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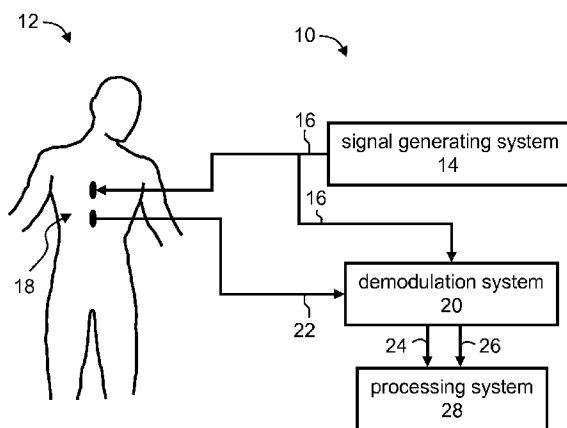


FIG. 1

(57) Abstract: A system for monitoring hemodynamics of a subject is disclosed. The system comprises: a signal generating system configured for providing at least an output electric signal and transmitting the output signal to an organ of the subject. The system also comprises a demodulation system configured for receiving an input electrical signal sensed from the organ responsively to the output electric signal, and for modulating the input signal using the output signal to provide an in-phase component and a quadrature component of the input signal. The system also comprises a processing system configured for monitoring the hemodynamics based on the in-phase and the quadrature components.

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METHOD AND SYSTEM FOR MONITORING HEMODYNAMICS

RELATED APPLICATION

This application claims the benefit of priority of U.S. Provisional Patent
5 Application No. 61/511,163 filed on July 25, 2011, the contents of which are
incorporated herein by reference in their entirety.

FIELD AND BACKGROUND OF THE INVENTION

The present invention, in some embodiments thereof, relates to the medical field
10 and, more particularly, but not exclusively, to a method and system for monitoring
hemodynamics.

Heart diseases are major causes of morbidity and mortality in the modern world.
Generally, heart diseases may be caused by (i) a failure in the autonomic nerve system
where the impulses from the central nervous system control to the heart muscle fail to
15 provide a regular heart rate and/or (ii) an insufficient strength of the heart muscle itself
where even though the patient has a regular heart rate, its force of contraction is
insufficient. Either way, the amount of blood or the rate at which the blood is supplied
by a diseased heart is abnormal and it is appreciated that an assessment of the state of a
patient's circulation is of utmost importance.

20 The simplest measurements, such as heart rate and blood pressure, may be
adequate for many patients, but if there is a cardiovascular abnormality then more
detailed measurements are needed.

Cardiac output (CO) is the volume of blood pumped by the heart during a time
interval, which is typically taken to be a minute. Cardiac output is the product of heart
25 rate (HR) and the amount of blood which is pumped with each heartbeat, also known as
the stroke volume (SV). For example, the stroke volume at rest in the standing position
averages between 60 and 80 ml of blood in most adults. Thus, at a resting heart rate of
80 beats per minute the resting cardiac output varies between 4.8 and 6.4 L per min.

Several methods of measuring cardiac output are presently known.

30 One such method employs transoesophageal echocardiography (TOE) which
provides diagnosis and monitoring of a variety of structural and functional abnormalities
of the heart. TOE is used to derive cardiac output from measurement of blood flow

velocity by recording the Doppler shift of ultrasound reflected from the red blood cells. The time velocity integral, which is the integral of instantaneous blood flow velocities during one cardiac cycle, is obtained for the blood flow in a specific site (*e.g.*, the left ventricular outflow tract). The time velocity integral is multiplied by the cross-sectional
5 area and the heart rate to give cardiac output.

U.S. Patent No. 6,485,431 discloses a technique in which the arterial pressure, measured by a pressure cuff or a pressure tonometer, is used for calculating the mean arterial pressure and the time constant of the arterial system in diastole. The compliance of the arterial system is then determined from a table and used for calculating the cardiac
10 output as the product of the mean arterial pressure and compliance divided by a time constant.

An additional method of measuring cardiac output is known as thermodilution. This method is based on a principle in which the cardiac output can be estimated from the dilution of a bolus of saline being at a different temperature from the blood. The
15 thermodilution involves an insertion of a fine catheter into a vein, through the heart and into the pulmonary artery. A thermistor, mounted on the tip of the catheter senses the temperature in the pulmonary artery. A bolus of saline (about 5 ml. in volume) is injected rapidly through an opening in the catheter, located in or near to the right atrium of the heart. The saline mixes with the blood in the heart and temporarily depresses the
20 temperature in the right atrium. Two temperatures are measured simultaneously: the blood temperature is measured by the thermistor sensor on the catheter and the temperature of the saline to be injected is typically measured by means of a platinum temperature sensor. The cardiac output is inversely related to the area under the curve of temperature depression.

25 A non-invasive method, known as thoracic electrical bioimpedance, was first disclosed in U.S. Patent No. 3,340,867 and has recently begun to attract medical and industrial attention (see, *e.g.*, U.S. Patent Nos. 3,340,867, 4,450,527, 4,852,580, 4,870,578, 4,953,556, 5,178,154, 5,309,917, 5,316,004, 5,505,209, 5,529,072, 5,503,157, 5,469,859, 5,423,326, 5,685,316, 6,485,431, 6,496,732 and 6,511,438;
30 U.S. Patent Application No. 20020193689]. The thoracic electrical bioimpedance method has the advantages of providing continuous cardiac output measurement at no risk to the patient.

Various methods employing bioimpedance are found in: International Publication Nos. WO2004098376, WO2006087696, WO2008129535, WO2009022330 and WO2010032252 all assigned to the common assignee of the present invention and fully incorporated herein by reference.

5

SUMMARY OF THE INVENTION

According to an aspect of some embodiments of the present invention there is provided a system for monitoring hemodynamics of a subject. The system comprises: a signal generating system configured for providing at least an output electric signal and transmitting the output signal to an organ of the subject. The system also comprises a demodulation system configured for receiving an input electrical signal sensed from the organ responsively to the output electric signal, and for modulating the input signal using the output signal to provide an in-phase component and a quadrature component of the input signal. The system also comprises a processing system configured for monitoring the hemodynamics based on the in-phase and the quadrature components.

According to an aspect of some embodiments of the present invention there is provided a method of monitoring hemodynamics of a subject. The method comprises generating at least an output electric signal, and transmitting the output signal to an organ of the subject. The method further comprises sensing an input electrical signal from the organ responsively to the output electric signal, and modulating the input signal using the output signal to provide an in-phase component and a quadrature component of the input signal. The method further comprises monitoring the hemodynamics based on the in-phase and the quadrature components.

According to some embodiments of the invention the processing system and/or method combines the in-phase component with the quadrature component thereby to generate a hybrid signal, wherein the monitoring is based at least in part on the hybrid signal.

According to some embodiments of the invention the signal generating system and/or method provides a first output electric signal and a second output electric signal, and transmits each of the output signals to a separate part of the organ. According to some embodiments of the present invention the demodulation system and/or method receives an input electrical signal sensed from each part of the organ responsively to a

respective output electric signal, and modulates the signals to provide an in-phase component and a quadrature component of each of the input signals.

According to some embodiments of the invention the processing system and/or method combines, for each input signal, a respective in-phase component with a
5 respective quadrature component thereby to generate a hybrid signal corresponding to the input signal. According to some embodiments of the present invention the monitoring is based at least in part on the hybrid signals.

According to some embodiments of the invention the processing system and/or method combines the hybrid signals, thereby to provide a combined hybrid signal, and
10 wherein the monitoring is based at least in part on the combined hybrid signals.

According to some embodiments of the invention the processing system and/or method combines an in-phase component of a first input signal with an in-phase component of a second input signal to provide a combined in-phase signal. According to some embodiments of the invention the monitoring is based at least in part on the
15 combined in-phase signal.

According to some embodiments of the invention the processing system and/or method combines a quadrature component of a first input signal with a quadrature component of a second input signal to provide a combined quadrature signal. According to some embodiments of the invention the monitoring is based at least in part on the
20 combined quadrature signal.

According to some embodiments of the invention the processing system and/or method calculates, for each input signal, a phase component, an amplitude component, and a phase-amplitude hybrid signal defined as a combination of the phase component with the amplitude component. According to some embodiments of the invention the
25 monitoring is based at least in part on this combination.

According to some embodiments of the invention the processing system and/or method combines a phase-amplitude hybrid signal corresponding to the first input signal with a phase-amplitude hybrid signal corresponding to the second input signal, thereby to provide a combined phase-amplitude hybrid signal. According to some embodiments
30 of the invention the monitoring is based at least in part on the combined phase-amplitude hybrid signal.

According to an aspect of some embodiments of the present invention there is provided a system for monitoring hemodynamics of a subject. The system comprises a signal generating system configured for providing a first output electric signal and a second output electric signal, and for transmitting each of output signals to a separate
5 part of an organ of the subject. The system further comprises a processing system configured for receiving an input electrical signal sensed from each part of the organ responsively to a respective output electric signal, and for monitoring the hemodynamics based on input electrical signals.

According to an aspect of some embodiments of the present invention there is provided a method for monitoring hemodynamics of a subject. The method comprises:
10 generating a first output electric signal and a second output electric, and transmitting each of the output signals to a separate part of an organ of the subject. The method further comprises sensing an input electrical signal from each part of the organ responsively to a respective output electric signal, and monitoring the hemodynamics
15 based on the input electrical signals.

According to some embodiments of the invention the system and/or method combines the input signals to provide a combined signal, wherein the monitoring is based at least in part on the combined signal.

According to some embodiments of the invention any of the above signal
20 combinations is the combination is a linear combination.

According to some embodiments of the invention any of the above signal combinations is a non-linear combination.

According to some embodiments of the invention the processing system and/or method assesses, based on the combined hybrid signal and/or the combined phase-
25 amplitude hybrid signal and/or the combined signal, at least one property selected from the group consisting of stroke volume (SV), cardiac output (CO), ventricular ejection time (VET), cardiac index (CI), thoracic fluid content (TFC), total peripheral resistance index (TPRI), blood vessel compliance.

According to some embodiments of the invention the processing system and/or
30 method estimates exercise capacity of the subject based on the combined hybrid signal and/or the combined phase-amplitude hybrid signal and/or the combined signal.

According to some embodiments of the invention the processing system and/or method identifies sleep apnea events based on the combined hybrid signal and/or the combined phase-amplitude hybrid signal and/or the combined signal.

5 According to some embodiments of the invention the processing system and/or method assesses the likelihood that the subject develops sepsis based on the combined hybrid signal and/or the combined phase-amplitude hybrid signal and/or the combined signal.

10 According to some embodiments of the invention the processing system and/or method predicts onset of electromechanical dissociation based on the combined hybrid signal and/or the combined phase-amplitude hybrid signal and/or the combined signal.

According to some embodiments of the invention the processing system and/or method assesses blood hematocrit based on the combined hybrid signal and/or the combined phase-amplitude hybrid signal and/or the combined signal.

15 According to some embodiments of the invention the first and the second output electric signals are dependent electrical signals.

According to some embodiments of the invention the first and the second output electric signals are independent electrical signals.

20 Unless otherwise defined, all technical and/or scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments of the invention, exemplary methods and/or materials are described below. In case of conflict, the patent specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and are not intended to be necessarily limiting.

25 Implementation of the method and/or system of embodiments of the invention can involve performing or completing selected tasks manually, automatically, or a combination thereof. Moreover, according to actual instrumentation and equipment of embodiments of the method and/or system of the invention, several selected tasks could be implemented by hardware, by software or by firmware or by a combination thereof
30 using an operating system.

For example, hardware for performing selected tasks according to embodiments of the invention could be implemented as a chip or a circuit. As software, selected tasks

according to embodiments of the invention could be implemented as a plurality of software instructions being executed by a computer using any suitable operating system. In an exemplary embodiment of the invention, one or more tasks according to exemplary embodiments of method and/or system as described herein are performed by a data processor, such as a computing platform for executing a plurality of instructions. 5 Optionally, the data processor includes a volatile memory for storing instructions and/or data and/or a non-volatile storage, for example, a magnetic hard-disk and/or removable media, for storing instructions and/or data. Optionally, a network connection is provided as well. A display and/or a user input device such as a keyboard or mouse are optionally 10 provided as well.

BRIEF DESCRIPTION OF THE DRAWINGS

Some embodiments of the invention are herein described, by way of example only, with reference to the accompanying drawings. With specific reference now to the drawings in detail, it is stressed that the particulars shown are by way of example and for 15 purposes of illustrative discussion of embodiments of the invention. In this regard, the description taken with the drawings makes apparent to those skilled in the art how embodiments of the invention may be practiced.

In the drawings:

20 FIG. 1 is a schematic block diagram illustrating a system suitable for monitoring hemodynamics of a subject, according to some embodiments of the present invention;

FIG. 2 is a schematic block diagram illustrating the system, according to other embodiments of the present invention;

25 FIG. 3 is a is a schematic block diagram illustrating a system which is a combination of the system illustrated in FIG. 1 and the system illustrated in FIG. 2, according to some embodiments of the present invention;

FIG. 4 is a schematic illustration of an operational principle of a demodulation system according to some embodiments of the present invention;

30 FIGs. 5A and 5B are schematic block diagrams of a demodulation system (FIG. 5A) and a processing system (FIG. 5B) according to some embodiments of the present invention;

FIGs. 6A and 6B show representative examples of a dynamically varying frequency bounds, according to some embodiments of the present invention;

FIG. 6C shows a dynamically varying band pass filter (BPF), according to some embodiments of the present invention;

5 FIG. 7 is a schematic illustration of a typical morphology of a single beat of a signal and its first derivative, as a function of the time, according to some embodiments of the present invention;

FIG. 8 is a schematic illustration of a prototype system built according to some embodiments of the present invention;

10 FIG. 9A shows the left ventricle volume signal in ml (blue) as derived by a 3-Fr Micromanometer secured with a purse string suture, as a function of time, synchronized with the ECG signal (black);

FIG. 9B shows a signal $S_{CT}(t)$ obtained according to some embodiments of the present invention (red) synchronized with the ECG signal (black);

15 FIG. 10 shows a left ventricle flow signal as derived by an ultrasonic flow probe around the ascending aorta (blue), and a $dS_{CT}(t)$ signal obtained according to some embodiments of the present invention (black);

FIG. 11 shows mean cardiac output as derived by an aortic ultrasonic flow probe (blue), and mean cardiac output derived by a $dS_{CT}(t)$ signal obtained according to some
20 embodiments of the present invention (red) during infusion of Dobutamine;

FIG. 12A shows mean cardiac output as derived by an aortic ultrasonic flow probe (blue), and mean cardiac output derived by a $dS_{CL}(t)$ signal obtained according to some embodiments of the present invention (black), after infusion of Dobutamine;

25 FIG. 12B shows mean cardiac output as derived by an aortic ultrasonic flow probe as a function of the number of heart beat (blue), and mean cardiac output derived by a $dS_{CR}(t)$ signal obtained according to some embodiments of the present invention (black);

30 FIG. 13A shows mean cardiac output derived by an aortic ultrasonic flow probe (blue), and mean cardiac output derived by a $dS_{CR}(t)$ signal obtained according to some embodiments of the present invention (black) during progression of Severe Edema;

FIG. 13B shows mean cardiac output derived by an aortic ultrasonic flow probe (blue), and mean cardiac output derived by a $dS_{CL}(t)$ signal obtained according to some embodiments of the present invention (black); and

FIG. 14 shows mean cardiac output as derived by an aortic ultrasonic flow probe (blue), and mean cardiac output derived by a $dS_{PT}(t)$ signal obtained according to some
5 embodiments of the present invention (black) during infusion of 500cc fluid bolus.

DESCRIPTION OF SPECIFIC EMBODIMENTS OF THE INVENTION

The present invention, in some embodiments thereof, relates to the medical field
10 and, more particularly, but not exclusively, to a method and system for monitoring hemodynamics.

Before explaining at least one embodiment of the invention in detail, it is to be understood that the invention is not necessarily limited in its application to the details of construction and the arrangement of the components and/or methods set forth in the
15 following description and/or illustrated in the drawings and/or the Examples. The invention is capable of other embodiments or of being practiced or carried out in various ways.

