for storing said data samples and in that a Fourier transforming means is provided for determining LF and/or VLF Mayer

wave components of said measured physiologic parameter as well as the amplitudes of these components.

18. The device according to claim 1, **characterized in** that said signal processing means (6) are adapted to determine the spectrogram of at least one of the Mayer wave components, and in that said analyser is adapted to analyze said determined spectrogram in relation to a predetermined template spectrogram to determine the status of the cardiovascular disease.
19. The device according to any one of the preceding claims, **characterized in** that an alerting means (14) is provided to alert the patient to contact a medical doctor, if the deviation of the determined Mayer wave component from said reference value exceeds a predetermined threshold.
20. The device according to any one of the preceding claims, **characterized in** that its heart stimulator (10,12) comprises controlling means for controlling the heart stimulation therapy depending on detected status of the patient's heart disease.
21. A method for monitoring the status of a cardiovascular disease associated with sympathetic activation of a patient having an implantable electric heart stimulator, wherein a physiologic parameter affected by said cardiac disease is measured, at least one of a low frequency, LF, and a very low frequency, VLF, Mayer wave component in said parameter is determined, and said wave component is analysed in relation to a predetermined reference value to determine the status of the cardiovascular disease, **characterized in** that a mechanical change in at least one of the four chambers of the heart is measured as said physiologic parameter.
22. The method according to claim 21, **characterized in** that the electric transcardiac bio-impedance is measured to determine said mechanical change.
23. The method according to claim 21, **characterized in** that the electric bio-impedance is measured quadropolarly between right atrium and right ventricle to determine said mechanical change.

24. The method according to claim 21, **characterized in** that the electric bio-impedance is measured bipolarly to determine said mechanical change.
25. The method according to claim 21, **characterized in** that the electric bio-impedance over the left ventricle is measured.
26. The method according to claim 25, **characterized in** that the bio-impedance is measured between two electrodes, one adapted for positioning in the right ventricle and the other one adapted for positioning in a coronary vein on the left ventricle.
27. The device according to claim 21, **characterized in** that blood pressure variations in one of the four chambers of the heart are measured to determine said mechanical change.
28. The method according to claim 21, **characterized in** the left ventricular contractility is measured to determine said mechanical change.
29. The method according to claims 25 and 28, **characterized in** that the slope of a predetermined portion of the signal, corresponding to the measured bio-impedance, is determined as a measure of the left ventricular contractility.
30. Method according to claim 28, **characterized in** that heart sound amplitudes indicating mitral and/or aortic valve closures are measured as measures of ventricular contractility.
31. The method according to claim 21, **characterized in** that at least one of the quantities mechanical AR-interval and pre-ejection period is measured to determine said mechanical change.
32. The method according to claim 21, **characterized in** that said physiologic parameter is measured for a period of at least several minutes, and in that at least one corresponding data sample is calculated per heartbeat.
33. The method according to claim 32, **characterized in** that said data samples are stored and in that said stored data are filtered and the amplitudes of at least one of the LF and VLF Mayer wave components of said measured physiologic parameter is determined.
34. The method according to claim 32, **characterized in** that said data samples are stored and in that said stored data are Fourier

transformed for determining at least one of the LF and VLF Mayer wave components of said measured physiologic parameter as well as the amplitude of said at least one of the LF and VLF Mayer wave components.

- 5 35. Method according to any one of the claim 21, **characterized in** that the spectrogram of at least one of the Mayer wave components is determined and analyzed in relation to a predetermined template spectrogram to determine the status of the cardiovascular disease.
- 10 36. The method according to any one of the claims 21 - 35, **characterized in** that the patient is alerted to contact a medical doctor if the deviation of the determined Mayer wave component from said reference value exceeds a predetermined threshold.
- 15 37. Method according to any one of the claims 21 – 36, **characterized in** that heart stimulation therapy is controlled depending on the detected status of the patient's heart disease.
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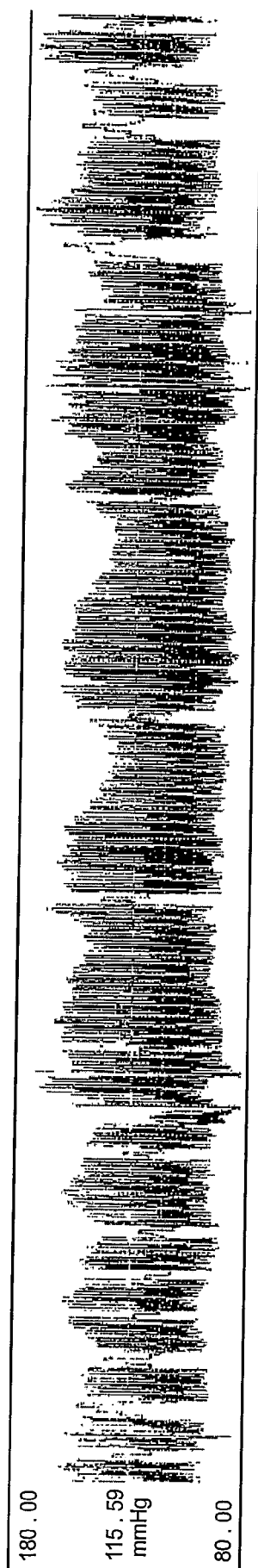


