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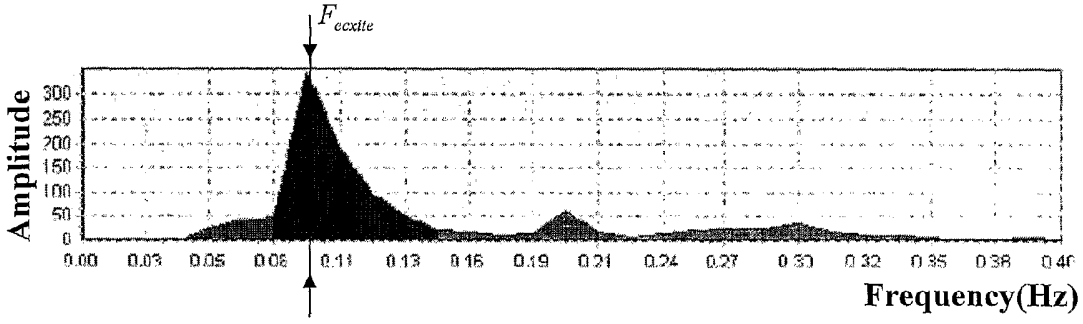
(54) Title: METHOD AND SYSTEM FOR CARDIOVASCULAR SYSTEM DIAGNOSIS



(57) Abstract: The present invention is directed to a method and system for monitoring function and/or diagnosing dysfunction of the cardiovascular system of a human subject. The method comprise measuring pulse wave signals of the subject during rapid excitation of the cardiovascular system, analyzing the measured signals and computing indicators reflecting a response to said excitation. The cardiovascular excitation preferably comprise a controlled breathing protocol characterized by a predefined frequency of breaths (e.g., about 0.1 Hz).

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METHOD AND SYSTEM FOR CARDIOVASCULAR SYSTEM DIAGNOSIS

Field of the Invention

The present invention relates to a method and system for diagnosing and monitoring the cardiovascular system. More particularly, the invention relates to a method and system for diagnosing and monitoring the cardiovascular system of a subject by analyzing the response of the cardiovascular system to a controlled stimulation protocol.

Background of the Invention

Heart rate is controlled by a part of the Autonomic Nervous System (ANS) known as the cardiac autonomic system (parasympathetic and sympathetic activity). Heart Rate Variability (HRV) is a measure of the beat-to-beat variability of a subject's heart rate and provides a valuable noninvasive mean for evaluating the functioning of the cardiac autonomic system. It is known that HRV measurement can be used for assessment of cardiac autonomic status, and that disease severity in heart failure can be assessed via continuous 24 hour HRV measurement.

Assessment of HRV from 24-hour Holter ECG (a portable ECG monitoring device) recordings has sometimes been of prognostic value in patients after Myocardial Infarction (MI) ("*Heart rate variability assessment after acute myocardial infarction: pathophysiological and prognostic correlates.*", Singh N. et al. Circulation 1996;93:1388-95) and in Congestive Heart Failure (CHF) patients ("*Reproducibility of heart rate variability measures in patients with chronic heart failure.*" Ponikowski P. et al, Clin. Sci. 1996; 91:391-8). However, this test is burdensome and does not provide quick results. According to a recent study, measures of HRV under physiologic stress (head-

up-tilt) were able to differentiate between healthy control subjects and subjects with asymptomatic left ventricular dysfunction.

It is also known that the reproducibility of HRV in patients with CHF is poor (Ponikowski P. et al). As the clinical state of a patient deteriorates, although intrinsic HRV will fall, the standard measure of HRV does not reflect this fall because of the rise in ectopic beat frequency, which increases the degree of variability.

Reduced HRV during a single deep breath, or 1-2 minutes of repeated slow (0.1 Hz) breathing has been used as a measure of cardiac autonomic dysfunction for many years. It was shown to be better at differentiating between subjects with and without diabetes mellitus than the differences between horizontal and standing HRV and the Standard Deviation of Normal-Normal R-R intervals (SDNN), ("*A simple bedside test of 1-minute heart rate variability during deep breathing as a prognostic index after myocardial infarction.*", Katz A. et al. Am. Heart J. 1999 Jul. 138:32-8;).

US 2004/0059236 to *Margulies Lyle Aaron* et al., describes physiological monitoring for detection of ANS activity during sleep. This publication teaches detection of frequent brief micro arousals by a pulse oximetry and EEG methods. ANS changes are determined by analyzing changes in the slope variations of the rising edge of the pulsatile blood volume waveform.

US 6,319,205 and US 6,322,515 to *Daniel A. Goor* et al., describes non-invasive detection and monitoring of a physiological state or medical condition by monitoring changes in the peripheral arterial vasoconstriction in reaction to such

state or condition. Changes related to cardiopulmonary distress and blood pressure are monitored in order to detect or monitor physiological state or medical condition. A test is carried out with a finger probe capable of applying a pressure on the finger by a pressurizing cuff. In this way blood pooling in the veins at the measuring site can be prevented during the test.

EP1419730 to *Dehchuan Sun* et al., describes a non-invasive apparatus for monitoring the side effects to the ANS caused by drugs used to prevent acute or chronic side effects to the brain nerves, and for monitoring the aging of nervous system by measuring the "physiological age" of the patient based on the ANS. Artery sphygmograms, or heart potential electric wave signals are obtained using a sensor and analyzed. HRV parameters are calculated by spectral analysis methods such as Fourier Transform.

US2003163054 to *Andreas Lubbertus · Aloysius Johannes Dekker* describes monitoring patient respiration based on a pleth signal. The pleth signal is analyzed to identify a heart rate variability parameter associated with respiration rate.

The prior art fails to provide simple and rapid (about 1 minute long) noninvasive methods and systems for analyzing the status of the cardiovascular system, and in particular of the coronary blood system.

It is therefore an object of the present invention to provide a noninvasive method and system for quickly diagnosing and monitoring the cardiovascular system, and in particular the coronary blood system and cardiac ischemia of a subject based on the response of the blood flow to stimulation.

It is another object of the present invention to provide a method and system for processing and analyzing the response of the blood flow to stimulation in order to indicate the physiological condition of a subject.

It is a further object of the present invention to provide a method and system for quickly diagnosing and monitoring the cardiovascular system of a subject based on blood flow measurements.

It is a still another object of the present invention to provide a method and system for quickly diagnosing and monitoring the status of the cardiovascular system of a subject based on a test that can be performed anywhere and which does not require attendance of professionals.

Other objects and advantages of the invention will become apparent as the description proceeds.

Summary of the Invention

It has now been found that it is possible to obtain valuable diagnostic information from blood Pulse Wave (PW) signals of a human subject during rapid excitation of the cardiovascular system of said subject. More specifically, the inventor of the present invention has devised a method and system for monitoring function and/or diagnosing dysfunction of the cardiovascular system of a human subject.

The method preferably comprise measuring PW signals of the subject during excitation of the cardiovascular system, analyzing the measured signals and computing indicators reflecting a response to said excitation.

The phrase PW signal is used herein to refer to a signal measured by a sensing device capable of sensing blood flow, volume, and/or pressure.

The phrase "excitation of the cardiovascular system" is used herein to indicate causing the cardiovascular system to increase its output and/or to experience load conditions or load simulation conditions.

In one preferred embodiment, the cardiovascular excitation may comprise a controlled breathing protocol characterized by a predefined frequency of breaths (e.g., about 0.1 Hz).

Optionally and conveniently, the pulse wave signals are measured at a peripheral region (e.g., body extremity) including, but not limited to - a finger, ear, neck, wrist, toe, ankle, chest, of the subject.

The method may further comprise segmenting the measured PW signals to distinct pulse waves. The segmentation is preferably carried out by finding a dominant frequency (F_{heart}) from the measured signals when transformed into the frequency domain, defining a scan window (W) according to the dominant frequency found (e.g., having a width of a bout $1/(3 \cdot F_{heart})$ or $1/(4 \cdot F_{heart})$), partitioning the PW signals into consecutive portions, the size of each is determined according to the scan window, finding a maximal value of said PW signal within each one of the portions, and finding a minimal value between pairs of consecutive maximal values found.

The method may further comprise calculating beat rate values by computing the inverse of the time difference between consecutive peaks (maximal values). A measure of the response

to the excitation may be determined by performing time domain analysis, frequency domain analysis, and/or pulse wave morphology analysis to the measured PW signal.

Conveniently, the signals may be measured in a finger, ear, wrist, ankle, toe, neck, or chest, of the subject. The computed indicators may include one or more of the following indicators: PWA range, AI, Pulse Period Range, HF integral, LF integral, BPM STDEV, PNN50, and BPM range, wherein said indicators are computed using signals obtained during the excitation and for normal pulse wave signals.

The PWA range indicator is the difference between the maximal and minimal values of the PW signal and it provides an indication of the response to excitation.

The AI (Augmentation Index) indicator provides a measure of the artery stiffness and is the calculated ration of two critical points on a pulse wave of the PW signal relative to an adjacent minimum value. These critical points are preferably found based on a forth derivative of the PW signal.

The Pulse Period Range is the range of variations of the time intervals of the pulse waves of the measured PW signals, and it provides an indication of ANS function.

The LF integral and RF integral indicators indicates sympathetic and parasympathetic effects on heart rate and are preferably calculated by using methods known in the art.

The BPM STDEV indicator is the standard deviation of the pulse rate (BPM series) computed from the measured signal. This indicator provides an indication of ANS function.

The BPM range is the difference between the maximal and minimal values in a beat rate series (BPM series) obtained from the measured signal. The BPM range indicated ANS function.

The pNN50 indicator is the percentage of the time intervals between consecutive peaks in the filtered PW signal which differs by more then 50 mS from a subsequent time intervals between consecutive peaks. This indicator provides an indication of ANS function.

The method may further comprise comparing the signals measured during cardiovascular excitation, and/or indicators computed therefrom, to the subject's normal blood flow or blood pressure signals (e.g., before applying the excitation), and/or indicators computed therefrom.

The method may further comprise extracting a Peripheral Flow Reserve (PFR) indicator by computing the ratio between averaged amplitude of the PW signal measured during the excitation and the averaged amplitude of normal blood PW signals of the subject.

The method may further comprise extracting a Respiratory Modulation Response (RMR) indicator by computing the ratio between a first and a second areas defined under the curve of the frequency domain representation of the PW signal. These areas are defined by two adjacent minimal values on said curve adjacently located on the two sides of the breath frequency. The first area is the area under said curve between the minimal values and the second area is the remainder obtained when subtracting the area under the line connecting the minimal values from the first area.

Preferably, a Responsive Augmentation Index Ratio (RAIR) indicator may be also extracted by computing the ratio between the AI indicator of the subject's normal blood PW signals and the AI indicator of the subject's responsive to the excitation.

The method may further comprise computing arterial flow, arterial stiffness, and ANS function, scores for indicating physiological functions, by calculating a weighted summation of the indicators. These scores may be used for computing a total score, wherein said total score is the linear combination of the scores. In addition, the scores may be manipulated for obtaining risk evaluations for one or more of the following cardiovascular events: acute coronary syndrome; sudden cardiac death; arrhythmia; stroke; and myocardial infarction.

According to another aspect the present invention is directed to a system for diagnosing and monitoring the function or malfunction of the cardiovascular system of a human subject. The system preferably comprise a sensor for measuring PW signals of a human subject, means for converting said signals into a data format, and a means for processing and analyzing the converted signals and extracting diagnostic indicators therefrom, wherein these signals are measured during excitation of the cardiovascular system of said subject.