The present inventors observed that the components of a decomposition of signals can be used to assess the hemodynamic state of a subject, wherein different
20 components are complementary to each other in terms of the information they carry. The present inventors also observed that signals obtained from different parts of the same section of the vasculature are also complementary to each other. The present Inventors devised a technique which utilizes one or both the above observations for the purpose of monitoring hemodynamics of a subject.

Referring now to the drawings, FIG. 1 is a schematic block diagram illustrating a
25 system **10** suitable for monitoring hemodynamics of a subject **12**, according to some embodiments of the present invention. System **10** typically comprises a signal generating system **14** which preferably provides one or more output electric signals **16** and transmits signal **16** to an organ **18** of subject **12**. Signal(s) **16** can be transmitted via
30 a medical lead as known in the art.

For clarity of presentation, medical leads are designated herein by the reference signs of the signals they carry.

Organ **18** can be any part of a body of human or animal. Preferably, organ **18** is external organ so that the transmission of signals can be done non-invasively. Representative example of organ **18** include, without limitation, a chest, a hip, a thigh, a neck, a head, an arm, a forearm, an abdomen, a back, a gluteus, a leg and a foot. In
5 some embodiments of the present invention organ **18** is a chest.

In some embodiments of the present invention system **10** comprises a demodulation system **20** configured for receiving an input electrical signal **22** sensed from organ **18** responsively to output signal **16**, and for modulating input signal **22** using output signal **16** to provide an in-phase component **24** and a quadrature component **26** of
10 input signal **22**. System **10** can further comprise a processing system **28** which, in some embodiments, is configured for monitoring the hemodynamics based on in-phase component **24** and quadrature component **26**.

FIG. 2 is a schematic block diagram illustrating system **10**, according to other embodiments of the present invention. In the embodiments illustrated in FIG. 2, signal
15 generating system **14** provides two signals, referred to herein as first output electric signal **32** and a second output electric signal **34**, and transmits them to separate parts of organ of **18**. For example, signal **32** can be transmitted to the left side of organ **18** and signal **34** can be transmitted to the right side of organ **18**. In some embodiments of the present invention signals **32** and **34** are dependent signals. Alternatively, signals **32** and
20 **34** can be independent signals.

As used herein, “dependent signals” means signals which are synchronized in at least one, more preferably at least two, more preferably any of: their frequency, phase and amplitude.

As used herein, “independent signals” means signals which are not synchronized
25 in at least one, more preferably at least two, more preferably any of: their frequency, phase and amplitude.

Also contemplated are embodiments in which signal generating system **14** provides more than two (depended or independent) signals.

In the embodiments illustrated in FIG. 2, processing system **28** receives first
30 input electrical signal **36** sensed from the first part of organ **18** (the right side in the above example) responsively to first output signal **32**, and a second input electrical signal **38** sensed from the second first part of organ **18** (the left side, in the above

example) responsively to second output signal **34**. Processing system **28** preferably monitors the hemodynamics based on input signals **36** and **38**.

In various exemplary embodiments of the invention the embodiment illustrated in FIG. 1 are combined with the embodiments illustrated in FIG. 2. A representative
5 example of such combination is illustrated in FIG. 3. In the present embodiment, generating system **14** provides two or more output signals, preferably, but not necessarily independent signals and transmits them to separate parts of organ of **18**. In the schematic illustration of FIG. 3 which is not to be considered as limiting, generating system **14** provides two signals **32** and **34**, and transmits them to the right and left sides
10 of organ **18**, respectively.

In some embodiments of the present invention demodulation system **20** receives an input electrical signal sensed from each part of organ **18** responsively to the respective output signal. For example, demodulation system **20** can receive first input
15 signal **36** sensed from the first part of organ **18** responsively to first output signal **32**, and second input signal **38** sensed from the second first part of organ **18** responsively to second output signal **34**. Demodulation system **20** optionally and preferably modulates all input signals using the input signals to provide, for each input signal, an in-phase component and a quadrature component. Thus, demodulation system **20** preferably provides $2N$ signals, where N is the number of the received input signals.

In the above example in which demodulation system **20** receives input signals **36**
20 and **38**, the output of system **20** is a first in-phase component **40** and a first quadrature component **42** both being demodulations of first input signal **36**, and a second in-phase component **44** and a second quadrature component **46** both being demodulations of second input signal **38**.

25 A more detailed description of system **10** as delineated hereinabove and in accordance with some embodiments of the present invention will now be provided.

The signals provided by generating system **14** are preferable alternate current (AC) signals which can be at any frequency. It was found by the present inventors that radiofrequency signals are useful, but it is not intended to limit the scope of the present
30 invention to any particular frequency. Specifically, the frequency of the transmitted signals can be below the radiofrequency range, within the radiofrequency range or above the radiofrequency range. A representative frequency range suitable for the present

embodiments include, without limitation, from 20 KHz to 800 KHz, *e.g.*, about 75 KHz. Current, generated by the signal generating system of the present embodiments, flows across the organ and causes a voltage drop due to the impedance of the body. The input radiofrequency signals are typically, but not obligatorily, relate to the impedance of an organ of the subject. In various exemplary embodiments of the invention the parameters (*e.g.*, frequency, amplitude, phase) of the output signal(s) is selected such that the input signal is indicative of the impedance of organ **18**. A typical pick to pick amplitude of the signal is, without limitation, below 600 mv.

Without loss of generality, the input signals are referred to below as “impedance”, but it should be understood that a more detailed reference to impedance is not to be interpreted as limiting the scope of the invention in any way, and that the signal be expressed as other measurable electrical quantities, including, without limitation, voltage, current, resistance, reactance, and any combination thereof.

It is recognized that an impedance signal can be expressed as a complex number that satisfies any of the following equations:

$$Z_P = |Z| \exp(j \times \varphi_Z) \quad (\text{EQ. 1})$$

and

$$Z_C = Z_r + jZ_i \quad (\text{EQ. 2})$$

where, Z_P denotes a Polar representation and Z_C denotes a Cartesian representation, and where $|Z|$ is the absolute amplitude of the impedance, φ_Z is the phase of impedance, Z_r is the real component of the impedance, Z_i is the imaginary component of the impedance, and j is a pure imaginary number satisfying $j^2 = -1$.

The relation between the components ($|Z|$, φ_Z) and (Z_r , Z_i) is given by:

$$Z_r = |Z| \cos(\varphi_Z); \quad Z_i = |Z| \sin(\varphi_Z). \quad (\text{EQ. 3})$$

and

$$|Z| = \sqrt{Z_r^2 + Z_i^2}; \quad \varphi_Z = \arctan(Z_i / Z_r) \quad (\text{EQ. 4})$$

The polar components $|Z|$ and φ_Z can be detected using a Amplitude Modulation (AM) envelope detector, and a Phase Modulation (PM) detector, respectively, as disclosed for example, in WO2010032252 *supra*.

It was found by the present inventors that it is advantage to directly extract from the signal the Cartesian components using quadrature demodulation, which preferably performed by demodulation system **20** for any input signal S received thereby. A

preferred operational principle of demodulation system **20** is schematically illustrated in FIG. 4.

In any signal manipulation described herein, the signal and its components are to be understood as varying as function of the time.

5 Received input signal R is multiplied, in parallel, by (i) a signal A which is in-phase with the transmitted output signal, and (ii) a signal B which is phase-shifted, typically using a phase-shifter **404**, relative to the corresponding transmitted output signal T . This procedure provides two multiplication signals, $R \times A$ and $R \times B$, respectively. The multiplication signals can be obtained using signal multipliers M_A and
10 M_B . The multiplication signals $R \times A$ and $R \times B$, are then filtered using low pass filters **402**. In some embodiments of the present invention multiplication signals $R \times A$ and $R \times B$ are also using a high pass filter. This can be achieved, for example, by adding a high pass filter immediately before or immediately after filters **402**, or by making filters **402** band pass filters.

15 A typical cutoff frequency for the low pass filters is, without limitation from about 5 Hz to about 20 Hz or from about 5 Hz to about 15 Hz or from about 8 Hz to about 12 Hz, *e.g.*, a cutoff frequency of about 9 Hz or less. A typical cutoff frequency for the high pass filters LPF is, without limitation from about 0.5 Hz to about 1.5 Hz, or from about 0.6 Hz to about 1.4 Hz or from about 0.7 Hz to about 1.3 Hz, *e.g.*, a cutoff
20 frequency of 0.8 Hz. In various exemplary embodiments of the invention the multiplication signals $R \times A$ and $R \times B$ are filtered by a dynamically adaptive filter, as further detailed hereinbelow. The dynamically adaptive filter can be in addition to one or both of filters **402**. Alternatively, one or both of filters **402**, can be replaced by the dynamically adaptive filter.

25 The filtered signal obtained from $R \times A$ is referred to as the in-phase component I of the input signal R and the filtered signal obtained from $R \times B$ is referred to as the quadrature component Q of the input signal R .

Typically, the phase shifter generates a phase shift of $\pi/2$, so that B is $\pi/2$ shifted relative to T . However, this need not necessarily be the case since in some embodiments
30 of the present invention phase shifter generates a phase shift which is other than $\pi/2$.

Thus, as used herein, “quadrature component” refers to any signal which is a result of the low-pass filtered multiplication between a received input signal R and a signal B which is phase-shifted with respect to the corresponding output signal T, wherein the phase-shift $\Delta\phi$ of B relative to T is other zero.

5 In some embodiments of the present invention $\Delta\phi$ is about $\pi/2$.

The demodulation performed by system **20** can be using any known circuitry capable of performing quadrature demodulation. The circuitry can be digital or analog, as desired. In some embodiments of the present invention the circuitry is analog. Suitable analog circuitry is marked under catalog No. AD8333 of Analog Devices
10 Analog Devices, Inc., Norwood, MA.

In some embodiments of the present invention, demodulation system **20** performs the processing in a digital manner. In these embodiments, demodulation system **20** comprises an analog to digital converter and a digital data processor or/and a digital signal processor or/and a field-programmable gate array. A representative
15 example of a system **20** having an analog to digital converter (ADC) **50** and a digital signal processor (DSP) **52** is illustrated in FIG. 5A. Analog signals are received by ADC **50** are digitized according to a predetermined sampling rate and transmitted as vectors of discrete data to data DSP **52**. A typical sample rate is, without limitation, from about 200 KHz to about 1.5 MHz. DSP **52** receives the input signal R and the
20 transmitted signal T, and calculate the I and Q signals as further detailed hereinabove except that it is performed digitally. Thus, referring again to FIG. 4, when demodulation system **20** performs the processing in a digital manner, phase shifter **404**, signal multipliers M_A and M_B , and filters **402** can each independently be digital elements.

Processing system **28** serves for providing the monitoring information carried by
25 the input signals. System **28** receives the signals from system **20** (FIGs. 1 and 3) or directly from the organ (FIG. 2), processes the signals and generates an output pertaining to the processed signals. Preferably, the output is a graphical output, which is transmitted to a computer readable medium, such as a display card, a network card or memory medium of a computer. From the computer readable medium the output can be
30 read by a local or remote computer and displayed, *e.g.*, on a display device.

Optionally and preferably processing system **28** performs the processing in a digital manner. In these embodiments, processing system **28** can comprise an analog to

digital converter and a digital data processor or a digital signal processor. When demodulation system **20** is digital, it is not required for processing system **28** to include an analog to digital converter since in these embodiments processing system **28** receives digital signals from demodulation system **20**.

5 A representative example of a system **28** having an analog to digital converter (ADC) **54** and a data processor **56** is illustrated in FIG. 5B. This embodiment is useful when the output of demodulation system **20** (e.g., after filters **402**) includes analog signals. The analog signals are received by ADC **54**, digitized according to a predetermined sampling rate and transmitted as vectors of discrete data to data processor
10 **56**. A typical sample rate is, without limitation, from about 200 Hz to about 800 Hz.

 Data processor **56** can be a general purpose computer or dedicated circuitry. Computer programs implementing the processing technique of the present embodiments can commonly be distributed to users on a distribution medium such as, but not limited to, a floppy disk, CD-ROM or flash memory. From the distribution medium, the
15 computer programs can be copied to a hard disk or a similar intermediate storage medium. Alternatively, the computer program can be distributed as a data stream downloadable, e.g., from an http or ftp internet site, in which case the computer program is copied to the computer directly from the internet site. The computer programs can be
20 run by loading the computer instructions either from their distribution medium or their intermediate storage medium into the execution memory of the computer, configuring the computer to act in accordance with the method of this invention. All these operations are well-known to those skilled in the art of computer systems.

 Processing system **28** can provide hemodynamic monitoring in more than one way.

25 In some embodiments, system **28** generates a separate output based on each of the signals as received by system **20**. The output can include a graphical representation (e.g., as a function of the time) of the signals themselves, or their time-derivative (e.g., first time-derivative) or the area under the curves of the signals. Optionally and preferably system **28** performs a normalization procedure before generating the output,
30 for example, to obtain similar scales for different output types.

 In some embodiments, system **28** generates an output based on a combination of signals as received by system **20**. Representative examples of such combinations are

provided hereinbelow. When more than one combination is calculated by system **28** a separate output can optionally provided for each signal combination.

In some embodiments of the present invention system **28** applies a dynamically adaptive filter to the signal before displaying it. The filtration is preferably performed
5 responsively to the physiological condition of the subject. The filtration can be done, for example, by employing the filtering techniques described in International Patent Publication No. 2009/022330 the contents of which are hereby incorporated by reference, separately to the phase and to the absolute components.

Generally, the dynamically variable filter filters the data according to a
10 frequency band which is dynamically adapted in response to a change in the physiological condition of the subject. It was found by the Inventors of the present invention that the dynamical adaptation of the frequency band to the physiological condition of the subject can significantly reduce the influence of unrelated signals on the measured property.

Thus, in the present embodiment, system **28** employs a process in which first the
15 physiological condition of the subject is determined, then a frequency band is selected based on the physiological condition of the subject, and thereafter the received signals are filtered according to frequency band. The frequency band is dynamically adapted in response to a change in the physiological condition.

The physiological condition is preferably, but not obligatorily, the heart rate of
20 the subject. The data pertaining to the physiological condition can be collected via a suitable data collection unit either in analog or digital form, as desired. For example, the physiological condition can be a heart rate which can be determined, *e.g.*, by analysis of ECG signals or the like.

While the embodiments below are described with a particular emphasis to
25 physiological condition which is a heart rate, it is to be understood that more detailed reference to the heart rate is not to be interpreted as limiting the scope of the invention in any way. For example, in exemplary embodiments of the present invention the physiological condition is a ventilation rate of the subject, a repetition rate of a particular
30 muscle unit and/or one or more characteristics of an action potential sensed electromyography.

The adaptation of the frequency band to the physiological condition can be according to any adaptation scheme known in the art. For example, one or more parameters of the frequency band (*e.g.*, lower bound, upper bound, bandwidth, central frequency) can be a linear function of a parameter characterizing the physiological condition. Such parameter can be, for example, the number of heart beats per minute.

FIGs. 6A and 6B show representative examples of a dynamically varying frequency bounds, which can be employed according to some embodiments of the present invention separately to each signal received by system 28 and/or collectively to any combination of signals as further detailed hereinbelow.

Shown in FIGs. 6A and 6B is the functional dependence of the frequency bounds (upper bound in FIG. 6A and lower bound in FIG. 6B) on the heart rate of the subject. As shown in FIG. 6A, the upper bound of the frequency band varies linearly such that at a heart rate of about 60 beats per minute (bpm) the upper bound is about 6 Hz, and at a heart rate of about 180 bpm the upper bound is about 9 Hz. As shown in FIG. 6B, the lower bound of the frequency band varies linearly such that at a heart rate of about 60 bpm the lower bound is about 0.9 Hz bpm and at a heart rate of about 180 bpm the lower bound is about 2.7 Hz.

In some embodiments of the present invention the upper bound approximately equals the function $F_U(\text{HR})$ defined as $F_U(\text{HR}) = 6 + 1.5 \times [(\text{HR}/60) - 1]$ Hz, where HR is the heart rate of the subject in units of bpm. In some embodiments, the upper bound equals $F_U(\text{HR})$ at all times, while in other embodiments, the upper bound is set using an iterative process.