Fig. 1

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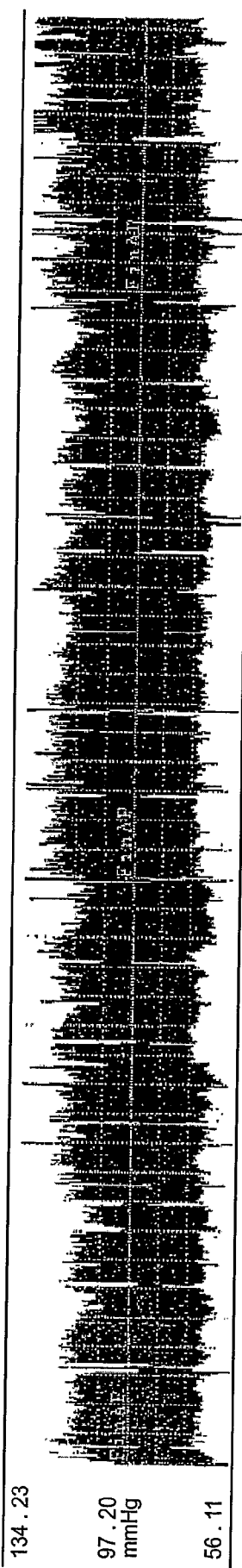