The system may further comprise a low pass filter for separating breath offsetting components from the converted signals, and a means for subtracting these components from the converted signal.

Optionally, the system may further comprise an additional low pass filter for filtering out high frequency noise and an

upsampler for interpolating the signal and thereby adding data thereto

Preferably, the system further comprises means for comparing the PW signals measured during the excitation with the subject's normal PW signals, and for outputting corresponding indications accordingly.

Optionally, the processing mean of the system may be adapted to compute one or more of the following indicators: PWA range, AI, Pulse Period Range, HF integral, LF integral, BPM STDEV, PNN50, and BPM range, RMR, PFR, and RAIR.

The invention may be used for one or more of the following applications: cardiovascular risk screening and assessment; cardiovascular intervention monitoring; cardiovascular intervention follow-up; and/or therapeutic strategy monitoring (including medications and life style changes such as diet and sports).

The invention may be used for diagnosing physiological dysfunctions such as: cardiac Ischemia, Endothelial dysfunction, coronary artery disease, coronary artery occlusion, arterial stiffness, autonomic nervous system dysfunction, myocardial infarction, and angina pectoris.

Optionally, the pulse wave signals may be measured invasively. The sensor may be selected from the group consisting of a Photoplethysmograph sensor; flow sensor; mechanical sensors; optical sensors, ultrasonic sensors; electrical impedance sensor.

Brief Description of the Drawings

In the drawings:

- Fig. 1 graphically illustrates the changes in the blood flow during rest and during stimulation in different VB conditions;
- Fig. 2 schematically illustrates a system for measuring the PW signal and analyzing said signal according to the invention;
- Fig. 3 is a flowchart illustrating the test and analysis process according to a preferred embodiment of the invention;
- Fig. 4 is a block diagram illustrating the signal processing and analysis of the measured flow pulse signal;
- Fig. 5 is a flowchart illustrating a preferable process for pulse wave segmentation;
- Fig. 6 shows a graphical presentation of the HRV obtained from a measured PW signal;
- Fig. 7 graphically demonstrates calculation of the augmentation index;
- Fig. 8 graphically demonstrates the change of the augmentation index in hyperemic state;
- Figs. 9A-9C graphically shows processed pulse wave signals demonstrating different conditions of patients' cardiovascular system and VBs (healthy, embolized, calcified);
- Figs. 10A-10C demonstrates few diagnostic determinations deduced from the geometry shape of pulse waves;
- Figs. 11A-11B demonstrates frequency domain analysis of signals measured according to the invention;
- Fig. 12 demonstrate computation of the respiratory modulation response indicator from the frequency transformation of a measured PW signal;

- Figs. 13A-C, 14A-C, 15A-C, and 16A-C, shows results of various tests according to the invention;
- Figs. 17A, 17B, and 17C, respectively shows an X-ray image of coronary blood vessels, pulse wave signal, and the power spectrum of the pulse wave signal, of a patient suffering from a coronary artery occlusion.
- Figs. 18A, 18B, and 18C, respectively shows an X-ray image of coronary blood vessels, pulse wave signal, and the power spectrum of the pulse wave signal, of the same patient of Figs. 17A-17C, after a stenting procedure.

Detailed Description of Preferred Embodiments

While many attempts has been made to monitor cardiovascular functioning level by analyzing body surface signals, none has provided satisfactory results. When the various physiological systems are functioning at a steady state, much of their shortcomings are not revealed, however, when stimulated into an excited state, some of their dysfunction can be exposed. The present invention is based on the analysis of stimulated physiological systems response.

Controlled breathing at a frequency of 0.1 Hz stimulates the autonomic nervous system, and other physiological systems, such as the cardiovascular system (the blood system), and also tests the Baro-Reflex Sensitivity ("*A noninvasive measure of baro-reflex sensitivity without blood pressure measurement.*", Davies LC et al. Am. Heart J. 2002 Mar. 143:441-7). The HRV response to 0.1 Hz breathing was proved to be a predictor of death, following MI (Katz A. et al.). It was also shown that failure of the parasympathetic system is highly correlated to the risk of subsequent coronary events.

Studies have shown that the Augmentation Index (AI - a measure of the artery stiffness) is associated with cardiovascular risk ("*Assessment of peripheral vascular endothelial function with finger arterial pulse wave amplitude Jeffrey*" T. Kuvin et al. Israel Am. Heart J. 2003;146:168-74), and that peripheral vascular endothelial function can be assessed by finger arterial pulse wave amplitude ("*Augmentation index is associated with cardiovascular risk.*" Nürnberger J. et al. J. Hypertens 2002 Dec 20:2407-14).

The graph of blood flow as a function of artery closure shown in Fig. 1, demonstrates the blood flow of a normally functioning VB at a rest-state **2** and at a hyperemic-state (e.g., during stimulation) **1**, which induces vasodilatation. As seen the blood flow in these states varies greatly, while for damaged (e.g. embolized, calcified or even partly dead) VB the blood flow at hyperemic-state **1** converges with the curve of flow at rest-state **2**. Thus, the flow difference between these two states can be used to provide indications regarding both the ability of the vasculature to cope with increased flow demands, and also its general state of health. More specifically, it is expected that variability and an increased Pulse Wave Amplitude (PWA) will be observed between the patterns of the blood PW signal measured in a healthy subject at rest-state and during hyperemic-state stimulation, while the observation of negligible response (or even reduced PWA) to the stimulation indicates an unhealthy VB.

The VB auto regulation maintains a constant flow at rest for moderate arteries closure (Singh N. et al.; Nolan J. et al.). The flow at rest is determined by oxygen consumption and may be characterized according to artery diameter and auto regulating wall shear stress parameters. Correspondingly, the resistance

of the VB is decreased in order to compensate for arterial closure and to preserve total vascular resistance in the rest-state. VB auto-regulation can maintain constant flow at rest-state only if the resistance of the VB is higher than the minimal VB resistance (resistance during maximal hyperemia). For severe arterial closure, VB resistance at rest-state is already minimal. If the difference between the signals measured at rest-state and hyperemic-state is insignificant, it is most probably since the cardiovascular system does not provide enough flow increase during the hyperemic-state.

As will be discussed in detail hereinafter, if the amplitude of the PW signals during the hyperemic-state does not increase significantly relative to PW signals obtained at the rest-state (baseline reference), the following diagnosis may be reached:
(i) blocked arteries;
(ii) a VB or myocardial problem; or
(iii) both VB problem and blocked arteries.

PREFERED TEST SYSTEM OF THE INVENTION

In the preferred embodiment of the invention shown in Fig. 2, blood PW signals are obtained via a Photoplethysmograph (PPG) sensor **5** placed on the finger tip **7** of the tested subject. The PW signals are analyzed by comparing the PW signals obtained from the tested subject (**7**) by PPG sensor **5** at rest-state to the PW signals obtained during hyperemic-state. An analog-to-digital converter **8** is used for digitizing the signals received from the PPG sensor **5**, and for providing the same to the PC (Personal Computer - Pocket PC, or any other means capable of reading the measured data, processing it, and outputting the data and the results) **9**. The A/D **8** may be embedded in the PPG sensor **5** (e.g., Dolphin Medical Oximetry sensor) or in PC **9**, or provided as an independent unit. Although each of the sensor **5**,

A/D **8**, and PC **9**, elements may be powered separately by a dedicated power supply, in the preferred embodiment of the invention the power supply of these elements is provided by PC **9**.

It is of course difficult to determine from the flow changes as reflected by the PW signals measured by the PPG sensor **5**, the cause of the problem (i.e., blocked arteries, VB, and/or myocardial problem). In order to distinguish between the above-identified determinations (i, ii, or iii) other criteria have been developed, and will be described in detail hereinbelow.

It should be clear that various types of sensors and signal acquisition systems can be used to acquire the pulse wave signals. PPG PW signals were found to be particularly preferable, due to the ease and simplicity of the measurement process. Other types of sensors that can be used include (but are not limited to): mechanical sensors, optical sensors, ultrasonic sensors or electrical impedance sensor. Specific examples of suitable devices include: finger mechanical plethysmograph - as developed by Itamar Medical (Itamar Medical Ltd., Caesarea, Israel); Carotid pressure wave plethysmograph- as developed by SphygmoCor (AtCor Medical Pty Ltd., NSW , Australi); Electrical Impedance plethysmograph as developed by cardiodynamics (Cardiodynamics International Corp., san diego, California) or any other similar devices. The PC **9** may be any computerized (or analog) system that is able to receive input signals, process and analyze said signals, store and read data in/from memory(s) provided therein, and provide corresponding outputs for example *via* a graphical display unit (not shown). PC **9** can be a pocket-PC or a type of Personal Digital Assistance (PDA) device, or any other means capable of

inputting measurements, performing calculations, and outputting results.

THE TEST PROCESS

The sensor **5** is attached to the patient (**7**), and he is relaxed and mentally prepared for the test. The test process is illustrated in the flowchart shown in Fig. 3. In the first step **30** the PW signals at a rest-state are recorded. The recorded rest-state signals define the patient's baseline signal and used as a reference for determining the response to stimulations. Next, in step **31** the cardiovascular system of the patient is stimulated. Various stimulations techniques can be employed, most preferably, a controlled breathing at 0.1 Hz, which will be used hereinafter to demonstrate the invention. In the case of controlled breathing stimulation the patient is guided to breathe deeply according to visual or auditory signs (e.g., via display device or speakers of PC **9**) or medical personnel instructions.

It should be noted that other stimulation of the cardiovascular system may be used for carrying out the test process of the invention. For example, a Brachial Artery Recovery (BRT) stimulation protocol may used in this system. In the BRT stimulation protocol the brachial artery is blocked for a few minutes by a blood pressure cuff, which is then opened up for analyzing the reactive hyperemia response.

In step **32** the PW signals during stimulation (hyperemic-state signals) are recorded (e.g., during the controlled breathing stimulation). The recorded, rest-state and hyperemic-state, PW signals (hereafter also referred to as raw-signals) are analyzed in step **33**, and in step **34** internal indicators are extracted utilizing the processed signals. The internal

indicators may include, but not limited to, indicators known in the art such as - PWA range, AI, HF integral, LF integral, BPM STDEV, PNN50, and BPM range. As will be explained herein later, such indicator can be used to determined the response of the cardiovascular system of the tested subject to the excitation. However, as will be explained hereinafter, new indicators particularly suitable for this invention were also developed for this purpose. The internal indicators are weighted and grouped to give 3 scores: a stiffness score **35**, flow score **36**, and ANS score **37**. These scores can then be used to determine a total score **38**, for assessing the status of the patient's cardiovascular system.

The rest-state signals acquired in step **30** can be measured, for example, during 10-100 seconds of spontaneous breathing, and the excitation-state signals acquired in steps **31-32** may be obtained during controlled breathing at a low and steady rate, for example, at a frequency of 0.1 Hz (5 seconds inspiration and 5 seconds expiration), for 30-300 seconds (e.g., 3-30 cycles of 10s each).

According to a preferred embodiment of the invention the first steps of the test process (steps **30** to **33**) are performed within a 90 seconds time interval, including 20 seconds of spontaneous breathing (step **30**), to set the baseline reference, and 70 seconds (steps **31** and **32**) of guided deep breathing at a low and steady rate of 0.1 Hz (namely, 7 cycles, 10 seconds each, comprising 5 seconds of inspiration and 5 seconds of expiration).