In some embodiments of the present invention the lower bound approximately equals the function $F_L(\text{HR})$ defined as $F_L(\text{HR}) = 0.9 \times (\text{HR}/60)$ Hz. In some embodiments, the lower bound equals $F_L(\text{HR})$ at all times while in other embodiments the lower bound is set by an iterative process.

Representative examples of iterative process suitable for some embodiments of the present invention are provided hereinunder.

A dynamically varying band pass filter (BPF) characterized by a dynamically varying upper frequency bound and a dynamically varying lower frequency bound, according to some embodiments of the present invention is illustrated in FIG. 6C. As shown, each heart rate is associated with a frequency band defined by a lower bound and

an upper bound. For example, for a heart rate of 60 bpm, FIG. 6C depicts a BPF in which the lower bound is about 0.9 Hz and the upper bound is about 6 Hz.

It is to be understood that the values presented above and the functional relations illustrated in FIGs. 6A-C are exemplary embodiments and should not be considered as
5 limiting the scope of the present invention in any way. In other exemplary embodiments, the functional relations between the frequency band and the physiological condition can have different slopes and/or offsets, or they can be non-linear.

Following is a description of an iterative process for determining the frequency band of the band pass filter which filters to the phase component and separately the
10 absolute component according to some embodiments of the present invention. The iterative process can, in some embodiments, be based a comparison between a value of a physiological parameter as extracted or calculated from the respective filtered component and a value of the same physiological parameter as extracted or calculated from a reference signal, for example, an ECG signal.

15 The term "physiological parameter" refers to any variable parameter which is measurable or calculable and is representative of a physiological activity, particularly, but not necessarily, activity of the heart. In various exemplary embodiments of the invention the physiological parameter is other than the heart rate *per se*. The physiological parameter can be a time-related parameter, amplitude-related parameters
20 or combination thereof.

Typically, the filter signal and the reference signal are expressed in terms of amplitude as a function of the time. Thus, time-related parameters are typically calculated using abscissa values of the signals and amplitude-related parameters are is typically calculated using ordinate values of the signals.

25 Representative of time-related physiological parameters suitable for the present embodiments include, without limitation, systolic time, diastolic time, pre-ejection period and ejection time. A representative example of amplitude-related physiological parameter suitable for the present embodiments includes, without limitation, maximal amplitude above zero during a single beat, maximal peak-to-peak amplitude during a
30 single beat, and RMS level during a single beat. Also contemplated are various slopes parameters, such as, but not limited to, the average slope between two points over the signal.

In various exemplary embodiments of the invention the physiological parameter is a ventricular ejection time (VET).

While the embodiments below are described with a particular emphasis to VET as the physiological parameter, it is to be understood that more detailed reference to VET is not to be interpreted as limiting the scope of the invention in any way.

The present inventors discovered that a significant amount of the biological information for a particular subject can be obtained from a frequency range between $F_L(\text{HR})$ and 5.5 Hz, where HR is the heart rate of the subject. It was further discovered by the present inventors that for some medical conditions some of the information can reside between 5.5 Hz and $F_U(\text{HR})$.

The advantage of the comparison between two different techniques for extracting or calculating the same physiological parameter, is that it allows to substantially optimize the upper frequency bound of the band pass filter. In various exemplary embodiments of the invention in each iteration of the iterative process, the comparison is repeated. If the comparison meets a predetermined criterion, the upper frequency bound is updated by calculating an average between a low threshold for the upper bound and a high threshold for the upper bound. The lower frequency bound can be a constant bound, *e.g.*, a constant frequency which is from about 0.9 Hz to about 2.7 Hz), or it can be dynamic, *e.g.*, $F_L(\text{HR})$, HR being the heart rate of the subject before or during the respective iteration.

The low and high thresholds for the upper bound can be set in more than one way. In some embodiments, the low and high thresholds are predetermined (namely they determined *a priori* before the iterative process), in some embodiments, the thresholds are set in a previous iteration of iterative process, in some embodiments one of the thresholds is predetermined and the other threshold is set in a previous iteration of iterative process. In any event, the first iteration is based on two thresholds which are determined *a priori* before the iterative process. It was found by the inventors of the present invention that, at least initially (*i.e.*, at the first iteration), the first threshold can be about $F_U(40)$, which in various exemplary embodiments of the invention is about 5.5 Hz, and the second threshold can be the calculated value of $F_U(\text{HR})$, HR being the heart rate of the subject before or during the respective iteration.

The predetermined criterion used during the iterations can be, for example, that the results of the two calculations are similar (*e.g.*, within about 40 % or 30 % or 25 % of each other). The predetermined criterion can also relate to the direction of difference between the two calculations. Broadly, for time-related parameters, the upper bound is updated if the value of the parameter as calculated based on the reference signal is higher than value of the parameter as calculated based on the filtered signal, and for amplitude-related parameters the upper bound is updated if the value of parameter as calculated based on the reference signal is lower than the value of the parameter as calculated based on the filtered signal. For slope-related parameters, the upper bound is typically updated if the value of the parameter as calculated based on the reference signal is higher than the value of the parameter as calculated based on the filtered signal.

A Boolean combination between the above criteria can also be used as a criterion. For example, an AND Boolean combination can be employed in which case the upper frequency bound can be updated if the results of the two calculations are similar and the calculation according to the filtered signal indicates an abnormal physiological condition while the calculation according to the reference signal indicates a normal physiological condition.

An iterative process for selecting the upper frequency bound, suitable for some exemplary embodiments of the present invention is described in International Patent Publication No. WO2010/032252, the contents of which are hereby incorporated by reference.

Following is a description of suitable signal combination which can be performed by processing system **28** according to some embodiments of the present invention. Each of the following signal combination can be used as a basis for generating an output indicative of the hemodynamics of organ **18**, as further detailed hereinabove.

In some embodiments of the present invention processing system **28** combines input signals as obtained from each part of organ **18** (*e.g.*, **36** and **38**). The combination can be linear or non-linear combination. For example, denoting signal **36** by S_R and signal **38** by S_L , system **28** can calculate a combined signal S_{LR} using the following equation:

$$S_{LR} = w_L \times S_L^{\alpha_L} + w_R \times S_R^{\alpha_R} \quad (\text{EQ. 5})$$

where w_L and w_R are predetermined weight parameters and α_L and α_R are predetermined power parameters. In some embodiment, $\alpha_L = \alpha_R = 1$, so that EQ. 5 expresses linear combination.

In some embodiments of the present invention processing system **28** combines
 5 the in-phase component with the quadrature component (e.g., components **24** and **26**). For example, denoting signal **24** by I and signal **26** by Q, system **28** can calculate a hybrid signal S_{IQ} using the following equation:

$$S_{IQ} = w_I \times S_I^{\alpha_I} + w_Q \times S_Q^{\alpha_Q} \quad (\text{EQ. 6})$$

where w_I and w_Q are predetermined weight parameters and α_I and α_Q are predetermined
 10 power parameters. In some embodiment, $\alpha_I = \alpha_Q = 1$, so that EQ. 6 expresses linear combination.

In some embodiments of the present invention processing system **28** combines, for each input signal, a respective in-phase component with a respective quadrature component. For example, for first input signal **36**, system **28** can combine first in-phase
 15 component **40** with first quadrature component **42**, and for second input signal **38**, system **28** can combine second in-phase component **44** with second quadrature component **46**.

Denoting components **40** and **42** by Z_{iR} and Z_{rR} , respectively, system **28** can calculate a hybrid signal S_{CR} using the following equation:

$$S_{CR} = w_{iR} \times Z_{iR}^{\alpha_R} + w_{rR} \times Z_{rR}^{\beta_R} \quad (\text{EQ. 8})$$

where w_{iR} and w_{rR} are predetermined weight parameters and α_R and β_R are predetermined power parameters. In some embodiment, $\alpha_R = \beta_R = 1$, so that EQ. 7 expresses linear combination.

Denoting components **44** and **46** by Z_{iL} and Z_{rL} , respectively, system **28** can
 25 calculate a hybrid signal S_{CL} using the following equation:

$$S_{CL} = w_{iL} \times Z_{iL}^{\alpha_L} + w_{rL} \times Z_{rL}^{\beta_L} \quad (\text{EQ. 8})$$

where w_{iL} and w_{rL} are predetermined weight parameters and α_L and β_L are predetermined power parameters. In some embodiment, $\alpha_L = \beta_L = 1$, so that EQ. 8 expresses linear combination.

30 In some embodiments of the present invention processing system **28** is configured to combine two or more hybrid signals. For example, system **28** can

combine hybrid signals S_{CR} and S_{CL} to provide a combined hybrid signal S_{CT} , according to the following equation:

$$S_{CT} = w_{CR} \times S_{CR}^{\gamma_R} + w_{CL} \times S_{CL}^{\gamma_L} \quad (\text{EQ. 9})$$

where w_{CR} and w_{CL} are predetermined weight parameters and γ_L and γ_L are
5 predetermined power parameters. In some embodiment, $\gamma_L = \gamma_L = 1$, so that EQ. 9 expresses linear combination.

In some embodiments of the present invention processing system **28** combines the in-phase components of two or more input signals. For example, system **28** can combine the first in-phase component **40** with the second in-phase component **44**. Using
10 the above notations for components **40** and **44**, system **28** can calculate a combined in-phase signal S_{iT} using the following equation:

$$S_{iT} = w_{iR} \times Z_{iR}^{\alpha_R} + w_{iL} \times Z_{iL}^{\alpha_L}. \quad (\text{EQ. 10})$$

As stated α_L and α_R can both be 1 so that EQ. 10 expresses linear combination.

In some embodiments of the present invention processing system **28** combines
15 the quadrature components two or more input signals. For example, system **28** can combine first quadrature component **42** with second quadrature component **46**, to provide a combined quadrature signal S_{rT} using the following equation:

$$S_{rT} = w_{rR} \times Z_{rR}^{\alpha_R} + w_{rL} \times Z_{rL}^{\alpha_L}. \quad (\text{EQ. 11})$$

When the power parameters satisfy $\alpha_L = \alpha_R = 1$ EQ. 11 expresses linear combination.

20 A combination of S_{iT} and S_{rT} is also contemplated. This combination is not explicitly formulated mathematically, but it can be obtained for example as described above with respect to EQ. 9.

In some embodiments of the present invention processing system **28** calculates, for each input signal, a phase component and an amplitude component. This can be
25 done using EQ. 4 above and substituting the in-phase component for Z_r , and quadrature component for Z_i .

For example, the phase component Z_{PMR} corresponding to the first input signal **36**, the amplitude component Z_{AMR} corresponding to the first input signal **36**, the phase component Z_{PML} corresponding to the second input signal **38**, and the amplitude
30 component Z_{AML} corresponding to the second input signal **38** by Z_{AMR} , can be calculated as follows:

$$\begin{aligned}
 Z_{PMR} &= \arctan(Z_{iR} / Z_{rR}) \\
 Z_{AMR} &= \sqrt{Z_{rR}^2 + Z_{iR}^2} \\
 Z_{PML} &= \arctan(Z_{iL} / Z_{rL}) \\
 Z_{AML} &= \sqrt{Z_{rL}^2 + Z_{iL}^2}
 \end{aligned}
 \tag{EQ. 12}$$

5 In some embodiments of the present invention processing system **28** calculates a combination of the phase component with amplitude component for each signal. For example, using EQ. 12, two phase-amplitude hybrid signals can be obtained:

$$S_{PL} = w_{AML} \times Z_{AML}^{\delta_L} + w_{PML} \times Z_{PML}^{\varepsilon_L} \tag{EQ. 13}$$

$$S_{PR} = w_{AMR} \times Z_{AMR}^{\delta_R} + w_{PMR} \times Z_{PMR}^{\varepsilon_R} \tag{EQ. 14}$$

10 where w_{AML} , w_{PML} , w_{AMR} and w_{PMR} are predetermined weight parameters and δ_L , ε_L , δ_R , and ε_R , are predetermined power parameters. When the power parameters satisfy $\delta_L = \varepsilon_L = 1$ EQ. 13 expresses linear combination, and when the power parameters satisfy $\delta_R = \varepsilon_R = 1$ EQ. 14 expresses linear combination.

 In some embodiments of the present invention processing system **28** combines
15 phase-amplitude hybrid signals corresponding to two or more input signals. For example, a combined phase-amplitude hybrid signal S_{PT} can be calculated as follows:

$$S_{PT} = w_{PR} \times S_{PR}^{\kappa_R} + w_{PL} \times S_{PL}^{\kappa_L} \tag{EQ. 15}$$

 where w_{PR} and w_{PL} are predetermined weight parameters and κ_L and κ_R are
20 predetermined power parameters. When the power parameters satisfy $\kappa_L = \kappa_R = 1$ EQ. 15 expresses linear combination.

 Any of the weight parameters w_L , w_R , w_I , w_Q , w_{iR} , w_{rR} , w_{iL} , w_{rL} , w_{CR} , w_{CL} , w_{iR} ,
25 w_{iL} , w_{rR} , w_{rL} , w_{AML} , w_{PML} , w_{AMR} , w_{PMR} , w_{PR} and w_{PL} ; and any of the power parameters α_L ,
 α_R , α_I , α_Q , β_R , β_L , γ_R , γ_L , δ_L , ε_L , δ_R , ε_R , κ_R and κ_L , can be found prior to the
monitoring for example, using a calibration curve. Typical values for the weight
parameters, include, without limitation, any value from 0 to about 10, and typical values
for the power parameters, include, without limitation any value from 0 to about 10.

 In some embodiments, a normalization factor is employed. The normalization
factor can be included in any of the signals of the present embodiments, including the
signals listed in EQs. 5-15 or derivatives thereof or the area under their curves. A
30 representative example of a normalization factor NF suitable for the present
embodiments, includes, without limitation:

$$NF = W_{NF} \times Z_0^a \quad (\text{EQ. 16})$$

where Z_0 is a baseline impedance either for each lead separately or for the entire organ, W_{NF} is a weight parameter and a is a power parameter. The parameters W_{NF} and a can be found, for example, using a calibration curve. Typical values for W_{NF} parameter
 5 include, without limitation, any positive number up to about 5, and typical values for the power parameter a include, without limitation, any number from about -10 to 0.

In other embodiments, the normalization factor is calculated using the following relation:

$$NF = m \times \tan^2(\varphi+c) + n \times \tan(\varphi+d), \quad (\text{EQ. 17})$$

10 where φ is the current phase in radians for each lead separately or for the entire organ, c and d are angle parameters, and m and n are multiplication parameters. The parameters c , d , m and n , can be found, for example, using a calibration curve. Typical values for the parameters c and d include, without limitation, any number from 0 to about 0.6 radians, and typical values for the parameters m and n include, without limitation, any
 15 number from -5 to about 5 radians.

For any of the signals of the present embodiments, including the signals listed in EQs. 5-15, a time-derivative, *e.g.*, a first time derivative can be calculated. The time derivative can be calculated numerically. For example, denoting the time-dependence of an arbitrary signal by $S(t)$, the first time derivative $dS(t)$ can be calculated numerically
 20 as:

$$dS(t) = (S(t) - S(t-\Delta t)) / \Delta t. \quad (\text{EQ. 18})$$

Any of the signals of the present embodiments, for example, the signals listed in EQs. 5-15, including any time-derivative thereof, particularly a first time-derivative, can be used for assessing one or more properties pertaining to the hemodynamics of the
 25 organ. In some embodiments of the present invention the property is calculated based on at least one signal selected from the group consisting of the combined signal S_{LR} (see, *e.g.*, EQ. 5), the combined hybrid signal S_{CT} (see, *e.g.*, EQ. 9), and the combined phase-amplitude hybrid signal S_{PT} (see, *e.g.*, EQ. 15).

Once the properties are calculated, system **28** can generate an output based on
 30 the calculated properties or their time-derivative. The output can include a graphical representation, *e.g.*, the calculated property as a function of the time.

For a given signal of the present embodiments, properties pertaining to the hemodynamics of the organ can be calculated using any technique known in the art, such as, but not limited to, the technique disclosed in International Publication Nos. WO2004/098376, WO2006/087696, WO2008/129535, WO2009/022330 and
5 WO2010/032252 the contents of which are hereby incorporated by reference.