Fig. 2

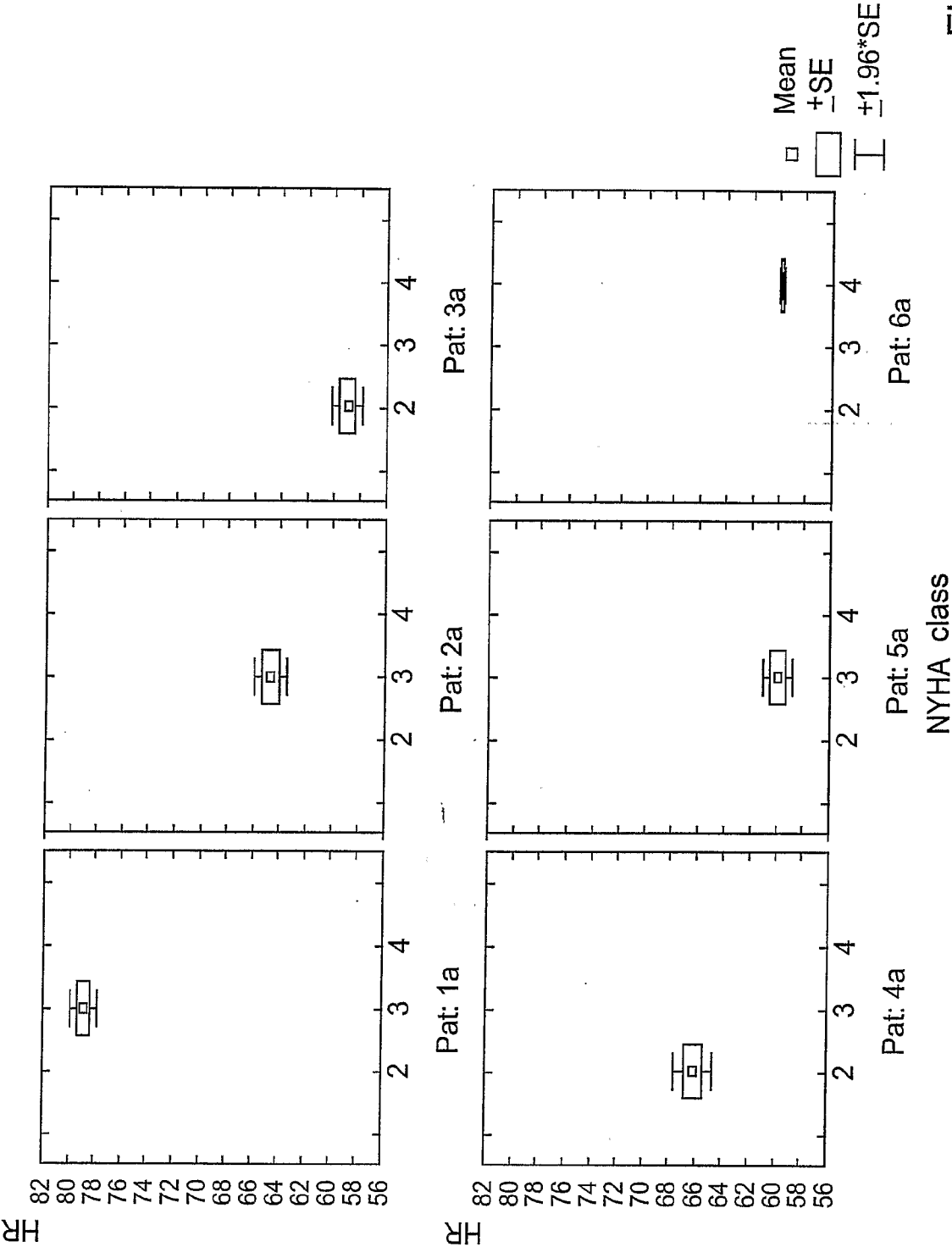


Fig. 3

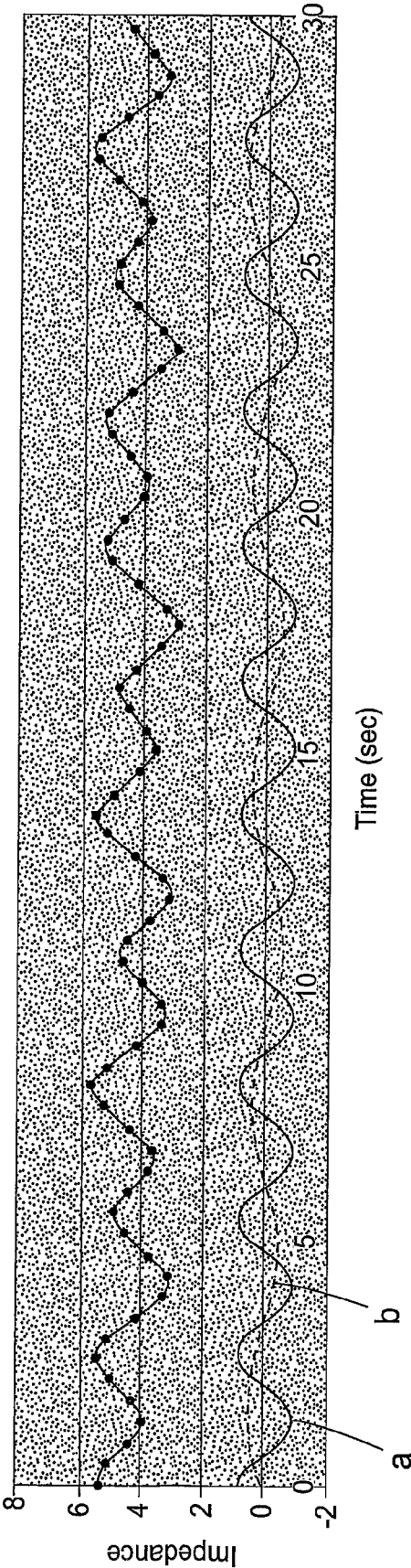


Fig. 4

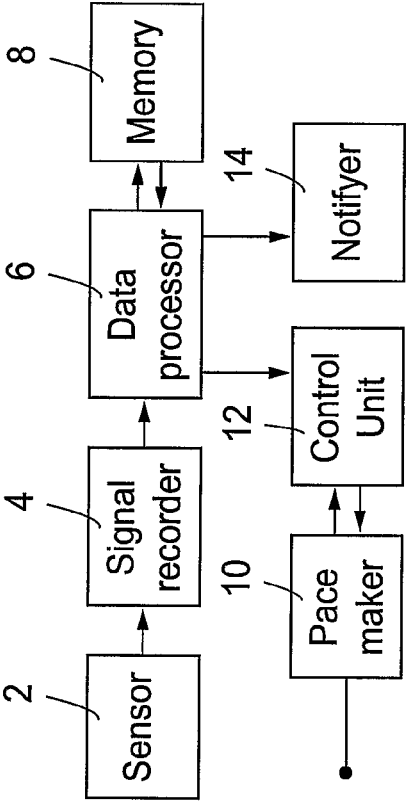


Fig. 5

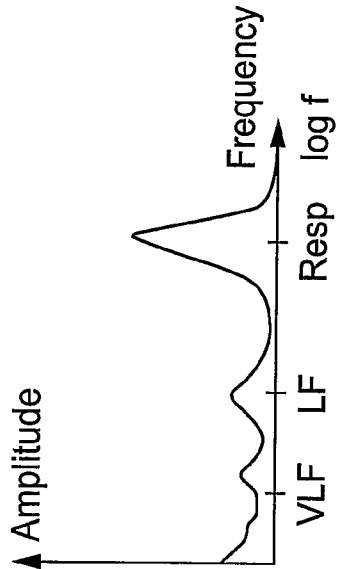


Fig. 7

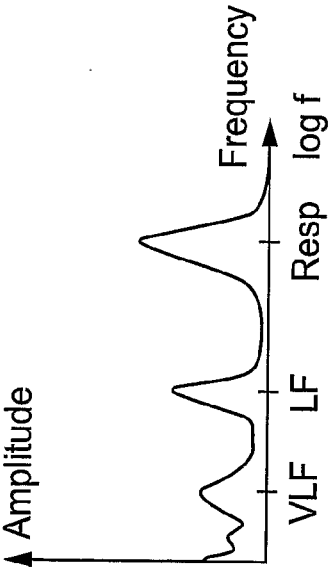


Fig. 6

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE2007/000288

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: A61N, A61B

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

SE,DK,FI,NO classes as above

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

EPO-INTERNAL, WPI DATA, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 7177686 B1 (TURCOTT,R), 13 February 2007 (13.02.2007), column 15, line 5 - line 60; column 19, line 24 - line 32, abstract --	1-37
A	US 6527729 B1 (TURCOTT,R), 4 March 2003 (04.03.2003), column 16, line 40 - line 47, claims 14-23, abstract --	1-37
A	EP 1151719 A2 (PACESETTER, INC.), 7 November 2001 (07.11.2001), Cited in the application, abstract --	1-37
A	US 20040260186 A1 (DEKKER,A L A J), 23 December 2004 (23.12.2004), abstract --	1-37

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

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

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

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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

"&" document member of the same patent family

Date of the actual completion of the international search

6 November 2007

Date of mailing of the international search report

08-11-2007

Name and mailing address of the ISA/

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Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2007/000288

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 20030163034 A1 (DEKKER, A L A J), 28 August 2003 (28.08.2003), abstract --	1-37
E	US 7206636 B1 (TURCOTT, R), 17 April 2007 (17.04.2007), column 15, line 8 - line 60; column 19, line 24 - line 32, claim 1, abstract -- -----	1-37

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2007/000288

International patent classification (IPC)

A61N 1/365 (2006.01)

A61N 1/37 (2006.01)

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Use the application number as username.

The password is **AJCDUPNAUM**.

Paper copies can be ordered at a cost of 50 SEK per copy from PRV InterPat (telephone number 08-782 28 85).

Cited literature, if any, will be enclosed in paper form.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2007/000288**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

- 1.
- ☒
- Claims Nos.: 21-37

because they relate to subject matter not required to be searched by this Authority, namely:

Claims 21-37 relate to a method of treatment of the human or animal body by surgery or by therapy, as well as diagnostic methods /Rule 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the device.