The rest-state PW signals obtained in step **30** are used as a baseline reference characterizing the normal state of the patient's cardiovascular system (CV). The rest-state PW signals

obtained in step **30** and the hyperemic-state PW signals obtained in steps **31-32** are analyzed using time domain analysis for finding the beat-to-beat heart rate series and heart cycles series, and for extracting indicators **34** and computing scores **35-38** therefrom. Frequency domain analysis (e.g., FFT - Fast Fourier Transform) is used for finding the power spectrum of the signal at several frequency bands and extracting additional indicators **34**. Pulse Wave morphology analysis is also used in order to extract more indicators, regarding endothelial dysfunction and arterial stiffness (the inability of a blood vessel to change its volume in response to changes in pressure). The indicators **34** may be combined to indicate performance level of physiological functions.

SIGNAL PROCESSING

Fig. 4 is a block diagram illustrating the signal processing and analysis and indicator extraction performed in steps **33-34** of the test process. The measured raw-signal **40** is filtered by a Low-Pass-Filter (LPF) **41**, for extracting the breath-curve signal **49**. LPF **41** is preferably a second order resonant LPF with a cut-off frequency of about 0.15 Hz. Subtractor **42** is used to subtract the breath-curve signal **49** from the raw-signal **40**, thereby providing a non-modulated (i.e., without offsetting components) PW signal **50**. Signal processing elements, LPF **41**, and subtractor **42**, may be implemented by software, and/or utilizing suitable of-the-shelf hardware devices. Alternatively, a dedicated Digital Signal Processing (DSP) device is used for this purpose. However, in a preferred embodiment of the invention the signal processing elements are implemented by software, and all the processing and analysis steps (**33-38**) are performed by the PC **9**.

It may be desired to upsample the non-modulated signal **50**. If so, the signal may optionally be filtered by LPF (e.g., FIR - Finite Impulse Response) **43** for removing interfering noise (e.g., above 8 Hz), and then upsampled by upsaple unit **44**, as shown in the dashed box **59**.

The obtained signal **50** (or **48** if upsamle unit **59** is used) can be used for calculating various indicators (**47**), as will be explained in detail hereinbelow..

PERIPHERAL FLOW RESERVE (PFR)

The calculation of the PFR indicator can be carried out according to the following equation:

$$PFR = \overline{Q_{hyper}} / \overline{Q_{rest}}$$

where $\overline{Q_{hyper}}$ is the average of the Pulse Wave Amplitude (PWA) of the processed signal corresponding to the hyperemic-state (steps **31-32**), and $\overline{Q_{rest}}$ is the PWA average of signal corresponding to the rest-state (step **30**).

It has been shown that the main flow parameters of the arterial auto regulation (the intrinsic ability of an organ to maintain a constant blood flow despite changes in perfusion pressure) in the peripheral arteries are similar to those of the coronary system. This may be used to provide diagnosis concerning the cardiovascular system of the tested subject.

There are three major indications that can be observed in the changes of the amplitude of the measured PW signal, for example:

- Healthy cardiovascular system allows significant increase of flow rates as a response to an excitation exercise (i.e.,

hyperemic-state) and this increase is manifested in a steady increase in the amplitude of the measured PW signal, as exemplified in the non-modulated PW signal shown in Fig. 9A.

- If the VB is partly damaged, it can not expand enough to allow significant increase of the blood flow in the hyperemic-state. In this case, the shape of the PW signal measured during the rest-state will be similar to the shape of the PW signal measured during hyperemic-state, exemplified in the non-modulated PW signal shown in Fig. 9B. However, the arteries in this case are not blocked and endothelial function of the larger arteries is still at least partly active.

- If the VB and endothelium function of larger arteries are damaged, the system can not expand enough to allow significant increase of the blood flow in the hyperemic-state, as exemplified in the non-modulated PW signal shown in Fig. 9C. Some of the arteries are probably blocked, so instead of the expected healthy increase in the amplitude of the pulse waves, as seen in Fig. 9C, the amplitude of the pulse waves may even be decreased.

SEGMENTATION

The processed signal is partitioned into distinct pulse segments in block **52**. The segmentation can be carried out utilizing conventional methods known in the art.

Fig. 5 is a flowchart illustrating a preferable process for pulse wave segmentation (**52**). This process starts in step **53** wherein a frequency transformation is applied to the measured time-domain PW signal $S_{(t)}$, thereby transforming it into the frequency domain, $S_{(F)} = F\{S_{(t)}\}$. In step **54** the frequency $F_{heart} = MAX(S_{(F)})$ is determined from the spectrum of the PW signal $S_{(F)}$. F_{heart} and the sampling time T_{sample} are used in step **55** to

define a scan window $W = f(F_{heart}, T_{sample})$. The temporal width of the scan window is preferably set to about $1/(3 \cdot F_{heart})$ or $1/(4 \cdot F_{heart})$ and the number of samples in the scan window is defined by the sampling time T_{sample}. The scan window is used to partition the time-domain PW signal $S_{(t)}$ into a number of sections $S_{(t)} = \{s_0, s_1, \ldots s_{W-1}\}, \{s_W, s_{W+1}, \ldots s_{2W-1}\}, \ldots, \{s_{r \cdot W}, s_{r \cdot W+1}, \ldots s_{(r+1)W-1}\}$ (r=0, 1, ...). In step **56** the maximal value $s_{\max}^{(r)} = MAX(S_r)$ in each section $S_r = \{S_{r \cdot W}, S_{r \cdot W+1}, \ldots, S_{(r+1)W-1}\}$ is found, and in step **57** the minimal value $s_{\min}^{(r)} = MIN(\{s_{\max}^{(r)}, s_{\max}^{(r+1)}\})$ between each consecutive maximal values $\{s_{\max}^{(r)}, s_{\max}^{(r+1)}\}$ is found. In this way the maximum (the peak) points (**75** in Fig. 7), and the minimum points (**73**) on the curve of each pulse wave are determined.

This process terminates in a validation step **58**, in which the validation of the width and height of the found pulse waves are checked according to various criteria. For example, pulse waveforms width validation can be performed by calculating time length between consecutive peaks and the slope of the peak systole. The widths are tested by checking the distances between the peaks, which should be within a predefined range (e.g., 40%) about the median width. Similarly, validation of the pulse heights (i.e., the amplitudes of each maximal value) can be performed.

COMPUTATION OF THE BEAT PER MINUTE (BPM) SERIES

The BPM series is extracted from the PP Series which is comprised of the time intervals between consecutive peaks in the PW signal (e.g., $Ts_{\max}^{(r+1)} - Ts_{\max}^{(r)}$).

Fig. 6 graphically shows a BPM series extracted from the pp series. The BPM series is obtained by inversing time intervals

between the pulse waves $(1/T_{PW}^{(0)}, 1/T_{PW}^{(1)}, 1/T_{PW}^{(2)}, \cdots$ where $T_{PW}^{(r)} = Ts_{\max}^{(r+1)} - Ts_{\max}^{(r)})$. The BPM therefore shows the variability of the heart rate over time.

RESPONSIVE AUGMENTATION INDEX RATIO (RAIR)

The AI indicator is calculated based on a method described by Takazawa, K., et al. ("*Assessment of vasoactive agents and vascular ageing by the second derivative of photoplethysmograph waveform*", 1998, Hypertension 32, 365-370). Figs. 7 and 8 graphically demonstrates the calculation of the AI for each pulse wave of the PW signal $S_{(t)}$. The magnitudes **77** (PT_1) and **78** (PT_2) of two critical points relative to the adjacent minimum **73** value are found based on a forth derivative of the PW signal ($\partial^4 S_{(t)}/\partial t^4$). The AI is obtained by calculating the ration - $AI = PT_2/PT_1$. As shown in Fig. 8, the geometry of the pulse waves is normally changed during the hyperemic-state **81**, in comparison with that measured in the rest-state **82**. This change will be indicated by an increase in the AI value.

The AI indicator provides a measure of the artery stiffness. AI values in the range 0.5 to 0.8 generally indicate good artery stiffness, while AI values in the range 1 to 1.3 generally indicates vasculature dysfunction.

It is helpful to define a Responsive Augmentation Index Ratio (RAIR), which indicates the large peripheral artery endothelial response to excitation. This indicator can be calculated in a way similar to the calculation of the PFR, namely the ratio of

the AI at hyperemic-state (AI_{Hyper}) to the AI at the rest-state (AI_{rest}), $RAIR = AI_{Hyper} / AI_{rest}$.

The AI and RAIR indicators can be extracted from a calculated average pulse wave (i.e., by averaging samples of numerous pulse waves), or alternatively by computing the average AI value of numerous pulse waves.

Inspection of the geometry of the pulse waves shown in Figs. 10A-10C can lead to the following determination:

Fig. 10A - low artery stiffness and low AI (AI~0.5-0.8). This pulse wave was extracted from the non-modulated PW signal shown in Fig. 9A, for which a healthy increase in the amplitude of the pulse waves was observed.

Fig, 10B - medium AI(AI~0.8-1.0), indicating the beginning of arterial stiffness and endothelial dysfunction. This pulse wave was extracted from the non-modulated PW signal shown in Fig. 9B, for which an insignificant response was observed in the hyperemic-state.

Fig. 10C - high AI (AI~1-1.3), indicating high artery stiffness and low endothelium function. This pulse wave was extracted from the non-modulated PW signal shown in Fig. 9C, which was taken from a subject sufferimng from blocked arteries and problematic VB (embolized or calcified).

RESPIRATORY MODULATION RESPONSE (RMR)

Additional observations for assessing the arterial flow response of a tested subject are attained from frequency domain analysis of the PW signal measured during the test. In this analysis the spectrum $S_{(F)}$ (e.g., FFT, wavelet) of the measured PW signal $S_{(t)}$ is analyzed. An additional indicator, RMR, is

extracted in this analysis, as exemplified in Fig. 12. The RMR provides indications concerning the cardiovascular and autonomic nervous systems response to the stimulation.

The RMR provides a measure of the influence of modulating excitation (e.g., breath excitation) on the measured PW signal . In the preferred embodiment of the invention the RMR is equal to the area of the respiratory peak (The peak around the 0.1Hz frequency) in the power spectrum of the monitored signal, and is calculated as follows:

The area under the power spectrum curve between two adjacent minimal values (e.g., ($S_{(f_{m1})}$ and $S_{(f_{m2})}$)) on said curve adjacently located on the two sides of the excitation frequency (e.g., 0..1Hz breath frequency)(e.g., $S_{(f_m)}$) is divided into two areas: (I) - The total peak area ($A_{Total} = A_{DBE}$); and (II) the area below the 'AC' line (A_{DACE} - in fig. 12). Where the 'AC' line is the line connecting two adjacently located minimums ($S_{(f_{m1})}$ and $S_{(f_{m2})}$) of the spectrum, as shown in Fig. 12). The RMR is then obtained by the following calculation - $RMR = \frac{A_{Total} - A_{DACE}}{A_{Total}}$.

For example, RMR may be computed as follows:

$$RMR = \frac{\left(\int_{f_{m1}}^{f_{m2}} S_{(F)} \cdot d_F\right) - \frac{1}{2}\left(S_{(f_{m1})} + S_{(f_{m2})}\right)\left(f_{m2} - f_{m1}\right)}{\int_{f_{m1}}^{f_{m2}} S_{(F)} \cdot d_F}$$

RMR values in the range 40% to 100% generally indicate good cardiovascular response, while AI values below 40 % generally indicates a cardiovascular dysfunction.