Representative examples of properties that can be calculated according to some embodiments of the present invention include, stroke volume (SV), cardiac output (CO), ventricular ejection time (VET), cardiac index (CI), thoracic fluid content (TFC), total peripheral resistance index (TPRI), blood vessel compliance and any combination
10 thereof.

For example, the VET can be extracted from the morphology of the pulses of the signal being used for the calculation. In some embodiments of the present invention points of transitions are identified on the pulse and the time interval between two such points is defined as the VET. An exemplified procedure is illustrated in FIG. 7, which
15 illustrates a typical morphology of a single beat of a signal S and its first derivative dS/dt , as a function of the time.

Signal S can be any of the signals of the present embodiments, *e.g.*, S_{LR} or S_{CT} or S_{PT} , optionally and preferably following the application of a dynamically varying filter as further detailed hereinabove.

The derivative dS/dt has two zeroes O_1 and O_2 over the beat, with a point of local maximum M_1 between the zeroes and a point of local minimum M_2 after the second zero. In some embodiments of the present invention the VET is defined as the time period (difference between the abscissa values) between the first zero O_1 and the first
20 minimum M_2 after the second zero O_2 .

Other examples include the stroke volume SV and the cardiac output CO. The SV can be calculated based on dS/dt , a characteristic time-interval T and optionally one or more global characteristics of the subject such as, but not limited to, the weight, height, age, BMI and gender of the subject. In some embodiments of the present invention the time-interval is VET. SV can depend on dS/dt and T linearly, for example,
25 $SV = c_{\text{subject}} \times T \times dS/dt$, where c_{subject} is a constant which depends of one or more global characteristics of the subject. However, it is not intended to limit the scope of the present invention only to linear relation for calculating SV. Generally, SV is calculated
30

according to the relation $SV=f(dS/dt, T, c_{\text{subject}})$ where f is a function (not necessarily linear of dS/dt , T and c_{subject} . Alternatively, the function f can be universal to all subjects, in which f does not vary with c_{subject} . In these embodiments, SV can be calculated according to the relation $SV= c_{\text{subject}}f(dS/dt, T)$ or $SV=f(dS/dt, T)$. A representative non-linear expression for the stroke volume SV include, without limitation:

$$SV = [(w_1 \times (\text{Age})^{p_1}) \times (w_2 \times (\text{Weight})^{p_2}) \times (w_3 \times (\text{Height})^{p_3}) \times (w_4 \times (dS/dt)^{p_4}) \times (w_5 \times (\text{VET})^{p_5})] \times w_6 \quad (\text{EQ. 19})$$

where Age is the age of the subject in years, Weight is the weight of the subject in Kg, Height is the height of the subject in cm, VET is the ventricular ejection time in ms, and dS/dt is the digital dimensionless representation of the first time derivative of the respective signal. The parameters w_1, w_2, \dots, w_6 are weight parameters and the parameters p_1, p_2, \dots, p_5 are power parameters.

The weight parameters w_1, w_2, \dots, w_6 and power parameters p_1, p_2, \dots, p_5 , can be found, for example, using a calibration curve. Typical values for the weight parameters w_1, w_2, \dots, w_6 include, without limitation, any number from about 10^{-10} to about 10^2 , and typical values for the power parameters p_1, p_2, \dots, p_5 include, without limitation, any number from -2 to about 2.

The cardiac output CO can be calculated using the relation $CO = SV \times HR$, where HR is the heart rate of the subject (*e.g.*, in units of beats per minutes).

The calculated cardiac output can optionally and preferably be used for estimating the exercise capacity of the subject. Generally, the exercise capacity correlates with the cardiac output. For example, when the cardiac output is below a predetermined threshold, processing system **28** can estimate that the subject's exercise capacity is low, and when the cardiac output is above a predetermined threshold, the method can estimate that the subject's exercise capacity is high. It was demonstrated by the present inventors that during exercise the cardiac output among normal subjects is about 34 % higher than that of Congestive Heart Failure (CHF) patients. The system of the present embodiments can therefore be used to assess or determine worsening of the condition of the subject, particularly subjects with congestive heart failure.

Optionally, a cardiopulmonary exercise testing is performed to provide one or more cardiopulmonary exercise (CPX) measures. The cardiac output can be combined with the CPX measure(s) and the combination can be used to estimate the exercise capacity, and/or to assess the quality of the estimation. For example, the maximal cardiac output is inversely correlated to the VE/VCO_2 slope, where VE is the ventilation efficiency and VCO_2 is the carbon dioxide production rate. The correlation coefficient between the maximal cardiac output during exercise and the VE/VCO_2 slope can be calculated and the quality of the exercise capacity estimation can be assessed based on this correlation coefficient, where negative and large in absolute value correlation coefficient corresponds to high quality of exercise capacity estimation and vice versa.

The maximal cardiac output is directly correlated to the oxygen uptake efficiency slope OUES. The correlation coefficient between the maximal cardiac output during exercise and the OUES can be calculated and the quality of the exercise capacity estimation can be assessed based on this correlation coefficient, where high positive correlation coefficient corresponds to high quality of exercise capacity estimation and vice versa.

The calculated cardiac output can optionally and preferably be used for identifying sleep apnea events. The present inventors conducted experiments in which cardiac output response to positive end expiratory pressure was evaluated. Without being bound to any theory, it is postulated that positive end expiratory pressure can be surrogate for sleep apnea because it creates positive thoracic pressure induced by mechanical ventilation in anesthetized subjects in intensive care units. The pressure dynamics in positive end expiratory pressure are similar to those observed during an apnea episode.

In various exemplary embodiments of the invention an apnea event is identified when the cardiac output is reduced by at least 30 %, more preferably at least 40 %, more preferably at least 50 % over a time period of less than two minutes. In some embodiments, arterial oxygen saturation (SPO_2) is monitored, for example, conventional non-invasive pulse oximeter. In these embodiments a lower threshold of comprises reduction can be employed. For example, an apnea event can be identified when the calculated cardiac output is reduced by at least 25 % and the value of SPO_2 is significantly decreased (say, by more than 40 %).

Optionally, the hemoglobin concentration of the subject is estimated or received as input, and used for estimating blood oxygen content. The blood oxygen content can be supplemented to the calculated cardiac output for the purpose of improving sensitivity and/or specificity. In some embodiments of the present invention the total oxygen delivery is estimated. The total oxygen delivery can be estimated by combining
5 the cardiac output, oxyhemoglobin saturation and hemoglobin concentration. For example, total oxygen delivery rate (typically expressed in units of mL of oxygen per minute) can be estimated by multiplying the cardiac output by the oxygen content.

When the total oxygen delivery falls below a predetermined threshold which can
10 be expressed as percentage of baselines, system **10** can generate a waking alarm sensible by the sleeping subject.

The present embodiments can also be employed for subjects who already been diagnosed with sleep apnea and for whom a CPAP device has been prescribed. Specifically, the present embodiments can be used as a supplement to a conventional
15 treatment (*e.g.*, a CPAP device) so as to assess the efficacy of treatment. For example, the present embodiments can be used for determining whether or not a sufficient amount of oxygen is delivered to vital organs such as the brain, heart and kidneys. It is recognized that even when a CPAP device pushes air to the lungs, oxygen delivery from the cardio-pulmonary system to vital tissues is not guaranteed. For example, a
20 significant drop in cardiac output may result in insufficient oxygen delivery even when the CPAP device increases the oxygen content in the blood. In this case, a system according to some embodiments of the present invention can signal the CPAP device to increase the positive airway pressure and/or generate a waking signal sensible by the sleeping subject. Thus, according to some embodiments of the present invention when
25 the total oxygen delivery falls below the predetermined threshold system **10** can control a CPAP device to increase pressure.

The calculated property can also be used for predicting onset of electromechanical dissociation. It was found by the present inventors that the onset of electromechanical dissociation can be predicted ahead of time, unlike traditional
30 techniques which only provide post occurrence identification of electromechanical dissociation. The present embodiments predict electromechanical dissociation onset by providing a quantitative estimate of the mechanical activity of the heart while

monitoring its electrical activity. Specifically, according to the present embodiments onset of electromechanical dissociation is likely to occur, if the flow rate characterizing the mechanical activity of the heart is lower than one predetermined threshold while the rhythm characterizing the electrical activity of the heart remains above another predetermined threshold.

Thus, in various exemplary embodiments of the invention an electrocardiac signal *e.g.*, electrocardiogram (ECG) signal or a signal which correlates with an ECG signal is obtained. The electrocardiac signal can be obtained from an external source, or be extracted from the signal of the present embodiments. Typically, the electrocardiac signal comprises a DC signal or a signal characterized by very low frequency (less than 150 Hz). ECG signals, for example, are typically characterized by amplitudes of 0.1-5 mV and frequencies of 0.05-130 Hz.

The extraction of DC signal or a very low frequency signal can be done using a suitable electronic circuitry or device which receives the signal of the present embodiments and filter out high frequency (typically radiofrequency) components. Such electronic circuitries are known in the art. For example, a feedback capacitor or an integrator type electronic circuitry can be constituted to extract the electrocardiac signal. Optionally, the electronic circuitry can amplify the electrocardiac signal as known in the art.

The electrical activity of the heart can be assessed based on the electrocardiac signal. Preferably, but not obligatorily one or more repetitive patterns are identified in the electrocardiac signal, and the repetition rate of the identified patterns is measured. For example, when the electrocardiac signal is an ECG signal, the QRS complex can be identified, and the QRS rate can be measured, for example, by measuring the RR interval and defining the rate as the inverse of the RR interval.

The mechanical activity of the heart can be assessed based on the calculated property, preferably, but not necessarily the cardiac output or cardiac index or stroke volume.

Once the electrical and mechanical activities are assessed, processing system **28** predicts the onset of electromechanical dissociation (EMD) or Pulseless Electrical Activity (PEA) according to predetermined criteria. Generally, when the electrical

activity is above a predetermined threshold and the mechanical activity is below a predetermined threshold, processing system 28 predicts onset of EMD or PEA.

For example, when the calculated property is cardiac output the predetermined threshold for the mechanical activity can be about X liters per minute, where X is a number ranging from about 1 to about 1.5. Alternatively, a baseline cardiac output for the subject can be defined and compared to the instantaneous cardiac output. In this embodiment, the predetermined threshold for the mechanical activity can be defined as 70 % or 60 % or 50 % of the baseline.

When the calculated property is cardiac index (cardiac output per unit surface area of the subject's body) the predetermined threshold for the mechanical activity can be about Y liters per minute per square meter, where Y is a number ranging from about 0.75 to about 1. Alternatively, a baseline cardiac index for the subject can be defined and compared to the instantaneous cardiac index, wherein the predetermined threshold for the mechanical activity can be defined as 70 % or 60 % or 50 % of the baseline.

Following are some representative for criteria suitable for predicting EMD. The onset of EMD can be predicted if the cardiac output is reduced by at least 50% and the electrical activity is characterized by pulse rate of at least 60 pulses per minute. The onset of EMD can also be predicted if, over a period of about five minutes, the cardiac output is less than 1 liter per minute and the electrical activity is characterized by a rhythm of at least 40 cycles per minute. The onset of EMD can also be predicted if, over a period of about five minutes, the cardiac index is less than 1 liter per minute per square meter and the electrical activity is characterized by a rhythm of at least 40 cycles per minute. The onset of EMD can be predicted if, over a period of about five minutes, the cardiac index is less than 0.75 liter per minute per square meter and the electrical activity is characterized by a rhythm of at least 40 cycles per minute.

The morphology of the signal of the present embodiments can be used according to some embodiments of the present invention to calculate the likelihood that the subject develops sepsis.

In various exemplary embodiments of the invention a sepsis indicator is extracted from the pulse morphology, and the likelihood is assessed based on the sepsis indicator. The assessment can be done, for example, by thresholding, wherein the sepsis indicator as obtained from the pulse morphology is compared to a predetermined

threshold which can be used as a criterion to assess whether or not the subject is likely to develop sepsis.

In some embodiments of the present invention the sepsis indicator is a ratio between the time-derivative of the obtained signal (*e.g.*, S_{LR} or S_{CT} or S_{PT}) and the
5 ventricular ejection time.

Without wishing to be bound by any particular theory, the present inventors identified that this ratio reflects the relative behavior of contractility per time to eject. Thus, this ratio also reflects the cardiac work against the after load pressures. In cases of hyperdynamic cardiac performance, such as septic shock and liver failure or cirrhosis,
10 the heart contracts in relatively enhanced contractile force against a low after load. This results in a higher value of the ratio. Thus, such a ratio can be used according to some embodiments of the present invention for assessing the likelihood for the subject to develop sepsis. The present inventors conducted experiments and uncovered that this ratio can be used as a discriminator for screening septic and non-septic subjects. It was
15 found that for septic subjects, this ratio is generally high, wherein for non-septic subjects this ratio is generally low.

When the above ratio is used as a sepsis indicator, the ratio is optionally and preferably compared to a predetermined threshold, wherein a ratio above the predetermined threshold indicates that the subject is likely to develop sepsis, and a ratio
20 above the predetermined threshold indicates that the subject is not likely to develop sepsis. Typical values for the predetermined threshold are from about 0.5 to about 0.8, or from about 0.6 to about 0.8, *e.g.*, about 0.7. It was found by the present inventors that using such threshold, the likelihood is characterized by a p-value less than 0.1, *e.g.*, 0.05.

Optionally and preferably a report is issued. The report can include the assessed
25 likelihood and optionally other parameters, particularly statistical parameters (*e.g.*, characteristic p-value and the like).

The signals of the present embodiments can also be used for other applications including, without limitation, predicting body cell mass, fat free mass and/or total body water of a subject, for example, as disclosed in U.S. Patent No. 5,615,689, the contents
30 of which are hereby incorporated by reference; determining hematocrit of blood in a body part of a subject, for example, as disclosed in U.S. Patent No. 5,642,734, the contents of which are hereby incorporated by reference; monitoring hydration status of a

subject, for example, as disclosed in U.S. Published Application No. 20030120170, the contents of which are hereby incorporated by reference; discriminating tissue, for example, as disclosed in U.S. Published Application No. 20060085048, the contents of which are hereby incorporated by reference; and calculating the circumference of a body segment for example, as disclosed in U.S. Published Application No. 20060122540, the contents of which are hereby incorporated by reference.

As used herein the term "about" refers to $\pm 10\%$.

The word "exemplary" is used herein to mean "serving as an example, instance or illustration." Any embodiment described as "exemplary" is not necessarily to be construed as preferred or advantageous over other embodiments and/or to exclude the incorporation of features from other embodiments.

The word "optionally" is used herein to mean "is provided in some embodiments and not provided in other embodiments." Any particular embodiment of the invention may include a plurality of "optional" features unless such features conflict.

The terms "comprises", "comprising", "includes", "including", "having" and their conjugates mean "including but not limited to".

The term "consisting of" means "including and limited to".

The term "consisting essentially of" means that the composition, method or structure may include additional ingredients, steps and/or parts, but only if the additional ingredients, steps and/or parts do not materially alter the basic and novel characteristics of the claimed composition, method or structure.

As used herein, the singular form "a", "an" and "the" include plural references unless the context clearly dictates otherwise. For example, the term "a compound" or "at least one compound" may include a plurality of compounds, including mixtures thereof.

Throughout this application, various embodiments of this invention may be presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the invention. Accordingly, the description of a range should be considered to have specifically disclosed all the possible subranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed subranges such as

from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 3, 4, 5, and 6. This applies regardless of the breadth of the range.

Whenever a numerical range is indicated herein, it is meant to include any cited numeral (fractional or integral) within the indicated range. The phrases “ranging/ranges between” a first indicate number and a second indicate number and “ranging/ranges from” a first indicate number “to” a second indicate number are used herein interchangeably and are meant to include the first and second indicated numbers and all the fractional and integral numerals therebetween.

10

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination or as suitable in any other described embodiment of the invention. Certain features described in the context of various embodiments are not to be considered essential features of those embodiments, unless the embodiment is inoperative without those elements.

15

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Various embodiments and aspects of the present invention as delineated hereinabove and as claimed in the claims section below find experimental support in the following examples.

EXAMPLES

25

Reference is now made to the following examples, which together with the above descriptions illustrate some embodiments of the invention in a non limiting fashion.