- 2.
- ☐
- Claims Nos.:

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

- 3.
- ☐
- Claims Nos.:

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

01/09/2007

International application No.
PCT/SE2007/000288

US	7177686	B1	13/02/2007	US	6942622 B	13/09/2005
				US	7206636 B	17/04/2007
				US	6409675 B	25/06/2002
				US	6477406 B	05/11/2002
				US	6480733 B	12/11/2002
				US	6491639 B	10/12/2002
				US	6527729 B	04/03/2003
				US	6600949 B	29/07/2003

US	6527729	B1	04/03/2003	US	6477406 B	05/11/2002
				US	6480733 B	12/11/2002
				US	6491639 B	10/12/2002
				US	6600949 B	29/07/2003
				US	6942622 B	13/09/2005
				US	7177686 B	13/02/2007
				US	7206636 B	17/04/2007
				US	6409675 B	25/06/2002

EP	1151719	A2	07/11/2001	US	6600949 B	29/07/2003

US	20040260186	A1	23/12/2004	US	7001337 B	21/02/2006
				AU	2003217564 A	00/00/0000
				CN	1646055 A	27/07/2005
				EP	1485009 A	15/12/2004
				JP	2005535359 T	24/11/2005
				US	6702752 B	09/03/2004
				US	20030163054 A	28/08/2003
				WO	03071938 A	04/09/2003
				US	6805673 B	19/10/2004
				US	20030163034 A	28/08/2003
				US	6896661 B	24/05/2005
				US	20030163050 A	28/08/2003
				US	6709402 B	23/03/2004
				US	20030163033 A	28/08/2003

US	20030163034	A1	28/08/2003	AU	2003217564 A	00/00/0000
				CN	1646055 A	27/07/2005
				EP	1485009 A	15/12/2004
				JP	2005535359 T	24/11/2005
				US	6805673 B	19/10/2004
				US	7001337 B	21/02/2006
				US	20040260186 A	23/12/2004
				WO	03071938 A	04/09/2003

US	7206636	B1	17/04/2007	US	6942622 B	13/09/2005
				US	7177686 B	13/02/2007
				US	6409675 B	25/06/2002
				US	6477406 B	05/11/2002
				US	6480733 B	12/11/2002
				US	6491639 B	10/12/2002
				US	6527729 B	04/03/2003
				US	6600949 B	29/07/2003

专利名称(译)	一种用于监测心血管疾病状态的可植入心脏装置和方法		
公开(公告)号	EP2129431A1	公开(公告)日	2009-12-09
申请号	EP2007747963	申请日	2007-03-23
申请(专利权)人(译)	ST.犹达医疗用品AB		
当前申请(专利权)人(译)	ST.犹达医疗用品AB		
[标]发明人	HOLMSTROM NILS OHLANDER MALIN NOREN KJELL BLOMQVIST ANDREAS LJUNGSTROM KARIN		
发明人	HOLMSTRÖM, NILS ÖHLANDER, MALIN NOREN, KJELL BLOMQVIST, ANDREAS LJUNGSTRÖM, KARIN		
IPC分类号	A61N1/365 A61N1/37 A61B5/00 A61B5/0215 A61B5/024 A61B5/053		
CPC分类号	A61N1/36521 A61B5/0215 A61B5/02405 A61B5/053 A61B5/4035 A61B5/4836 A61B5/7257 A61N1/36564 A61N1/36578 A61N1/36592 A61N1/3702		
其他公开文献	EP2129431A4 EP2129431B1		
外部链接	Espacenet		

摘要(译)

可植入心脏装置包括用于电刺激患者心脏的心脏刺激器 (10,12) , 用于测量生理参数的检测装置 (2,4) , 所述生理参数受与交感神经激活相关的心血管疾病状态的影响, 信号处理装置 (6) , 用于确定测量参数中的低频, LF和极低频率VLF, Mayer波分量中的至少一个, 以及用于分析所确定的Mayer波分量相对于预定参考值的分析器确定心血管疾病的状态。检测装置包括测量装置 (2) , 测量装置 (2) 设置成测量心脏的四个腔室中的至少一个腔室中的机械变化作为所述生理参数。在用于监测与具有可植入电心脏刺激器 (10,12) 的患者的交感神经激活相关的心血管疾病状态的相应方法中, 测量受心脏病影响的生理参数。确定参数中的低频, LF和极低频率VLF, Mayer波分量中的至少一个, 并且相对于预定参考值分析波分量以确定心血管疾病的状态。测量心脏的四个腔室中的至少一个腔室中的机械变化作为生理参数。