Fig. 11A graphically illustrates the spectrum of the PW signal of a subject tested according to the test process of the invention. In this example, the tested subject performed the 0.1 Hz controlled breathing excitation. As seen there is a weak response (negative RMR). Fig. 11B graphically illustrates the spectrum of the PW signal of the same subject tested according to the test process of the invention after a stenting procedure (PTCA - Percutaneous Transluminal Coronary Angioplasty). As seen there is a strong response about the frequency of the breathing excitation F_{ecxite} (0.1 Hz), which indicates an improvement in the coronary flow due to the stenting procedure.

It should be noted that RMR measures can be obtained utilizing spectral analysis other than FFT (e.g., wavelet transform). Moreover, the RMR may be obtained by a time domain analysis of the measured PW signal.

The above described computation can be performed using data extracted from the measured PW signal. For instance, an additional indicator (also termed herein 'PP RMR') may be computed using the pp series which was defined hereinabove.

ANS INDICATORS

The function of the ANS can be monitored according to the following indicators (step **34** in Fig. 3):

BPM Range - the difference between the maximal and minimal values of the BPM series. BPM Range values between 0 to 10 generally indicates ANS dysfunction, while values between 10 to 40 generally indicates normal functioning system.

pNN50 - The percentage of PP intervals, differing by more then 50 mS, from subsequent PP interval. pNN50 values in the range 0% to 3% generally indicates ANS dysfunction , while values in

the range 5% to 40% generally indicates normal functioning system.

Pulse Period Range - the range of variations of the PP series.

BPM STDEV - the standard deviation of the BPM series.

The following parasympathetic function indicators are extracted from the PW signal during excitation:

Responsive Pulse Rate Range (RPRR) - BPM series range during stimulation (e.g., controlled breath protocol). RPRR values in the range 0 to 10 generally indicates ANS dysfunction, while values in the range 11 to 40 generally indicates a normal functioning system .

Responsive Pulse Rate STDEV (RBPM-STDEV) - standard deviation of the BPM series obtained during the stimulation. RBPM-STDEV values in the range 0 to 2 generally indicates ANS dysfunction, while values in the range 3 to 10 generally indicates a normal functioning system.

Responsive pNN50 (RpNN50) - pNN50 during the stimulation. RpNN50 values in the range 0% to 5% generally indicates ANS dysfunction, while values in the range 6% to 80% generally indicates a normal functioning system.

Responsive Pulse Period Range (RPPR) - the range of variations of the PP series during stimulation. RPPR values in the range 0 to 30 generally indicates ANS dysfunction, while values in the range 50 to 100 generally indicates a indicates normal functioning system .

PP RMR - this indicator is the RMR computed from the power spectrum of the PP series.

DIAGNOSTIC SCORES

The extracted scores (stiffness, flow, ANS, and total - steps **35-38** in Fig. 3) are mapped to the range 1-10, where 1 indicates good health and 10 worst illness situation.

The score calculation can be carried out as follows:

a. Mapping

The mapping is preferably a linear mapping using the following equation:

$$Val_{mapped} = k \cdot Val + (Range_{MIN} - k \cdot Val_{MIN})$$

Where: $k = \frac{Range_{MAX} - Range_{MIN}}{Val_{MAX} - Val_{MIN}}$

$Range_{MAX}$ - upper value of the mapping range (=10).

$Range_{MIN}$ - lower value of the mapping range (=1).

Val_{MAX} - maximum possible value of the unmapped parameter.

Val_{MIN} - minimum possible value of the unmapped parameter.

Val_{mapped} - the parameter mapped in the new scale between $Range_{MIN}$ and $Range_{MAX}$.

b. Parameter inversion

If the parameter value should be inverted (when larger values actually indicates a better condition, which should be properly inverted to a corresponding smaller value), the inversion is preferably done as follows.

$$Val_{mapped} = Range_{MAX} - Val_{mapped}$$

c. The mapped score values are preferably remapped to a log scale, as follows - $Val_{mapped} = 10 \cdot \log_{10}(Val_{mapped})$.

d. The stiffness, flow and ANS, score values are calculated using the customized weighted coefficients Kparam, which are customized based on clinical results, as follows:

$$Val_{maped} = \frac{\sum_{i}^{N} K_{Param_i} \cdot Val_{mapped}^{Param_i}}{\sum_{i}^{N} K_{Param_i}}$$

The total score is calculated utilizing the following customized weighted coefficients Kstifness, KANS and KFlow:

$$Val_{mapped}^{total} = \frac{K_{stifness} Val_{mapped}^{stiffness} + K_{ANS} Val_{mapped}^{ANS} + K_{Flow} \cdot Val_{mapped}^{Flow}}{K_{stifness} + K_{ANS} + K_{Flow}}$$

The following examples demonstrate some of the possible applications of the system of the invention, such as:

I. Cardiovascular risk screening and assessment.

II. cardiovascular intervention monitoring.

III. cardiovascular intervention follow-up.

IV. therapeutic strategy monitoring (including medications and life style changes such as diet and sports).

Example 1

Figs. 13A to 13C show the results of the test procedure of the invention performed with a patient. In this example the patient had a mild non-ST MI few weeks after having the test. The patient went through a PTCA procedure, which revealed a blocked artery, and underwent a stenting procedure. The PW signal measured during test shown in Fig. 13A shows that the relative amplitude (with respect to the breath-curve) of the PW signals remained almost unchanged during the test, which indicates that the blood system of this patient responded very weakly to the breath control stimulation. Fig. 13B, which show the HRV plot of the measured PW signal, confirms that the patient had a weak response to the excitation performed in the test. This weak response is also reflected in the spectrum of the PW signal depicted in Fig. 13C.

Table 1 lists the indicators calculated in this test and their diagnostic indication:

Table 1:

Indicator	Result	Indication
RPRR	11	Marginal
RPRV - STDEV	2.6	Marginal
RpNN50	0%	High risk
IR RMR	-15%	Very high risk
AI	1.17	Very high risk
Conclusions		High risk for event

Conclusions:

- Flow indicators indicate a very high risk for an event.
- All pulse rate variability indicators are marginal.

Example 2

This example show the results of a test carried out with the same patient 1 day after the stenting procedure. As seen in Figs. 14A and 14C, the amplitude and spectrum of the measured PW signal reveals significant improvement in the patient's response to the stimulation of the test, but the HRV plot shown in Fig. 14B indicates a relative reduction in the heart rate in response to the stimulation. The calculated indicators are listed in table 2 below.

Table 2:

Indicator	Result	Indication
RPRR	4	Very high risk
RPRV - STDEV	1.0	Very high risk
RpNN50	0%	Very high risk
IR RMR	60%	Very good response
AI	0.44	Very good response
Conclusions		Med-High risk for event

Conclusions:

- Flow indicators are very strong after stent procedures.
- All Pulse rate variability indicators are very low (the MI probably damaged the patient's autonomic nervous system).

Example 3

This example show the results of a test carried out with the same patient 30 days after the event. During this time the patient received anti cholesterol medication (with a statin drug), and reported that he felt very ill. As seen in Figs. 15A-15C, the PW response is very weak, indicating a possible restenosis.

Table 3 lists the indicator calculated in this test and their diagnostic indication:

Table 3:

Indicator	Result	Indication
RPRR	4	Very high risk
RPRV - STDEV	1.6	Very high risk
RpNN50	0%	Very high risk
IR RMR	-10%	Very high risk
AI	1.35	high risk
Conclusion		Very high risk

Conclusions:

- Flow indicators have been regressing - possible restenosis.
- All pulse rate variability indicators are still very low.

Example 4

This example show the results of a test carried out with the same patient after changing medications, changed diet, and increased physical activity.

Table 4 lists the indicator calculated in this test and their diagnostic indication:

Table 4:

Indicator	Result	Indication
RPRR	10	Marginal
RPRV - STDEV	1.6	high risk
RpNN50	2.3%	high risk
IR RMR	40%	low risk
AI	1.11	med risk
Conclusion		Marginal

As seen in Figs. 16A-16C the conclusions:

- Flow indicators have recovered.
- Pulse rate variability indicators are improving due to diet and exercise.

Example 5

Figs. 17A, 17B, and 17C, respectively shows an X-ray image of coronary blood vessels, pulse wave signal, and the power spectrum of the pulse wave signal, of a patient suffering from a coronary artery occlusion. As shown in Fig. 17A, a coronary blood vessel **17a** of the patient is blocked, the PW signal (Fig. 17B) measured during the test process shows a decrease in the vascular system function in response to the excitation, and the frequency domain transformation of the PW signal shown in Fig. 17C indicates a low RMR.

Figs. 18A, 18B, and 18C, respectively shows an X-ray image of coronary blood vessels, pulse wave signal, and the power spectrum of the pulse wave signal, of the same patient of Figs. 17A-17C, after a stenting procedure. As shown in Fig. 18A the blood vessel blockage **18a** was opened by the stent, the PW signal measured during the test shown in Fig. 18B indicates an improvement in the cardiovascular response to the excitation, and the power spectrum shown in Fig. 18C also shows RMR improvement.

The system of the present invention was tested with 20 patients (mean age 63 ± 11 years, 13 male). The results obtain for 10 of the tested patients were compared with coronary angiography results, and the results obtained for the remaining 10 patients were compared with SPECT Thallium myocardial perfusion scan (TL - a test in which thallium is injected into the patient's blood system for diagnosing the blood flow to the heart muscle). The tested patients performed the controlled breathing protocol, which was previously described hereinabove, consisting of 20 second spontaneous breathing (baseline), followed by 70 seconds of guided deep breathing.

In the results obtained the average arterial flow score index, described in p.16, and item 36 in FIG.3 (normal ranges 1[best] to 10 [worst]) was lower in 3 patients shown to have moderate to severe ischemia in at least one segment compared with 6 patients shown to have no ischemia in the TL SPECT test (7.7. ± 0.6 vs. 3.5 ± 1.2). In one of the patients with minimal reversible ischemia, the arterial flow score index was 5. Coronary angiographies demonstrated severe CAD in 6 patients. In 5 patients the average flow score index was - 8.3 ± 1.4 (6 to 10). In the 6^{th} patient (with a score of - 4), collaterals were the likely explanation. In 2 patients with non-significant CAD the arterial flow score was low: 3±0. Post PCI (Percutaneous coronary intervention) in 5 patients, the result of average flow score improved from 8.0 ± 1.6 to 3 ± 2.5. These results shows that test scheme of the invention during deep breathing has potential for use as a screening tool for CAD.

As previously mentioned, although a PPG sensor is utilized to exemplify the preferred embodiment of the invention, the invention can be carried out utilizing other types of sensors. For example, similar results can be obtained by utilizing a pressure blood sensor. While some changes may be required, these changes can be easily carried out by those skilled in the art. In addition, while in the above examples the PW signal is obtained from the finger of tested subject, it should be clear that the PW signal can be measured in any other part of the body, such as the ear, neck, wrist, ankle, toe, chest, or even invasively.

Additional indicators for cardiovascular function assessment that have not yet been developed to date may be utilized with the present invention. While various embodiments of the present invention have been described in detail, it is apparent that

further modifications and adaptations of the invention will occur to those skilled in the art. However, it is to be expressly understood that such modifications and adaptations are within the spirit and scope of the present invention.

Some of the possible indicators that may be used in this invention are listed in table 5.

Table 5: additional possible indicators

Name	**Indication**	**Conventional analysis**	**Proposed analysis**
Baro-reflex sensitivity	CVD event	Blood pressure monitoring	PPG at 0.1Hz Breathing
Immediate Entrainment	CVD RISK	None	PPG time domain
Heart Rhythm Coherence	CVD event	ECG/PPG	Pattern Analysis
Perfusion Recovery Amplitude	Atherosclerosis, Endothelial dysfunction	Mechanical plethysmograph	Reactive hyperemia analysis
Perfusion Recovery Constant	Atherosclerosis, Endothelial dysfunction	none	Reactive hyperemia analysis

As was described hereinabove in detail, the present invention provides indications for various physiological parameters, including, but not limited to:

- Arterial stiffness (e.g., AI);
- Arterial flow (e.g., HRV); and
- Autonomic Nervous System control of cardiovascular activity (e.g., HRV Range).