Prototype System

30

A prototype system was built according to some embodiments of the present invention. The system included circuitry for generating and transmitting the output signals and receiving and demodulating the input signals. The circuitry is illustrated in FIG. 8.

The prototype system included left and right lead transmitters and two I/Q detectors for the detection of the thoracic impedance. Transmitted low current sinusoidal signals from a current source were transmitted, via balun circuits, separately to a left lead and a right lead (T_{xL} and T_{xR}). The signals were transmitted to the thorax via dedicated transmitting electrodes that were attached to the skin.

The received modulated signals from each lead (R_{xL} and R_{xR}) were filtered using a high pass filter having a cutoff frequency of about 50 Hz, and thereafter multiplied, in parallel, by (i) T_{xL} and T_{xR} , respectively, and (ii) T_{xL} and T_{xR} after they were shifted by $\pi/2$. The two resulting multiplication signals from each lead underwent a band pass filter with upper cutoff selected to obtain the in-phase and quadrature signals and low cutoff for eliminating respiratory, resulting in a left and right in-phase components (I_L , I_R , respectively) and a left and right quadrature components (Q_L , Q_R , respectively). The lower and upper cutoff frequencies of the band pass filter were 0.8 Hz and 9 Hz, respectively. These four signals were then sampled at a sampling rate of 500Hz by Analog to Digital Convertors for further processing in the digital processor (not shown).

Animal Study

Two pigs weighing 55Kg and two Beagle dogs weighing 9Kg were used for the experiment.

For the pigs, an ultrasonic flow probe was adjusted to the ascending Aorta and for the dogs a Electromagnetic flow probe was adjusted to the ascending Aorta both devices are considered Gold Standard in measuring the flow from the Left Ventricle to the aorta.

In addition, A Fr. micromanometer was inserted into the left ventricle via a stab in the apex and secured with a purse string suture for the measurement of pressure and volume within the left ventricle.

Four sensors were placed around the thorax for the detection of the different thoracic impedance based signal of the present embodiments. After the experimental setup, various pharmaceutical and surgical interventions were employed with the goal of creating acute, large hemodynamic variations which would be used to test the behavior of the system as compared with the invasive gold-standard.

The following Interventions were performed:

- (i) Baseline steady-state hemodynamic data was recorded for 10 minutes.

- (ii) Infusion of intravenous fluid - 500cc/200cc of normal saline (pigs/dogs respectively) was infused over 10 minutes to increase blood volume and CO.
- (iii) PEEP Test: The positive end expiratory pressure (PEEP) was increased to between 10 to 15 cmH₂O in order to reduce CO. PEEP testing is a recognized method to create acute reductions in CO, where the physiological mechanism works by reducing venous blood flow returning to the heart by creating a more positive pressure environment in the thorax.
- (iv) Dobutamine infusion for pigs and Phenilephrine infusion for dogs - a rapid onset, short-acting cardiac stimulant, Dobutamine/Phenilephrine progressively increases CO, generally to a level twice that present prior to drug administration; infusion was stopped after 5-10 minutes.
- (v) Esmolol injection - a fast onset, short duration beta-blocker, esmolol reverses the effects of Dobutamine/ Phenilephrine, rapidly decreasing CO.
- (vi) Oleic Acid Infusion – Oleic Acid was infused during 60 minutes to produce Pulmonary Edema resulting in declining blood flow and right Heart Insufficiency.
- (vii) Sacrifice and tissue harvest - saturated potassium chloride was injected into the heart to cause instant cardiac arrest; any offset in the aortic flow values were recorded.

Results

FIG. 9A shows the left ventricle volume signal in ml as derived by the Micromanometer (blue) synchronized with the ECG signal (black), as a function of time in seconds. The ECG is scaled for display purposes.

FIG. 9B shows the signal $S_{CT}(t)$ in ml (red) synchronized with the ECG signal in black. Both the S_{CT} signal and the ECG signal are scaled for display purposes.

FIGs. 9A-B demonstrate that the signal $S_{CT}(t)$ of the present embodiments correlates well with the volume of blood in the ventricles of the heart.

FIG. 10 shows the left ventricle flow signal as derived by the ultrasonic flow probe (blue), synchronized with the ECG signal (red), as a function of time in seconds.

FIG. 10 also shows the $dS_{CT}(t)$ signal of the present embodiments (black). Both the dS_{CT} signal and the ECG signal are scaled for display purposes.

FIG. 10 demonstrates that the area under the positive curve of the signal $dS_{CT}(t)$ correlates well with the flow of blood from the left ventricle to the aorta.

5 FIG. 11 shows the mean cardiac output in liters/minute as derived by the aortic ultrasonic flow probe (blue), and the mean cardiac output derived by the $dS_{CT}(t)$ signal of the present embodiments (red), during infusion of Dobutamine, as a function of the time in seconds.

10 FIG. 11 demonstrates that the signal $dS_{CT}(t)$ of the present embodiments correlates with high precision the hemodynamic behavior.

FIG. 12A shows, as a function of the number of heart beat, the mean cardiac output in liters/minute as derived by the aortic ultrasonic flow probe (blue), and the mean cardiac output in liters/minute derived by the signal $dS_{CL}(t)$ of the present embodiments (black), after the infusion of Dobutamine was ended. The signal $dS_{CL}(t)$ is scaled.

15 FIG. 12B shows, as a function of the number of heart beat, the mean cardiac output in liters/minute (blue) as derived by the aortic ultrasonic flow probe, and the mean cardiac output in liters/minute as derived by the signal $dS_{CR}(t)$ of the present embodiments (black). The signal $dS_{CR}(t)$ is scaled and is presented at the same time frame as in FIG. 12A. The left lead showed more correlation with the reference compared to the right lead.

20 FIG. 13A shows, as a function of the number of heart beat, the mean cardiac output in liters/minute derived by an aortic ultrasonic flow probe (blue), and the mean cardiac output in liters/minute as derived by the signal $dS_{CR}(t)$ of the present embodiments (black), during progression of Severe Edema. The signal $dS_{CR}(t)$ is scaled.

25 FIG. 13B shows, as a function of the number of heart beat, the mean cardiac output in liters/minute as derived by an aortic ultrasonic flow probe (blue), and the mean cardiac output in liters/minute as derived by the signal $dS_{CL}(t)$ of the present embodiments (black). The signal $dS_{CL}(t)$ is scaled and is presented at the same time frame as in FIG. 13A. The right lead showed more correlation with the reference compared to the left lead.

30

The present example demonstrates that the hemodynamic trends invoked by drug titration and captured with the experimental system of the present embodiments correlated well with the Gold Standard in $S_{CL}(t)$ (see FIGs. 12A-B) and hemodynamic trends invoked by fluid challenge or respiratory challenged were described in high correlation in $S_{CR}(t)$ (see FIGs. 13A-B).

These finding can be explained by the physiologic response wherein the volume and respiration challenges impact firstly the right heart, before blood flow continues to the left circulation after passing the pulmonary circulation. On the other hand, vasoactive drugs impact the peripheral arterial circulation or the heart itself, are first manifested in left heart output.

FIG. 14 shows, as a function of the number of heart beat, the mean cardiac output in liters/minute as derived by an aortic ultrasonic flow probe (blue), and mean cardiac output in liters/minute derived by the signal $dS_{PT}(t)$ of the present embodiments (black), during infusion of 500cc fluid bolus. The signal $dS_{PT}(t)$ is scaled. FIG. 14 demonstrates that the signal $S_{PT}(t)$ correlates with the cardiac output of the reference.

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5 Although the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all such alternatives, modifications and variations that fall within the spirit and broad scope of the appended claims.

10 All publications, patents and patent applications mentioned in this specification are herein incorporated in their entirety by reference into the specification, to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein by reference. In addition, citation or identification of any reference in this application shall not be construed as an admission that such reference is available as prior art to the present invention. To the extent that
15 section headings are used, they should not be construed as necessarily limiting.

WHAT IS CLAIMED IS:

1. A system for monitoring hemodynamics of a subject, comprising:
 - a signal generating system configured for providing at least an output electric signal and transmitting output signal to an organ of the subject;
 - a demodulation system configured for receiving an input electrical signal sensed from the organ responsively to said output electric signal, and for modulating said input signal using said output signal to provide an in-phase component and a quadrature component of said input signal;
 - a processing system configured for monitoring the hemodynamics based on said in-phase and said quadrature components.
2. The system according to claim 1, wherein said processing system is configured to combine said in-phase component with said quadrature component thereby to generate a hybrid signal, and wherein said monitoring is based at least in part on said hybrid signal.
3. The system according to claim 2, wherein said hybrid signal is a linear combination of said components.
4. The system according to claim 2, wherein said hybrid signal is a non-linear combination of said components.
5. The system according to claim 1, wherein said signal generating system is configured for providing a first output electric signal and a second output electric signal, and transmitting each of said output signals to a separate part of the organ; and
 - wherein said demodulation system is configured for receiving an input electrical signal sensed from each part of the organ responsively to a respective output electric signal, and for modulating said signals to provide an in-phase component and a quadrature component of each of input signals.

6. The system according to claim 5, wherein said first and second output electric signals are dependent electrical signals.

7. The system according to claim 5, wherein said first and second output electric signals are independent electrical signals.

8. The system according to any of claims 5-7, wherein said processing system is configured to combine, for each input signal, a respective in-phase component with a respective quadrature component thereby to generate a hybrid signal corresponding to input signal, and wherein said monitoring is based at least in part on said hybrid signals.

9. The system according to claim 8, wherein said processing system is configured to combine said hybrid signals, thereby to provide a combined hybrid signal, and wherein said monitoring is based at least in part on said combined hybrid signal.

10. The system according to claim 9, wherein said processing system is configured to assess, based on said combined hybrid signal, at least one property selected from the group consisting of stroke volume (SV), cardiac output (CO), ventricular ejection time (VET), cardiac index (CI), thoracic fluid content (TFC), total peripheral resistance index (TPRI), blood vessel compliance.

11. The system according to claim 9, wherein said processing system is configured to estimate exercise capacity of the subject based on said combined hybrid signal.

12. The system according to claim 9, wherein said processing system is configured to identify sleep apnea events based on said combined hybrid signal.

13. The system according to claim 9, wherein said processing system is configured to assess the likelihood that the subject develops sepsis based on said combined hybrid signal.

14. The system according to claim 9, wherein said processing system is configured to predict onset of electromechanical dissociation based on said combined hybrid signal.

15. The system according to claim 9, wherein said processing system is configured to assess blood hematocrit based on said combined hybrid signal.

16. The system according to any of claims 5-9, wherein said processing system is configured to combine an in-phase component of a first input signal with an in-phase component of a second input signal to provide a combined in-phase signal, and wherein said monitoring is based at least in part on said combined in-phase signal.

17. The system according to any of claims 5-16, wherein said processing system is configured to combine a quadrature component of a first input signal with a quadrature component of a second input signal to provide a combined quadrature signal, and wherein said monitoring is based at least in part on said combined quadrature signal.

18. The system according to any of claims 5-17, wherein said processing system is configured to calculate, for each input signal, a phase component, an amplitude component, and a phase-amplitude hybrid signal defined as a combination of said phase component with said amplitude component, and wherein said monitoring is based at least in part on said combination.

19. The system according to claim 18, wherein said processing system is configured to combine a phase-amplitude hybrid signal corresponding to first input signal with a phase-amplitude hybrid signal corresponding to second input signal, thereby to provide a combined phase-amplitude hybrid signal and wherein said monitoring is based at least in part on said combined phase-amplitude hybrid signal.

20. The system according to claim 19, wherein said processing system is configured to assess, based on said combined phase-amplitude hybrid signal, at least one property selected from the group consisting of stroke volume (SV), cardiac output (CO), ventricular ejection time (VET), cardiac index (CI), thoracic fluid content (TFC), total peripheral resistance index (TPRI), blood vessel compliance.

21. The system according to claim 19, wherein said processing system is configured to estimate exercise capacity of the subject based on said combined phase-amplitude hybrid signal.

22. The system according to claim 19, wherein said processing system is configured to identify sleep apnea events based on said combined phase-amplitude hybrid signal.

23. The system according to claim 19, wherein said processing system is configured to assess the likelihood that the subject develops sepsis based on said combined phase-amplitude hybrid signal.

24. The system according to claim 19, wherein said processing system is configured to predict onset of electromechanical dissociation, based on said combined phase-amplitude hybrid signal based on said combined phase-amplitude hybrid signal.

25. The system according to claim 19, wherein said processing system is configured to assess blood hematocrit based on said combined phase-amplitude hybrid signal.

26. A method of monitoring hemodynamics of a subject, comprising:
generating at least an output electric signal and transmitting output signal to an organ of the subject;
sensing an input electrical signal from the organ responsively to said output electric signal;
modulating said input signal using said output signal to provide an in-phase component and a quadrature component of said input signal; and
monitoring the hemodynamics based on said in-phase and said quadrature components.

27. The method according to claim 26, further comprising combining said in-phase component with said quadrature component to generate a hybrid signal, wherein said monitoring is based at least in part on said hybrid signal.

28. The method according to claim 27, wherein said hybrid signal is a linear combination of said components.

29. The method according to claim 27, wherein said hybrid signal is a non-linear combination of said components.

30. The method according to claim 26, wherein said generating and said transmitting comprises providing a first output electric signal and a second output electric signal, and transmitting each of said output signals to a separate part of the organ;
wherein said sensing comprises sensing an input electrical signal from each part of the organ responsively to a respective output electric signal; and
wherein said modulating comprise modulating each input signal to provide an in-phase component and a quadrature component of input signal.

31. The method according to claim 30, further comprising combining, for each input signal, a respective in-phase component with a respective quadrature component to generate a hybrid signal corresponding to input signal, wherein said monitoring is based at least in part on said hybrid signals.

32. The method according to claim 31, further comprising combining said hybrid signals to provide a combined hybrid signal, wherein said monitoring is based at least in part on said combined hybrid signals.

33. The method according to claim 32, further comprising assessing, based on said combined hybrid signal, at least one property selected from the group consisting of stroke volume (SV), cardiac output (CO), ventricular ejection time (VET), cardiac index (CI), thoracic fluid content (TFC), total peripheral resistance index (TPRI), blood vessel compliance.

34. The method according to claim 32, further comprising estimating exercise capacity of the subject based on said combined hybrid signal.

35. The method according to claim 32, further comprising identifying sleep apnea events based on said combined hybrid signal.

36. The method according to claim 32, further comprising assessing the likelihood that the subject develops sepsis based on said combined hybrid signal.

37. The method according to claim 32, further comprising predicting onset of electromechanical dissociation, based on said combined hybrid signal.

38. The method according to claim 32, further comprising assessing blood hematocrit based on said combined hybrid signal.

39. The method according to any of claims 30-32, further comprising combining an in-phase component of a first input signal with an in-phase component of a second input signal to provide a combined in-phase signal, wherein said monitoring is based at least in part on said combined in-phase signal.

40. The method according to any of claims 30-39, further comprising combining a quadrature component of a first input signal with a quadrature component of a second input signal to provide a combined quadrature signal, wherein said monitoring is based at least in part on said combined quadrature signal.

41. The method according to any of claims 30-40, further comprising calculating, for each input signal, a phase component, an amplitude component, and a phase-amplitude hybrid signal defined as a combination of said phase component with said amplitude component, wherein said monitoring is based at least in part on said combination.

42. The method according to claim 41, further comprising combining a phase-amplitude hybrid signal corresponding to first input signal with a phase-amplitude hybrid signal corresponding to second input signal to provide a combined phase-amplitude hybrid signal, wherein said monitoring is based at least in part on said combined phase-amplitude hybrid signal.

43. The method according to claim 42, further comprising assessing, based on said combined phase-amplitude hybrid signal, at least one electrical property selected from the group consisting of stroke volume (SV), cardiac output (CO), ventricular ejection time (VET), cardiac index (CI), thoracic fluid content (TFC), total peripheral resistance index (TPRI), blood vessel compliance.

44. The method according to claim 42, further comprising estimating exercise capacity of the subject based on said combined phase-amplitude hybrid signal.

45. The method according to claim 42, further comprising identifying sleep apnea events based on said combined phase-amplitude hybrid signal.