These parameters are combined to form a single risk factor.

The present invention can be employed for various uses, such as, but not limited to:

- Screening of the general population for identifying people at risk of cardiovascular events;

- Monitoring the effect of medications;
- Monitoring the effect of cardiovascular intervention;
- Monitoring the effect of life style changes, such as dieting and exercising;

The above examples and description have of course been provided only for the purpose of illustration, and are not intended to limit the invention in any way. As will be appreciated by the skilled person, the invention can be carried out in a great variety of ways, employing more than one technique from those described above, all without exceeding the scope of the invention.

CLAIMS

1. A method for monitoring function and/or diagnosing dysfunction of the cardiovascular system of a human subject, comprising measuring pulse wave signals of said subject during rapid excitation of said cardiovascular system, analyzing said signals and computing indicators reflecting a response to said excitation.

2. The method of claim 1, wherein the excitation of the cardiovascular system is provided by the use of controlled breathing characterized by a predefined frequency of breaths.

3. The method of claim 2, wherein the predefined frequency of breaths is about 0.1 Hz.

4. The method of claim 1, further comprising segmenting the measured pulse wave signals into distinct pulse waves.

5. The method of claim 4, wherein the segmentation is carried out by performing the following steps:

- finding a dominant frequency from the measured signals when transformed into the frequency domain;
- defining a scan window according to said dominant frequency;
- partitioning said PW signals into consecutive portions, the size of each is determined according to said scan window;
- finding a maximal value of said PW signals within each one of said portions; and
- finding a minimal value between pairs of consecutive maximal values found.

6. The method of claim 5, further comprising computing beat rate values by calculating the inverse of the time difference between consecutive maximal values.

7. The method of claim 1 or 5, further comprising performing time domain analysis, frequency domain analysis, and/or pulse wave morphology analysis to the measured signal in order to determine the response to excitation.

8. The method of claim 1, wherein the signals are measured in a region selected from the group consisting of a finger, ear, wrist, ankle, toe, neck, chest, of the subject.

9. The method of claim 1, wherein the signals are measured invasively.

10. The method of claim 1 or 4, further comprising comparing the signals measured during the excitation, and/or indicators computed therefore, to the subject's normal pulse wave signals, and/or indicators computed therefore.

11. The method of claim 4 or 10, further comprising computing one or more indicators selected from the group consisting of PWA Range, AI, Pulse Period Range, HF integral, LF integral, BPM STDEV, pNN50, and BPM range, wherein said indicators are computed using signals obtained during the excitation and for normal pulse wave signals.

12. The method of claim 1, further comprising computing arterial flow, arterial stiffness, and ANS function, scores for indicating physiological functions, by calculating a weighted summation of the indicators.

13. The method of claim 12, further comprising, computing a total score, wherein said total score is the linear combination of the scores for indicating physiological functions.

14. The method of claim 13, further comprising manipulating the scores for obtaining risk evaluations for one or more of the following cardiovascular events: acute coronary syndrome; sudden cardiac death; arrhythmia; stroke; and myocardial infarction.

15. The method of claim 1, further comprising extracting a Peripheral Flow Reserve (PFR) indicator by computing the ratio between averaged amplitude of the pulse wave signal measured during the excitation and the averaged amplitude of normal pulse wave signals of the subject.

16. The method of claim 2, further comprising extracting a Respiratory Modulation Response (RMR) indicator by computing the ratio between a first and a second areas defined under the curve of the frequency domain representation of the PW signal, wherein said areas are defined under said curve in a region defined by two adjacent minimal values adjacently located on the two sides of the breath frequency, and wherein a first area is defined to be the area under said curve between said minimal values and a second area is defined to be the subtraction of the area under the line connecting said minimal values and said first area.

17. The method of claim 1, used for one or more of the following applications:

- cardiovascular risk screening and assessment;
- cardiovascular intervention monitoring such as stenting and bypass surgery;
- cardiovascular intervention follow-up;
- therapeutic strategy monitoring such as medications;
- monitoring of life style changes such as diet and sports.

18. The method of claim 1, wherein one or more of the following cardiovascular dysfunctions are monitored or diagnosed:

- cardiac Ischemia;
- endothelial dysfunction;
- coronary artery disease;
- coronary artery occlusion;
- arterial stiffness;
- autonomic nervous system function;
- myocardial infarction;
- angina pectoris;
- atherosclerosis.

19. The method of claim 1, further comprising extracting a responsive augmentation index ratio indicator by computing the ratio between the AI indicator of the subject's normal blood PW signals and the AI indicator of the subject's responsive to the excitation.

20. A system for monitoring function and/or diagnosing dysfunction of the cardiovascular system of a human subject, comprising a sensor for measuring pulse wave signals of a human subject, means for converting said signals into a data format, and a means for processing and analyzing the converted signals and extracting diagnostic indicators therefrom, wherein said signals are measured during rapid excitation of the cardiovascular system of said subject.

21. The system of claim 20, wherein the excitation of the cardiovascular system is provided by the use of controlled breathing characterized by a predefined frequency of breaths.

22. The system of claim 21, wherein the predefined frequency of breaths is about 0.1 Hz.

23. The system of claim 20, further comprising a low pass filter for separating breath offsetting components from the converted signals, and means for subtracting said components from said converted signal.

24. The system of claim 23, further comprising an additional low pass filter for filtering out high frequency noise and an upsampler for interpolating the signal and thereby adding data thereto.

25. The system of claim 20, further comprising means for comparing the signals measured during the excitation with the subject's normal pulse wave signals, and for outputting corresponding indications.

26. The system of claim 20, wherein the processing mean is adapted to compute one or more of the following indicators: PWA range, AI, Pulse Period Range, LF integral, BPM STDEV, pNN50, and BPM range, during the excitation and for normal pulse wave signals.

27. The system of claim 20, used for one or more of the following applications: cardiovascular risk screening and assessment; cardiovascular intervention monitoring such as stenting and bypass surgery; cardiovascular intervention follow-up; therapeutic strategy monitoring such as medications; and life style changes such as diet and sports.

28. The system of claim 20, wherein one or more of the following cardiovascular dysfunctions are monitored or

diagnosed: cardiac Ischemia, endothelial dysfunction, coronary artery disease, coronary artery occlusion, arterial stiffness, autonomic nervous system, myocardial infarction, angina pectoris, and atherosclerosis.

29. The system of claim 21, wherein the processing mean is adapted to compute a respiratory modulation response indicator by computing the ratio between a first and a second areas defined under the curve of the frequency domain representation of the PW signal, wherein said areas are defined under said curve in a region defined by two adjacent minimal values adjacently located on the two sides of the breath frequency, and wherein a first area is defined to be the area under said curve between said minimal values and a second area is defined to be the subtraction of the area under the line connecting said minimal values and said first area.

30. The system of claim 21, wherein the processing mean is adapted to compute a responsive augmentation index ratio indicator by computing the ratio between the AI indicator of the subject's normal pulse rate signals and the AI indicator of the subject's responsive to the excitation.

31. The system of claim 20, wherein the processing mean is adapted to compute a peripheral flow reserve indicator by computing the ratio between averaged amplitude of the pulse wave signal measured during the excitation and the averaged amplitude of normal pulse wave signals of the subject.

32. The system of claim 20, wherein the sensor is selected from the group consisting of a Photoplethysmograph sensor; flow sensor; mechanical sensors; optical sensors, ultrasonic sensors; electrical impedance sensor.

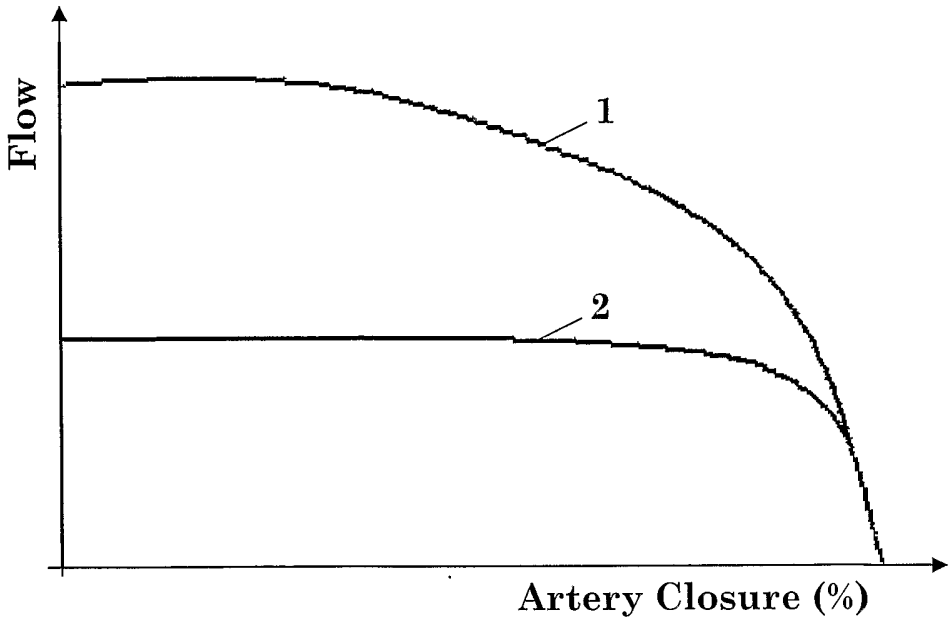


Fig. 1

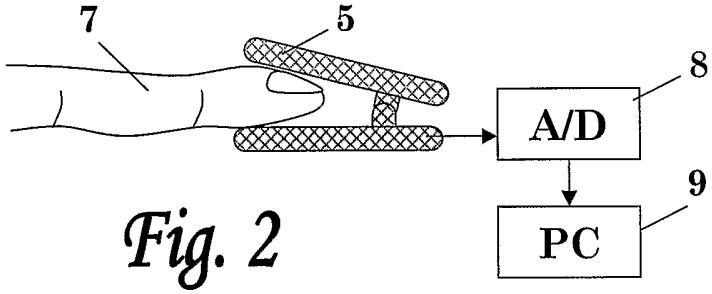


Fig. 2

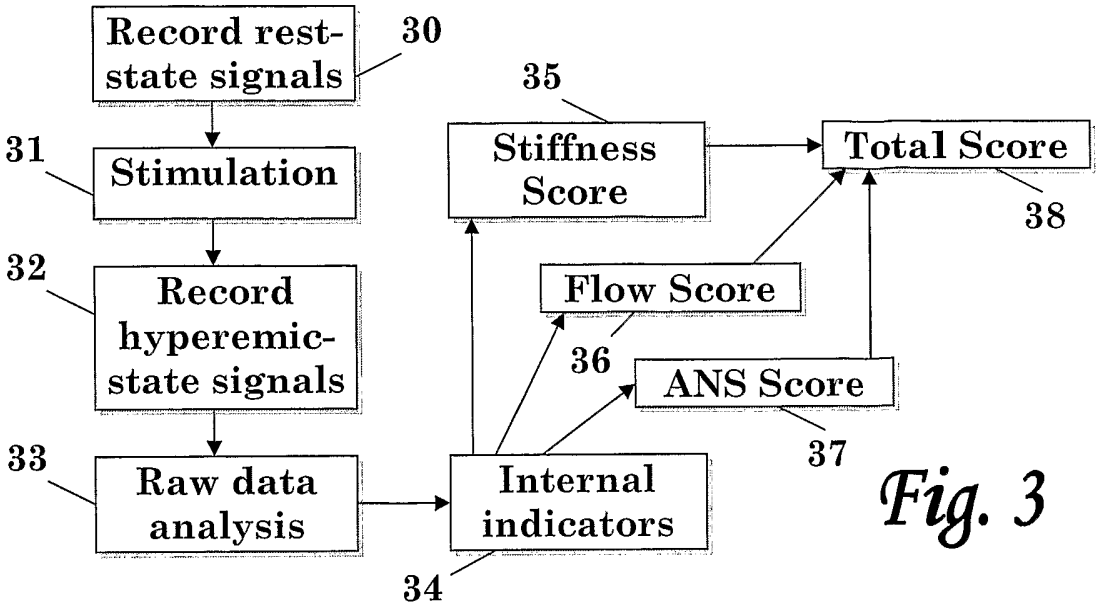


Fig. 3

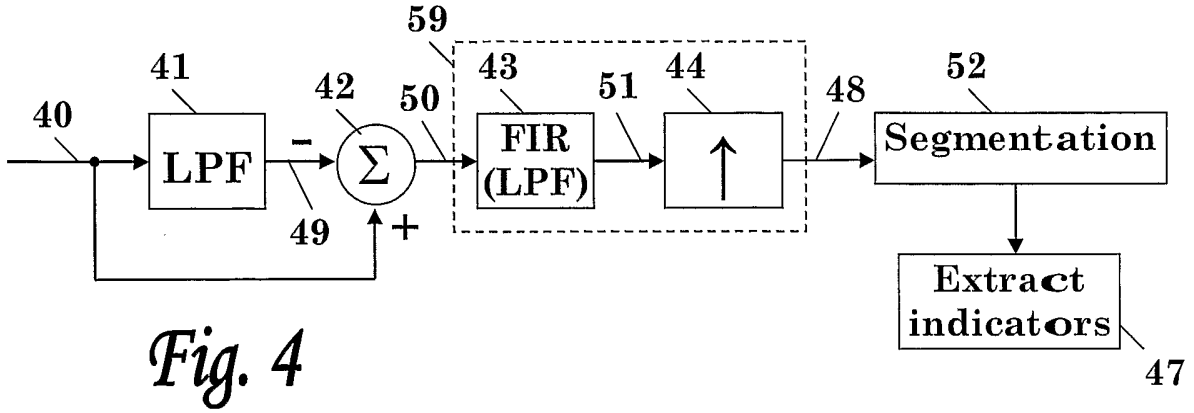


Fig. 4

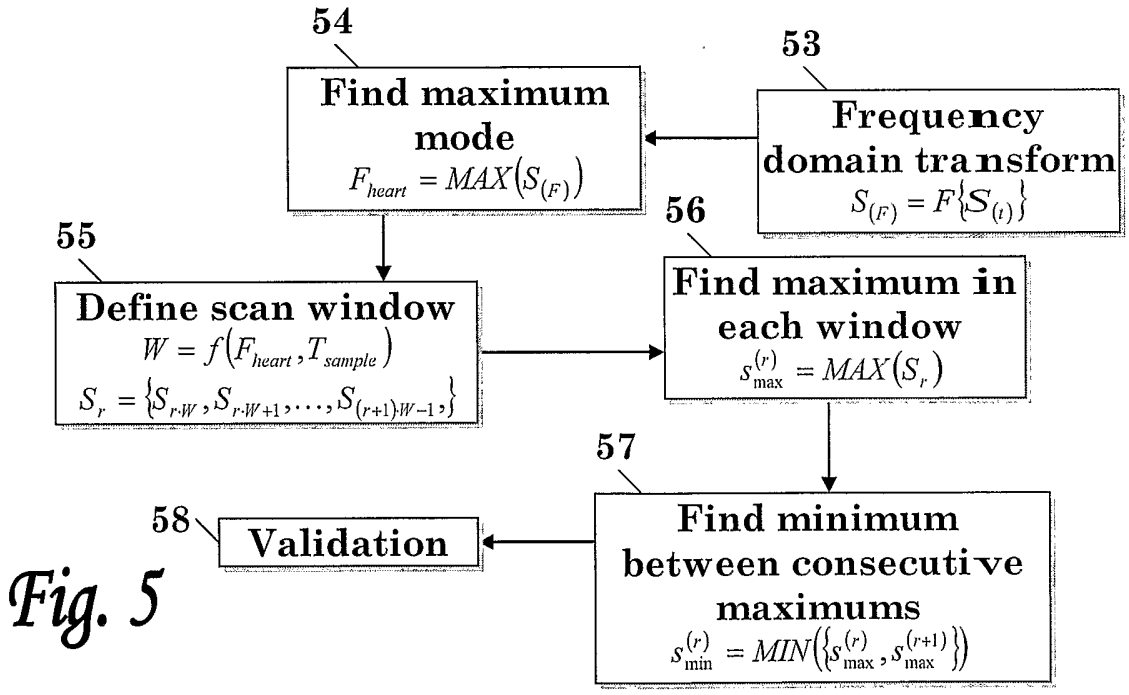


Fig. 5

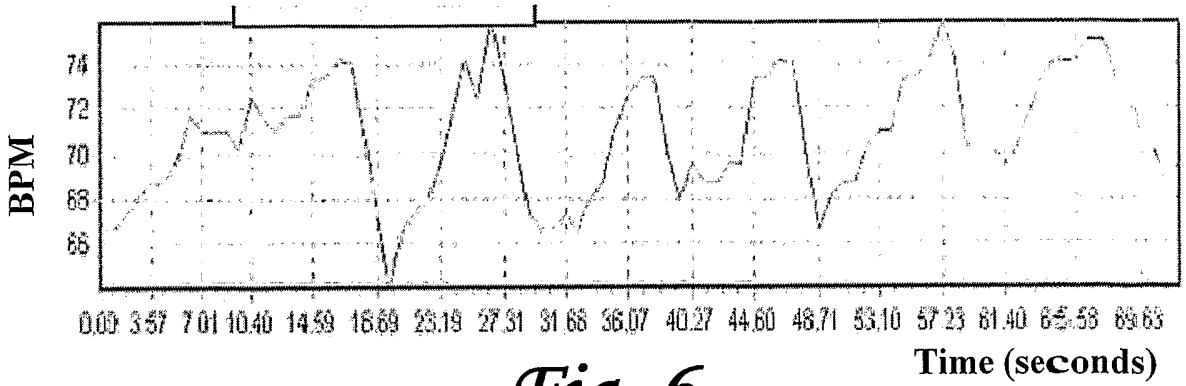


Fig. 6

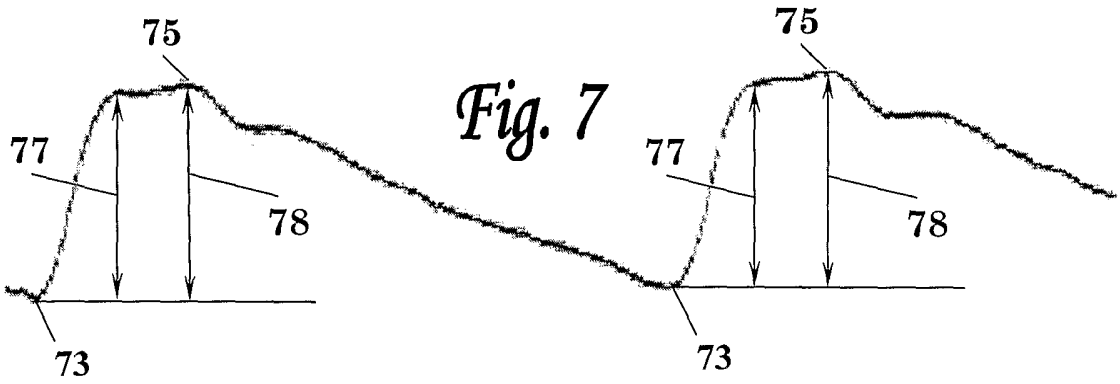


Fig. 7

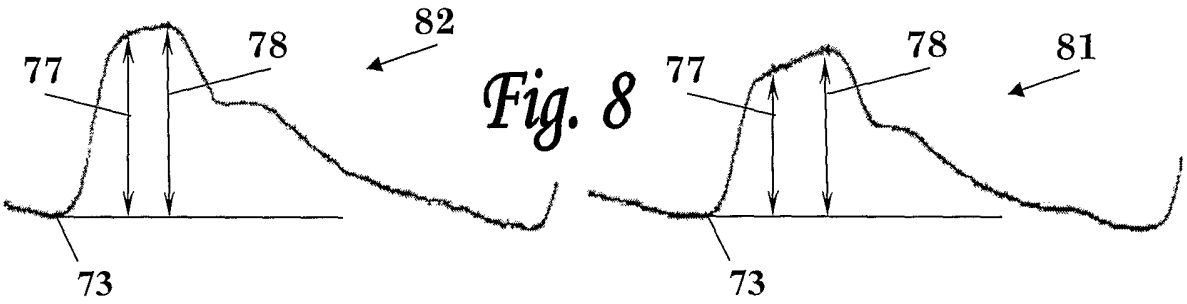


Fig. 8

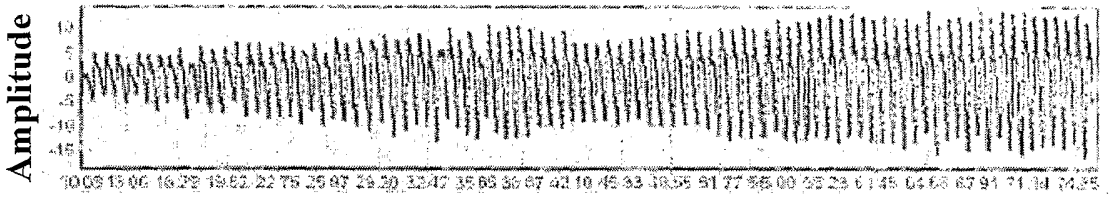