46. The method according to claim 42, further comprising assessing the likelihood that the subject develops sepsis based on said combined phase-amplitude hybrid signal.

47. The method according to claim 42, further comprising predicting onset of electromechanical dissociation based on said combined phase-amplitude hybrid signal.

48. The method according to claim 42, further comprising assessing blood hematocrit based on said combined phase-amplitude hybrid signal.

49. A system for monitoring hemodynamics of a subject, comprising:
a signal generating system configured for providing a first output electric signal and a second output electric signal, and transmitting each of said output signals to a separate part of an organ of the subject; and
a processing system configured for receiving an input electrical signal sensed from each part of the organ responsively to a respective output electric signal, and for monitoring the hemodynamics based on said input electrical signals.

50. The system according to claim 49, wherein said processing system is configured to combine said input signals, thereby to provide a combined signal, and wherein said monitoring is based at least in part on said combined signal.

51. The system according to claim 50, wherein said processing system is configured to assess, based on said combined signal, at least one electrical property selected from the group consisting of stroke volume (SV), cardiac output (CO), ventricular ejection time (VET), cardiac index (CI), thoracic fluid content (TFC), total peripheral resistance index (TPRI), blood vessel compliance.

52. A method for monitoring hemodynamics of a subject, comprising:
generating a first output electric signal and a second output electric, and transmitting each of said output signals to a separate part of an organ of the subject;
sensing an input electrical signal from each part of the organ responsively to a respective output electric signal; and
monitoring the hemodynamics based on said input electrical signals.

53. The method according to claim 52, further comprising combining said input signals to provide a combined signal, wherein said monitoring is based at least in part on said combined signal.

54. The method according to any of claims 52 and 53, further comprising assessing, based on said combined signal, at least one electrical property selected from the group consisting of stroke volume (SV), cardiac output (CO), ventricular ejection time (VET), cardiac index (CI), thoracic fluid content (TFC), total peripheral resistance index (TPRI), blood vessel compliance.

55. The system or method according to any of claims 50, 51, 53 and 54, wherein said combination is a linear combination.

56. The system or method according to any of claims 50, 51, 53 and 54, wherein said combination is a non-linear combination.

57. The system or method according to any of claims 50, 51, 53 and 54, wherein said combined signal is used for at least one of estimating exercise capacity of the subject, identifying sleep apnea events, assessing the likelihood that the subject develops sepsis, assessing blood hematocrit, and predicting onset of electromechanical dissociation.

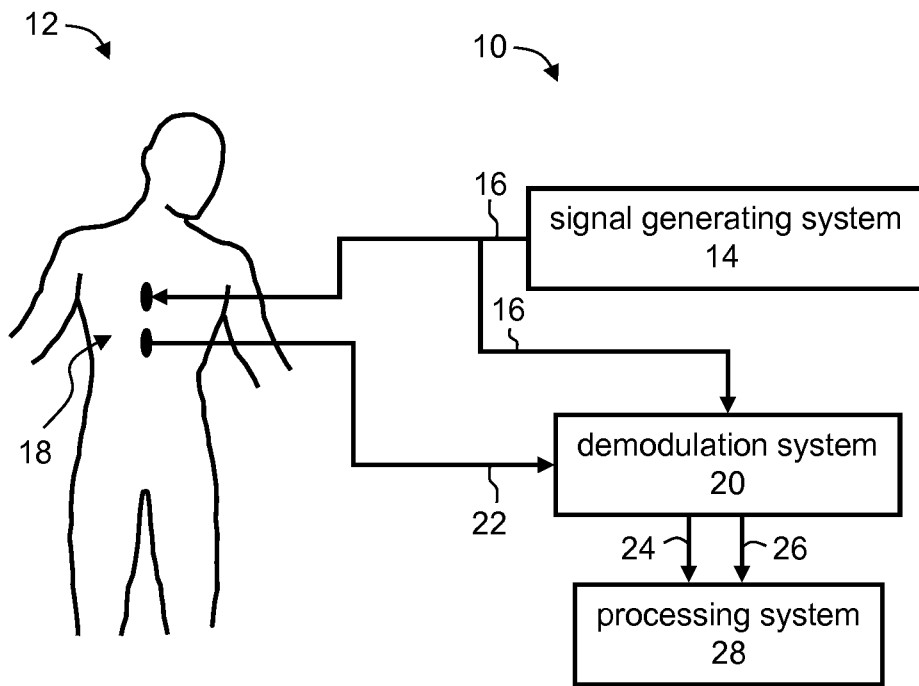


FIG. 1

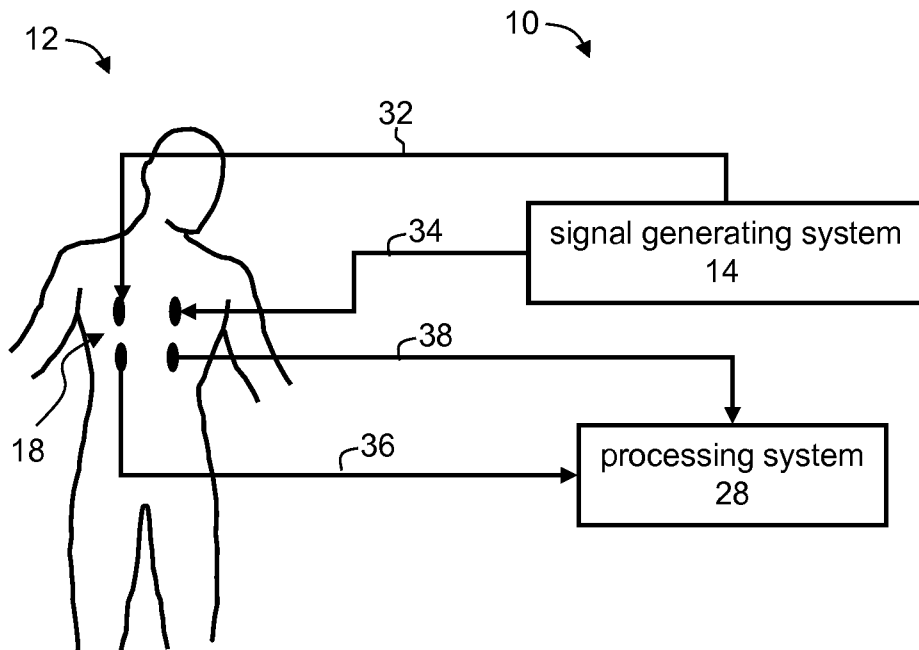


FIG. 2

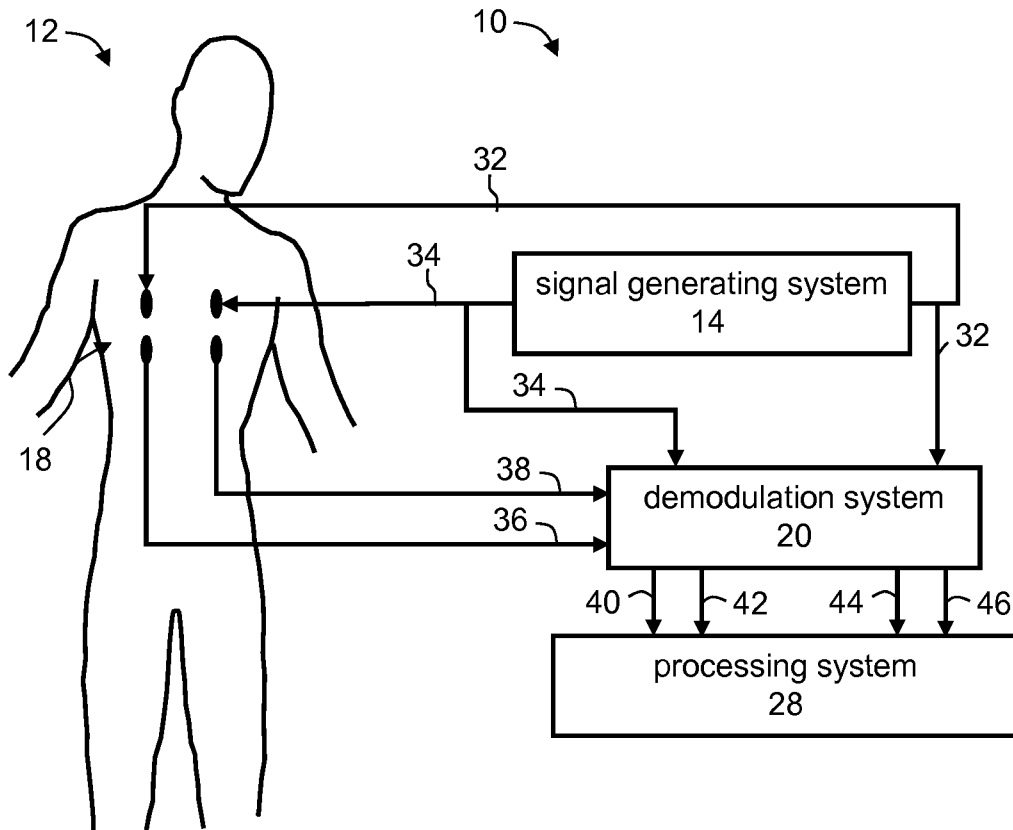


FIG. 3

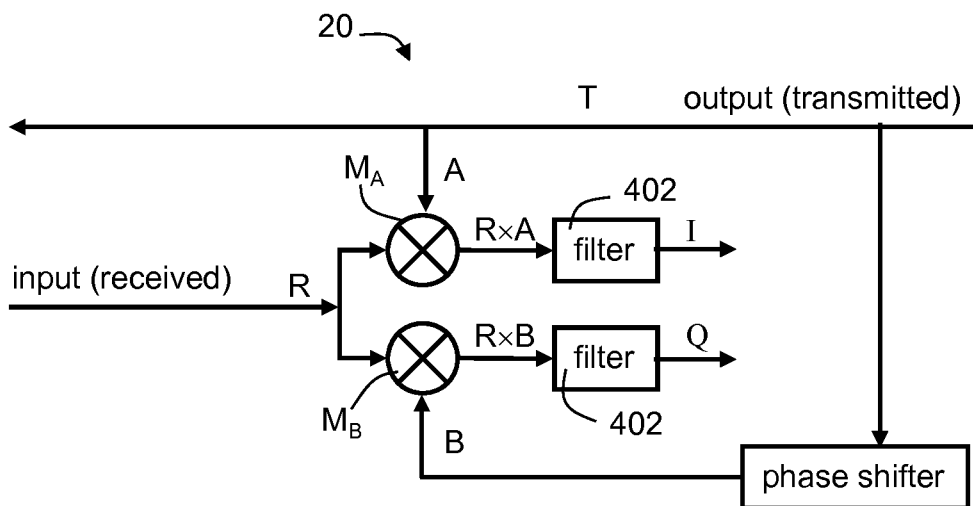


FIG. 4

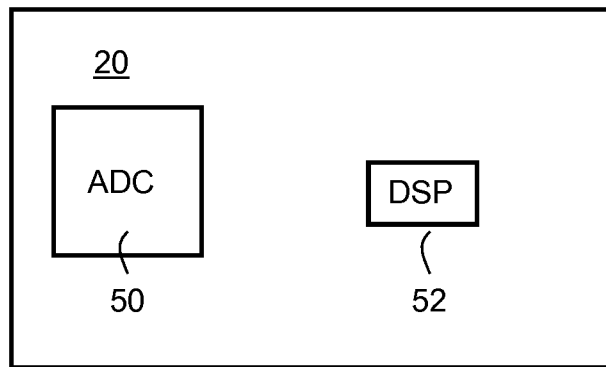


FIG. 5A

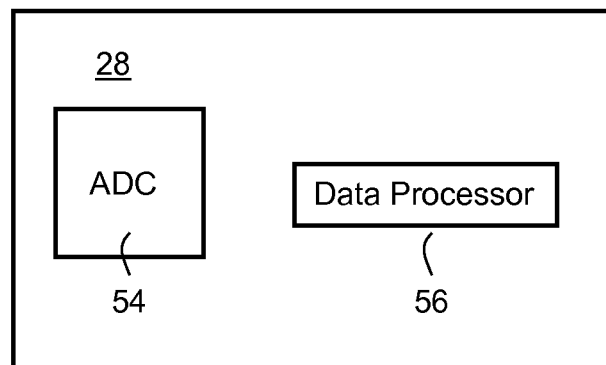


FIG. 5B

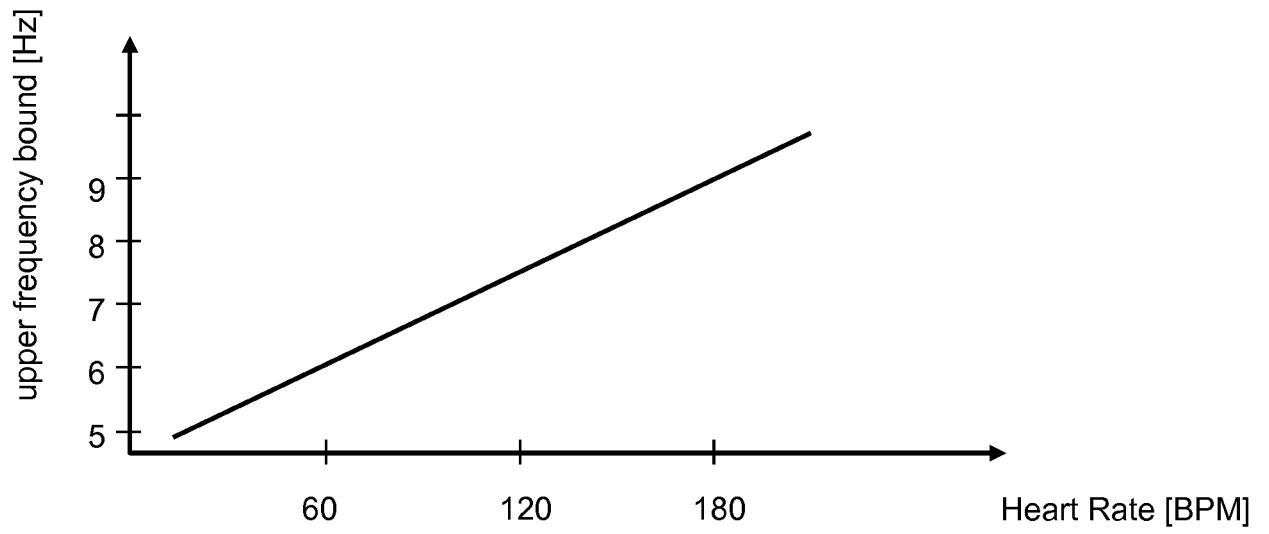


FIG. 6A

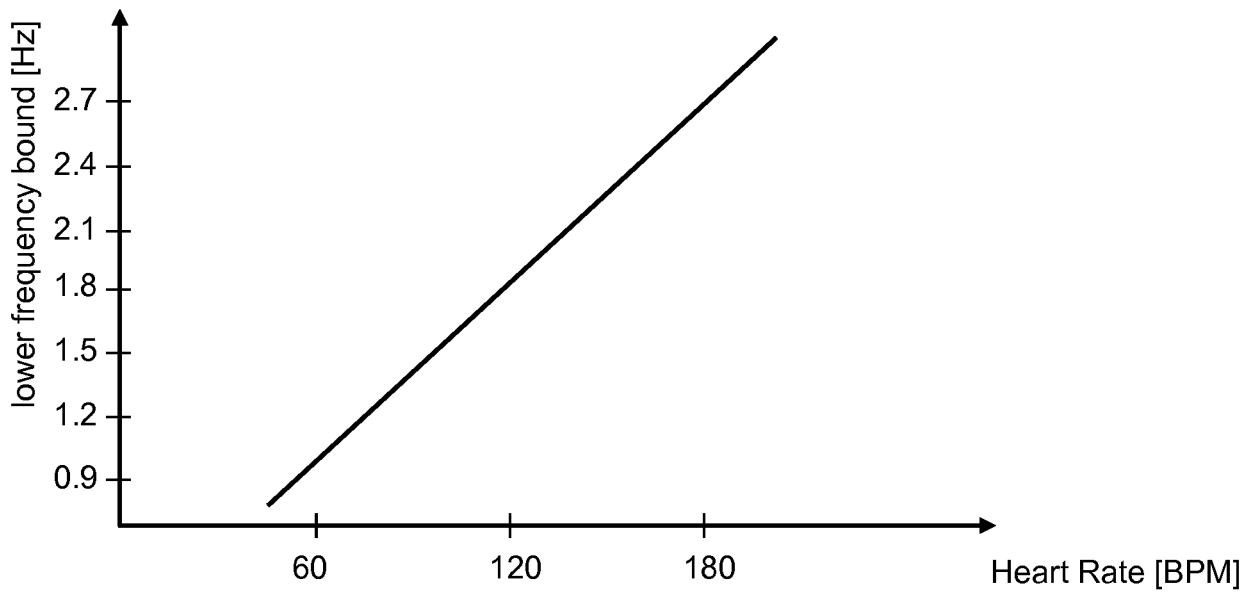


FIG. 6B

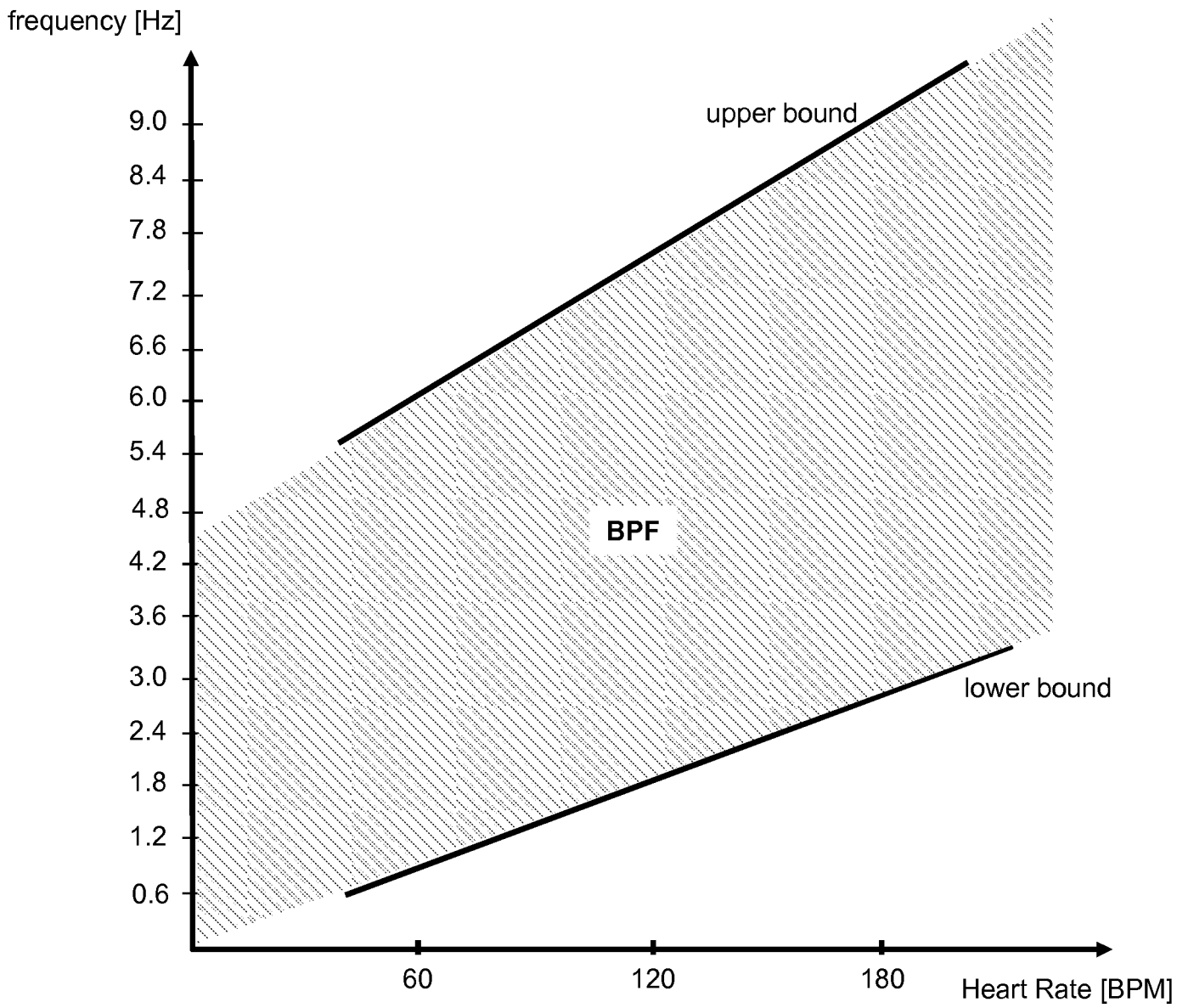


FIG. 6C

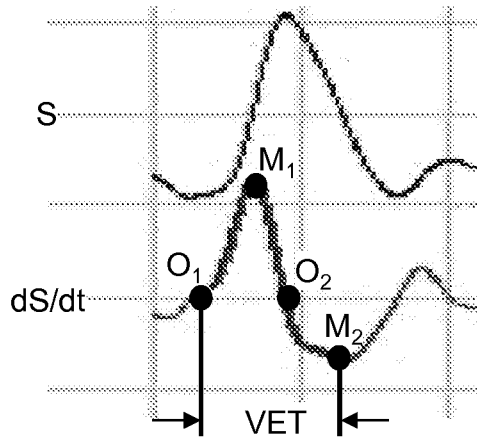


FIG. 7

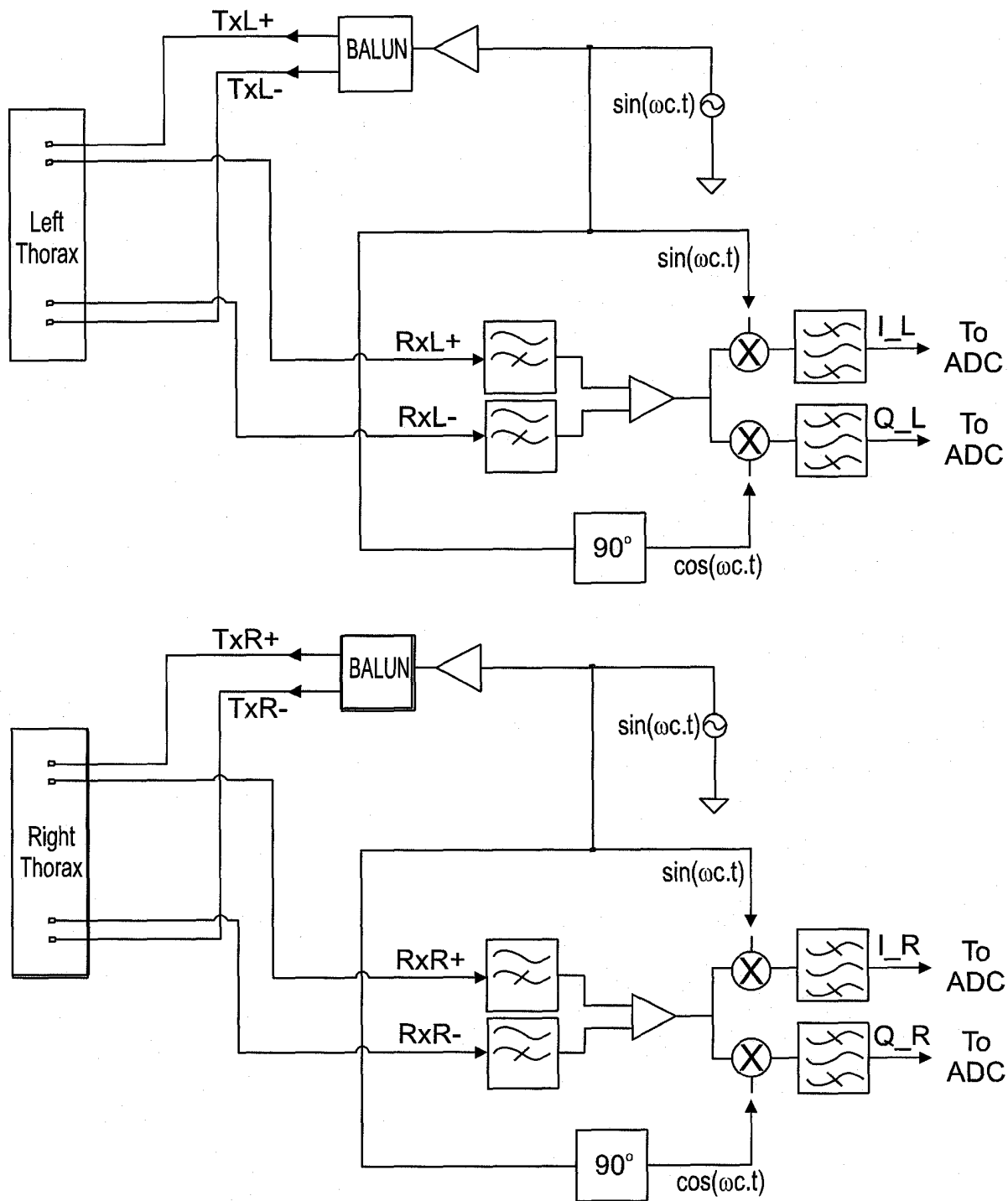


FIG. 8

8/12

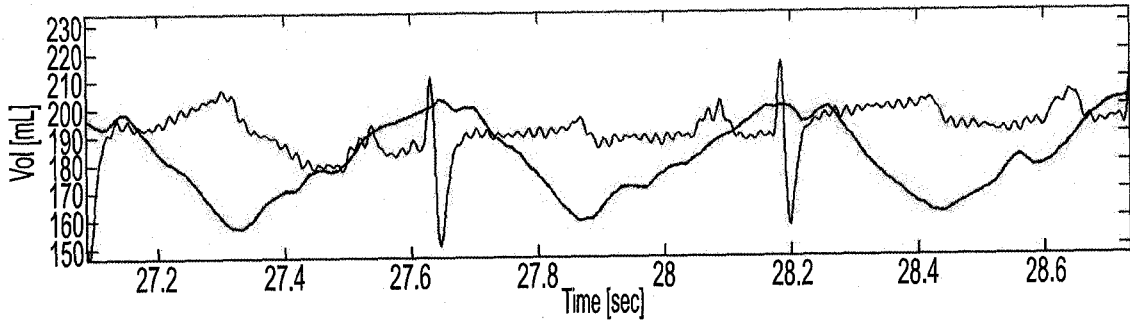


FIG. 9A

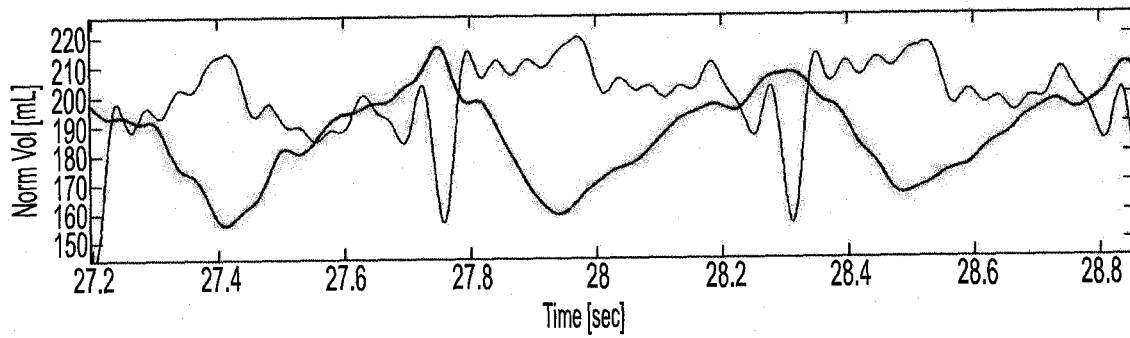


FIG. 9B

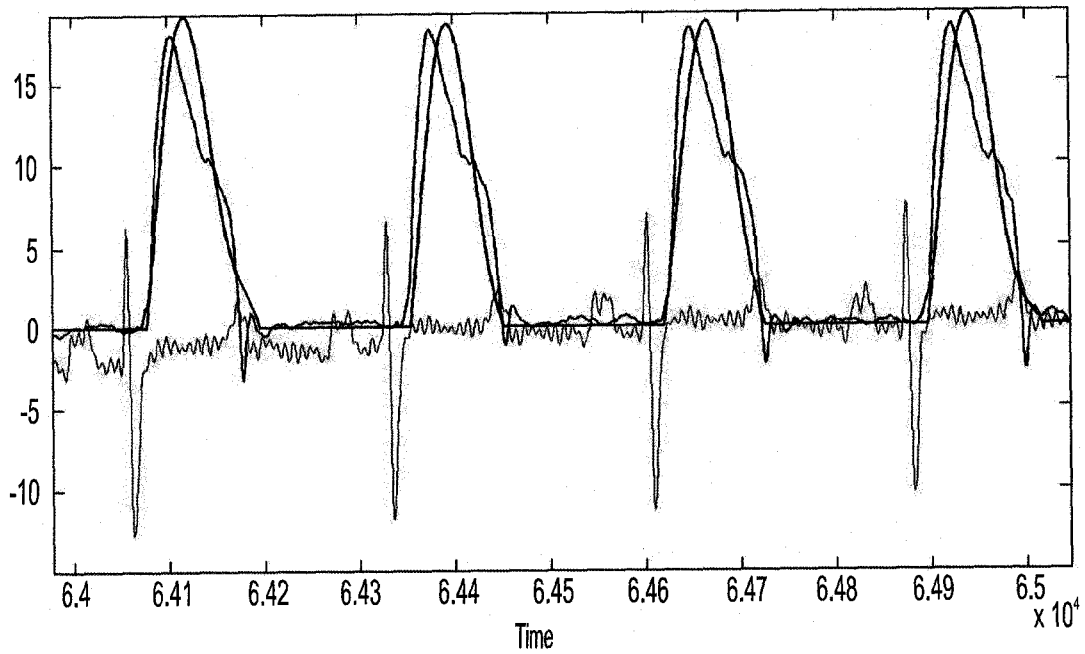


FIG. 10

9/12

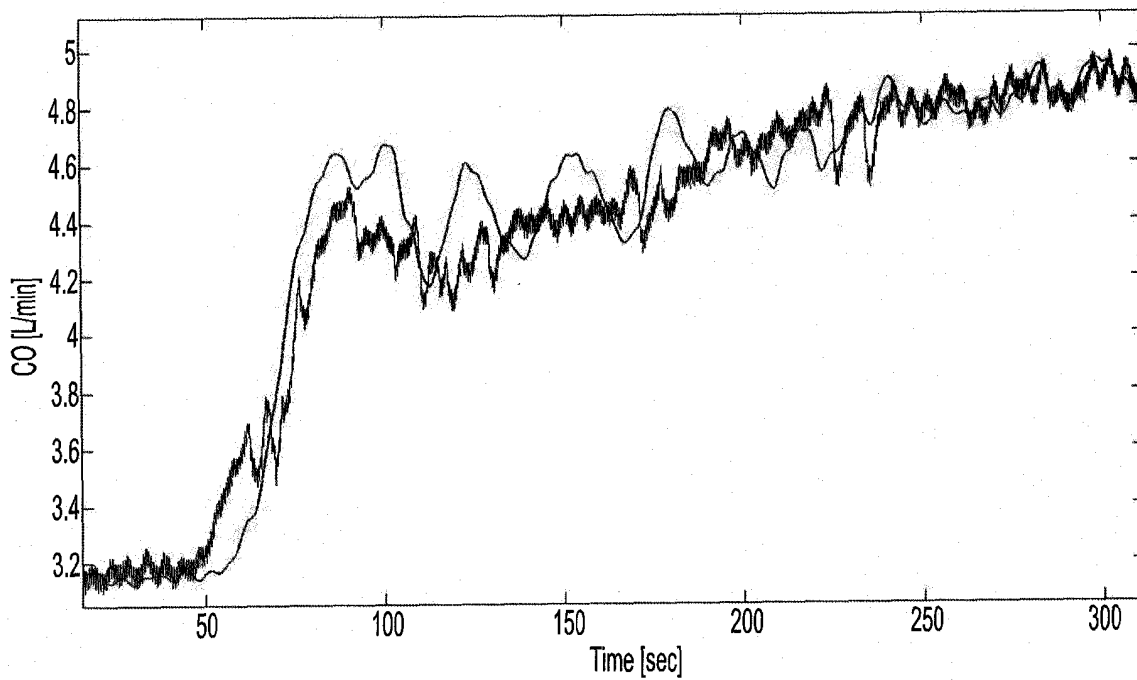


FIG. 11

10/12

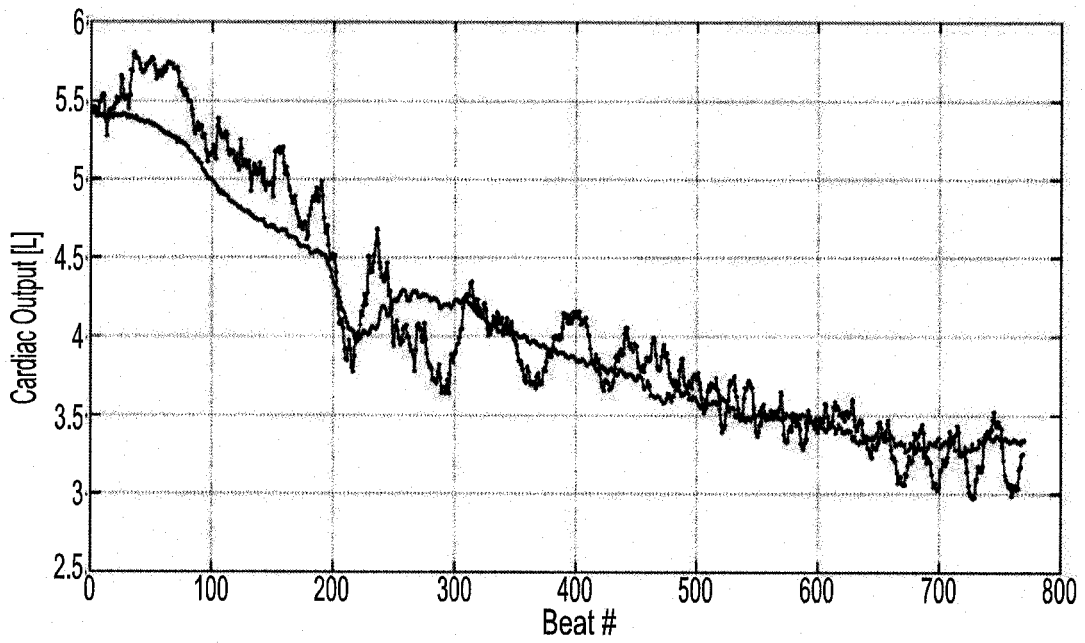


FIG. 12A

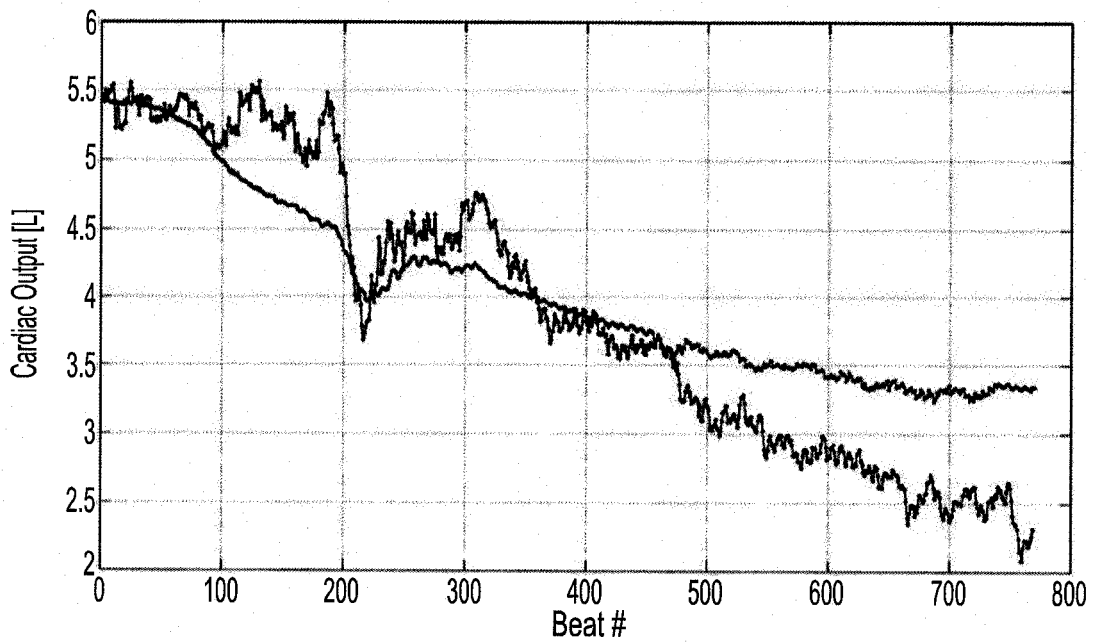


FIG. 12B

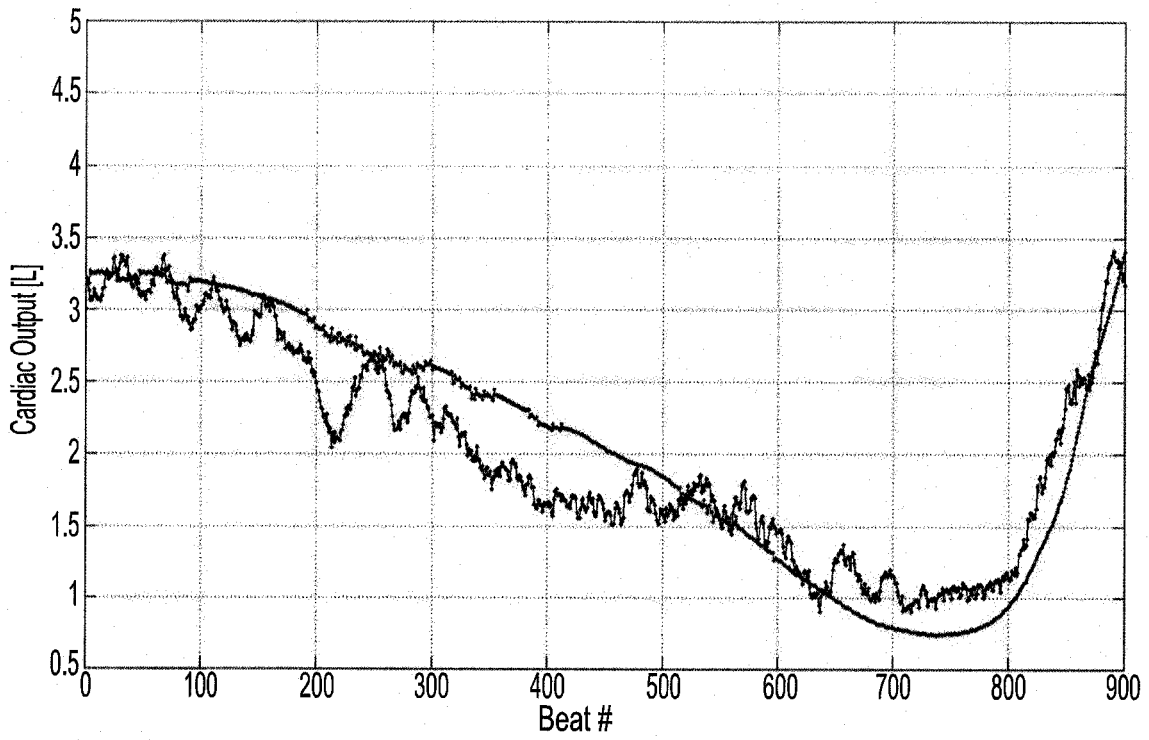


FIG. 13A

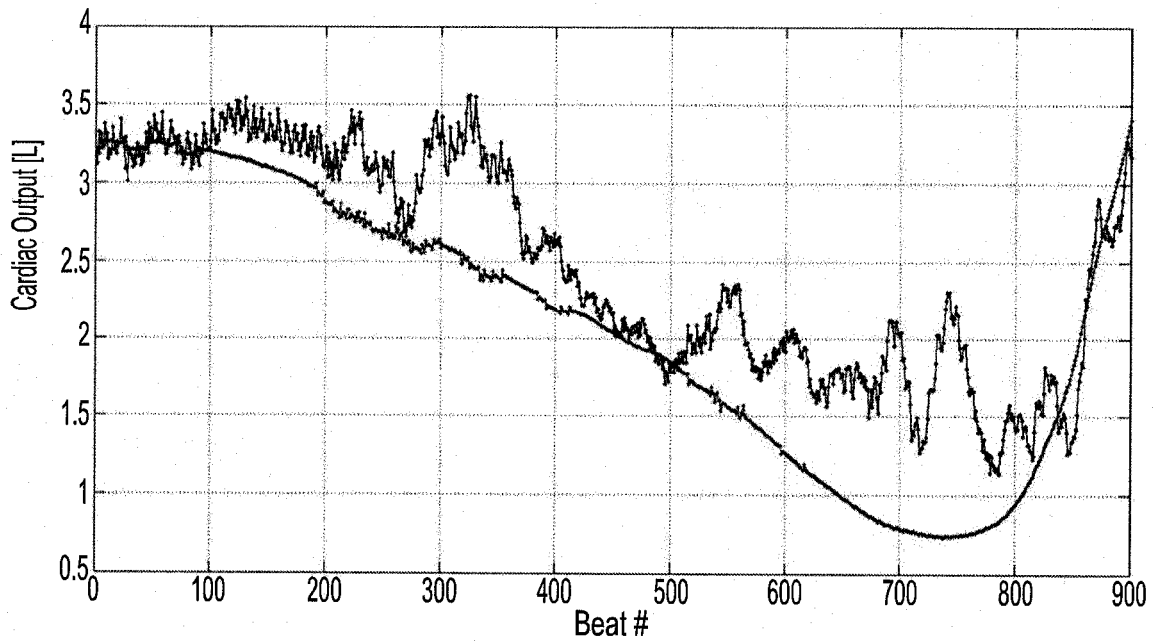


FIG. 13B

12/12

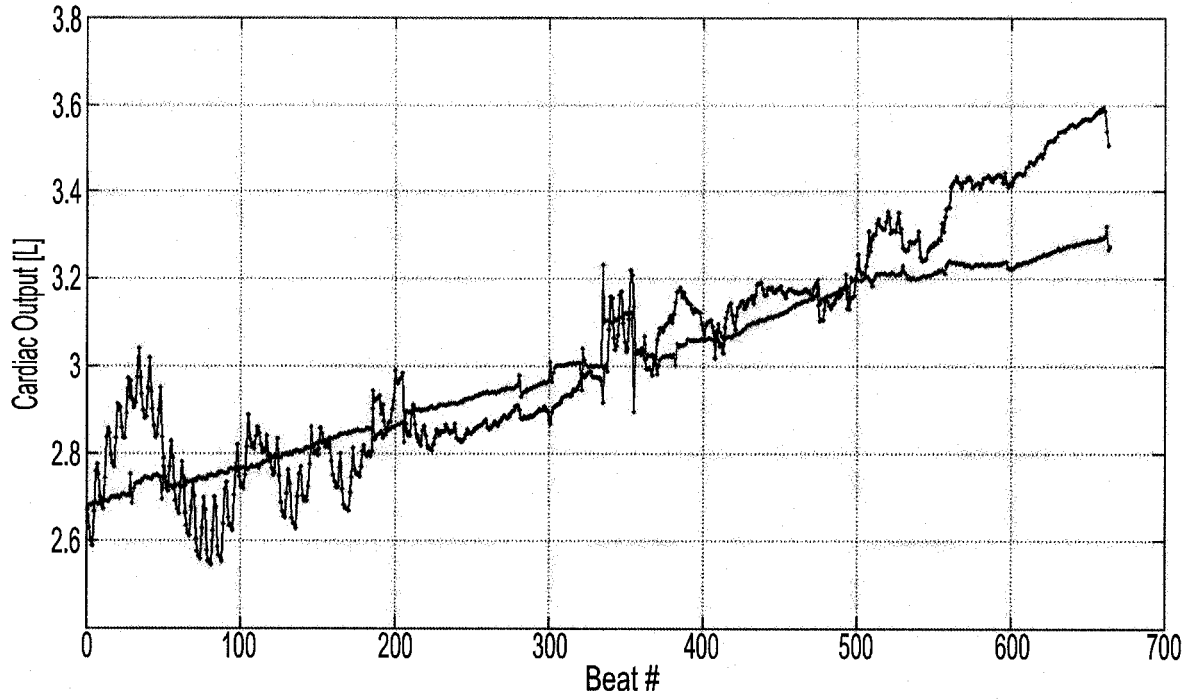


FIG. 14

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IL2012/050271

A. CLASSIFICATION OF SUBJECT MATTER IPC (2012.01) A61B 5/02		
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 (2012.01) A61B 5/02, A61B 5/029		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) Databases consulted: USPTO, THOMSON INNOVATION		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 20090287102 A1 WARD LEIGH CORDWIN [AU] 19 Nov 2009 (2009/11/19) paragraphs [0097] - [0098], [0103] - [0103], [0117] - [0119]	1,5-7,26,30,49,52
Y	paragraphs [0097] - [0098], [0103] - [0103], [0117] - [0119], [0148]	2-4,8-25,27-29,31-48,50,5 1,53-57
Y	US 4926868 A LARSEN LAWRENCE E [US] 22 May 1990 (1990/05/22) col. 6, l. 37-62	2-4,8-25,27-29,31-48,50,5 1,53-57