Fig. 9A

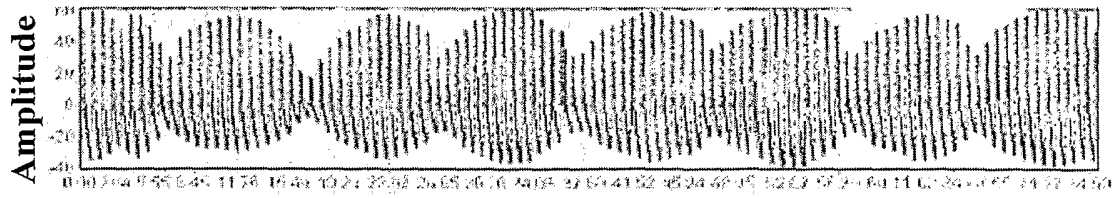


Fig. 9B

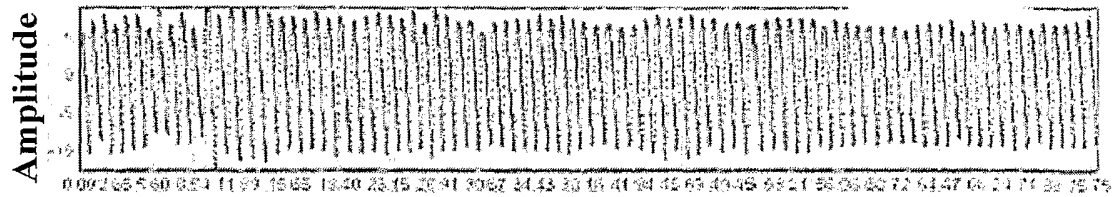


Fig. 9C

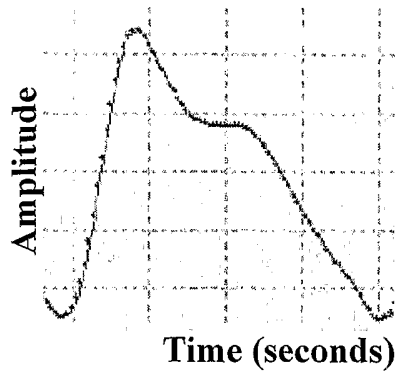


Fig. 10A

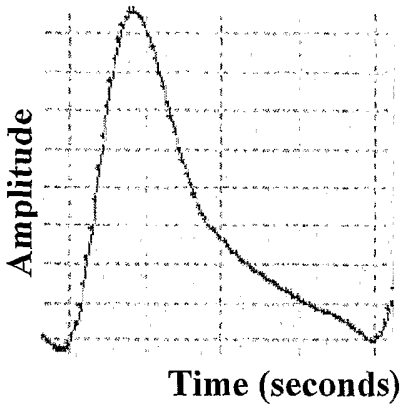


Fig. 10B

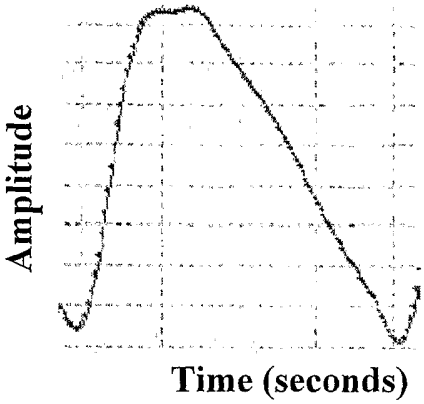


Fig. 10C

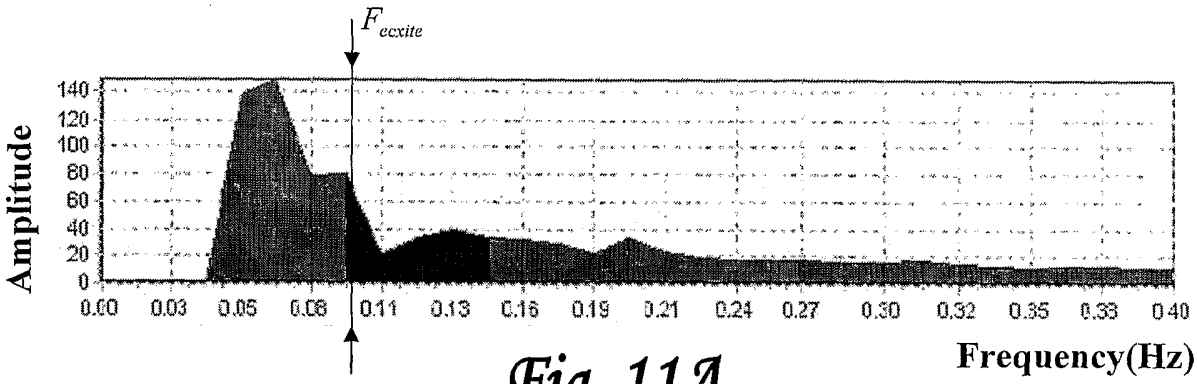


Fig. 11A

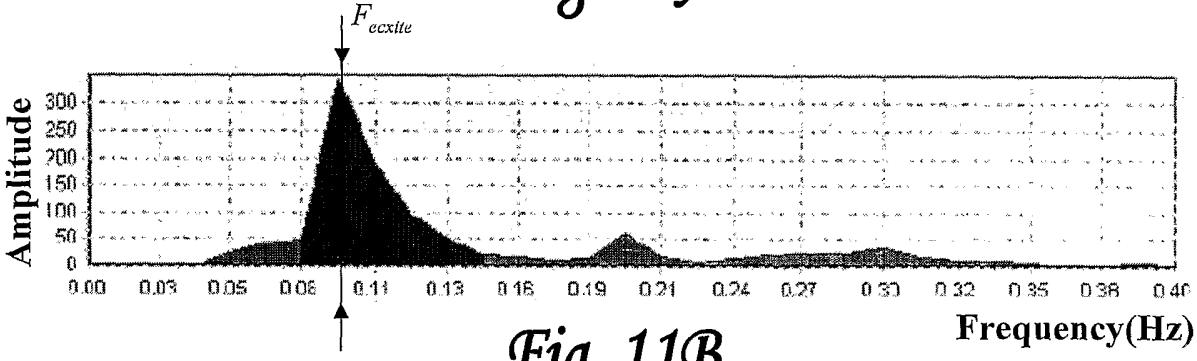
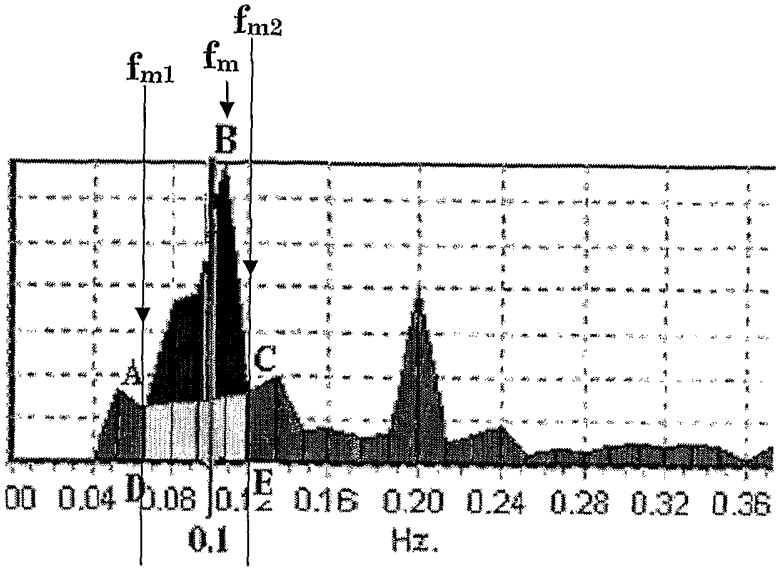


Fig. 11B

Fig. 12



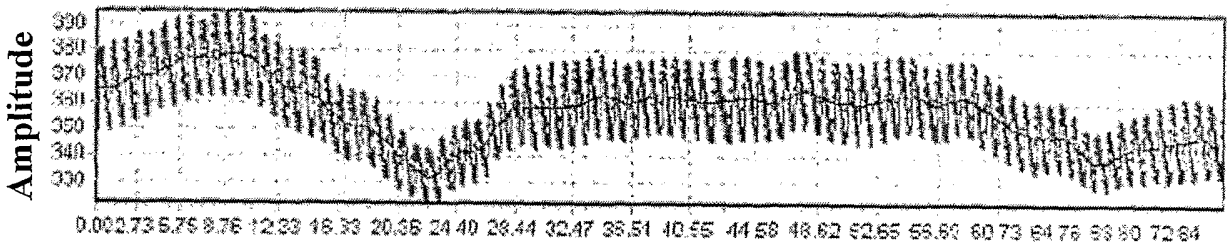


Fig. 13A

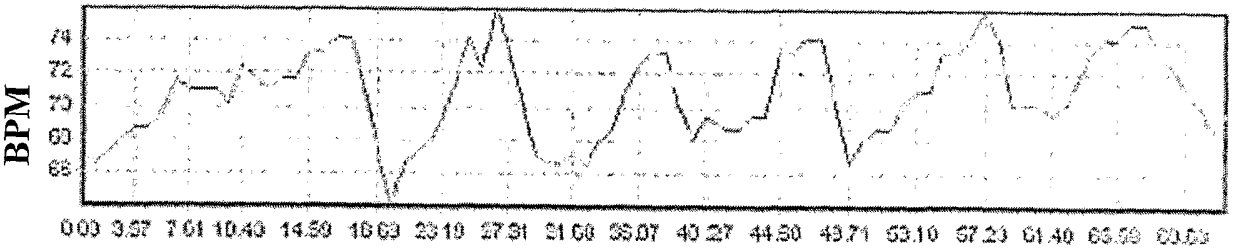


Fig. 13B

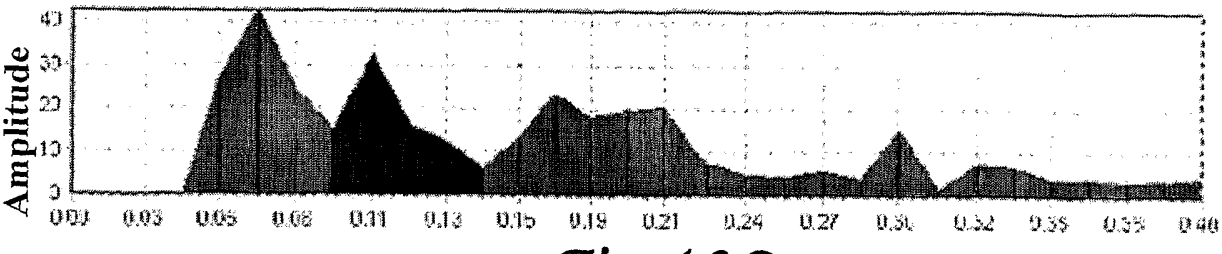


Fig. 13C

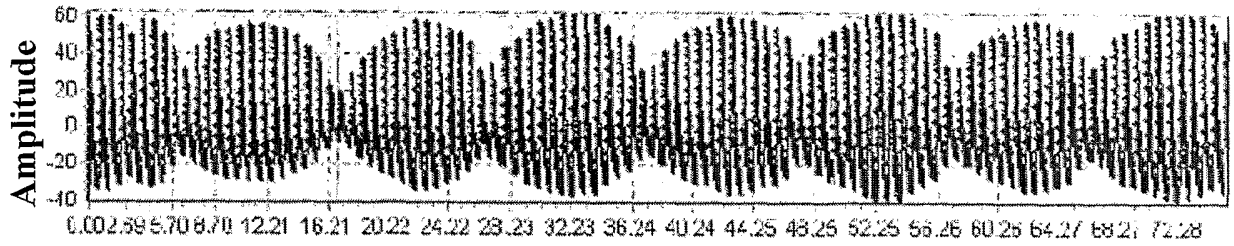


Fig. 14A

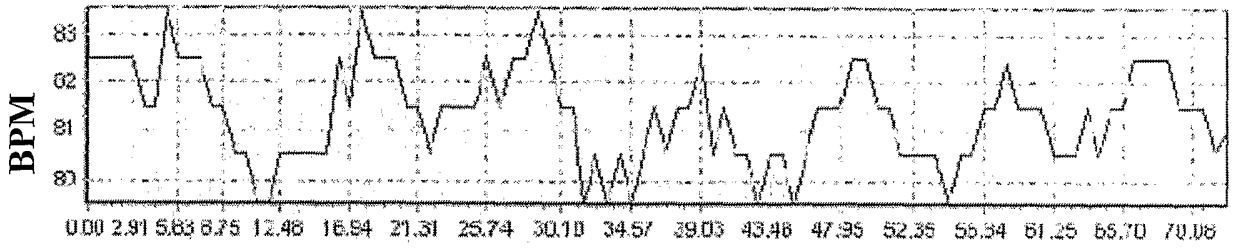


Fig. 14B

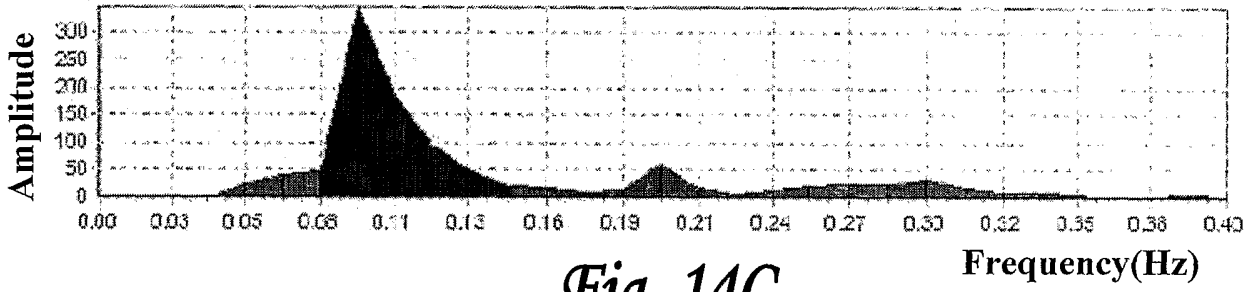


Fig. 14C

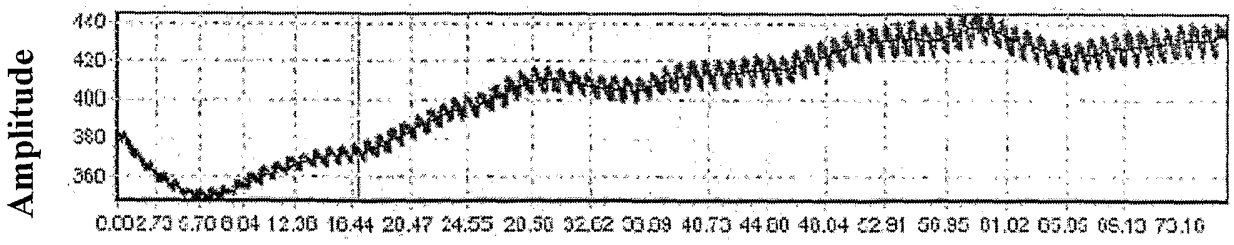


Fig. 15A

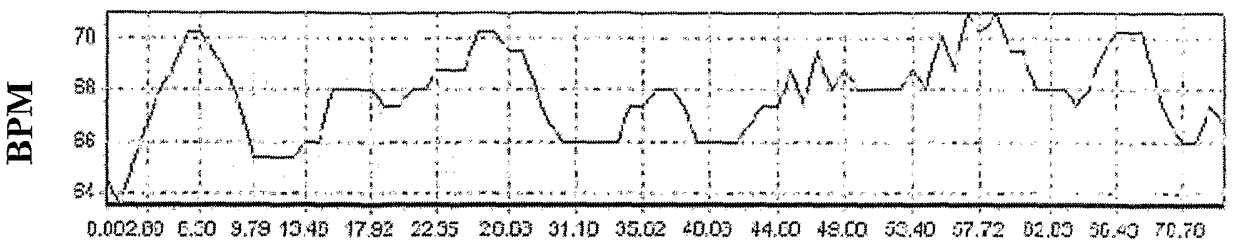


Fig. 15B

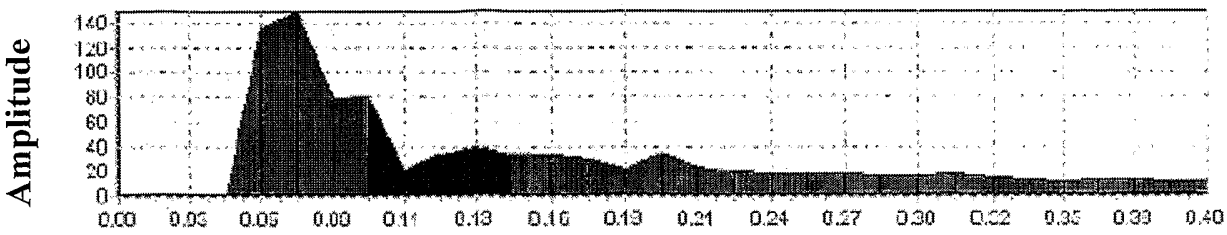


Fig. 15C

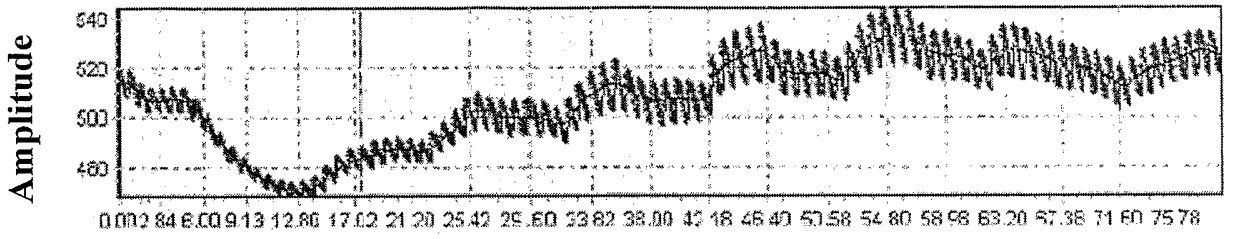


Fig. 16A

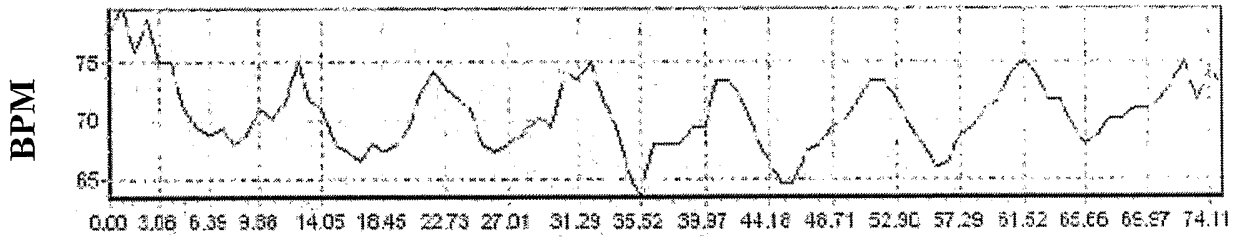


Fig. 16B

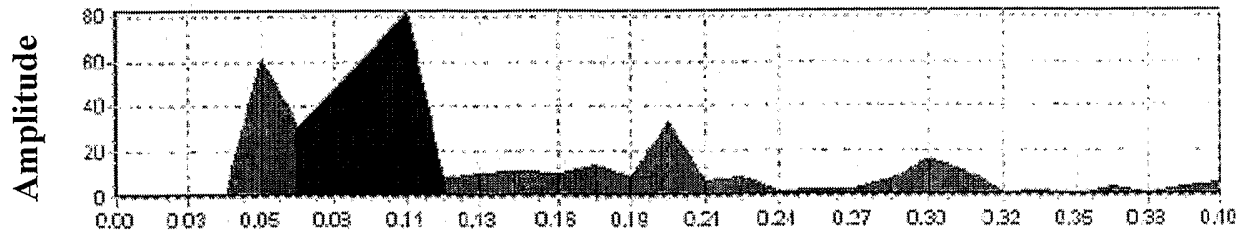


Fig. 16C

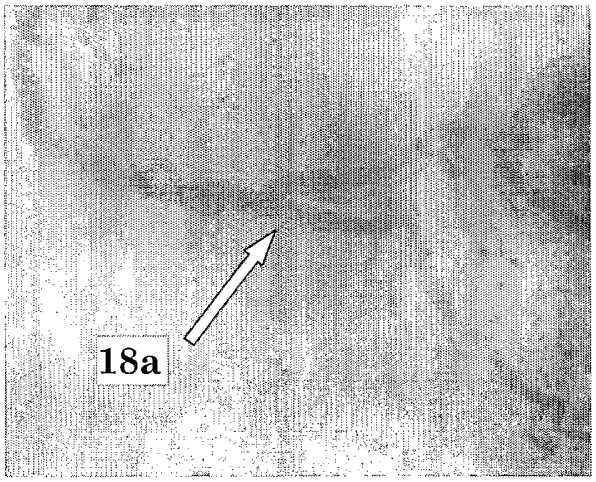


Fig. 18A

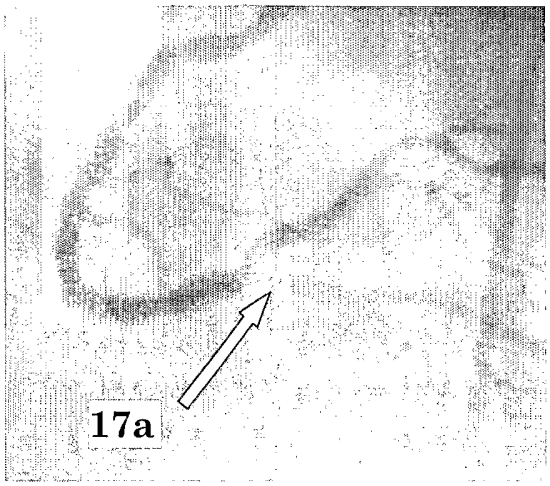
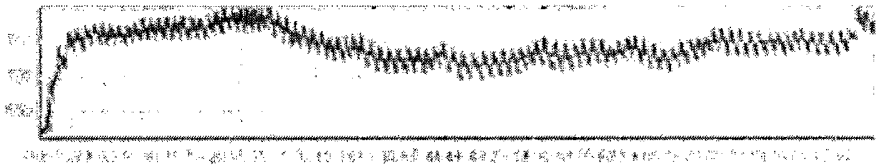


Fig. 17A

Fig. 17B



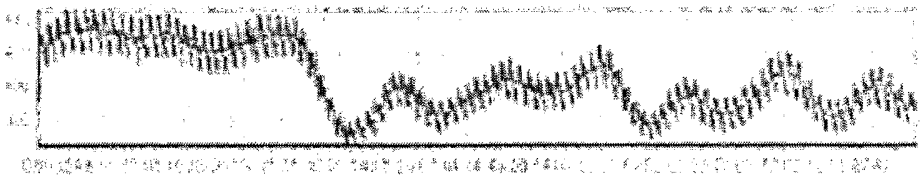
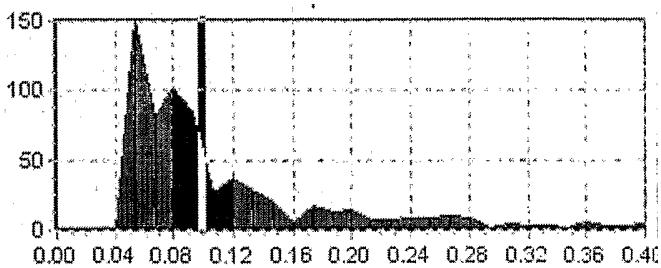


Fig. 18B

Fig. 17C



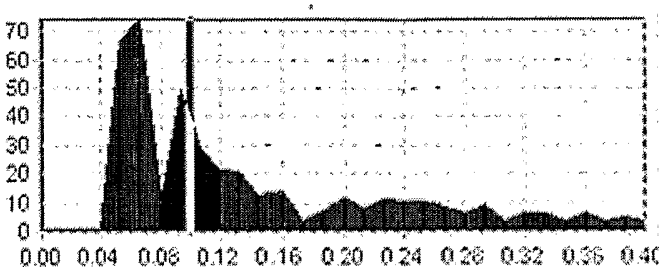


Fig. 18C