Y	US 2002062086 A1 MIELE FRANK R [US] 23 May 2002 (2002/05/23) paragraphs [0197] - [0203]	2-4,8-25,27-29,31-48,50,5 1,53-57
A	WO 2004028361 A1 SCHMIDT RALF [DE] 08 Apr 2004 (2004/04/08) see entire document	1-57
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> 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 23 Oct 2012		Date of mailing of the international search report 24 Oct 2012
Name and mailing address of the ISA: Israel Patent Office The Technology Park, Bldg.5, Malcha, Jerusalem, 96951, Israel Facsimile No. 972-2-5651616		Authorized officer MOSKOVICH Elad EladMo@justive.gov.il Telephone No. 972-2-5651607

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IL2012/050271

Patent document cited search report	Publication date	Patent family member(s)	Publication Date
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		WO 2004028361 A1	08 Apr 2004

专利名称(译)	用于监测血液动力学的方法和系统		
公开(公告)号	EP2736405A4	公开(公告)日	2015-02-11
申请号	EP2012817147	申请日	2012-07-25
申请(专利权)人(译)	CHEETAH MEDICAL , INC.		
当前申请(专利权)人(译)	CHEETAH MEDICAL , INC.		
[标]发明人	LEVY BARUCH MARCOVITCH SHMUEL SHUSMAN ELIEZER ROTENBERG DAVID AVIDOR YOAV		
发明人	LEVY, BARUCH MARCOVITCH, SHMUEL SHUSMAN, ELIEZER ROTENBERG, DAVID AVIDOR, YOAV		
IPC分类号	A61B5/02 A61B5/00 A61B5/024 A61B5/029 A61B5/0402		
CPC分类号	A61B5/02007 A61B5/02028 A61B5/024 A61B5/029 A61B5/0402 A61B5/053 A61B5/412 A61B5/4818 A61B5/4836 A61B5/4875 A61B5/7228 A61B5/7239 A61B5/0205 A61B5/026 A61B5/0452 A61B5 /14535 A61B8/065		
代理机构(译)	丹麦美国律师协会		
优先权	61/511163 2011-07-25 US		
其他公开文献	EP2736405A1		
外部链接	Espacenet		

摘要(译)

公开了一种用于监测受试者的血液动力学的系统。该系统包括：信号发生系统，被配置为至少提供输出电信号并将输出信号发送到受试者的器官。该系统还包括解调系统，该解调系统被配置为响应于输出电信号接收从器官感测的输入电信号，并且用于使用输出信号调制输入信号以提供输入信号的同相分量和正交分量。 。该系统还包括处理系统，该处理系统被配置用于基于同相和正交分量来监测血液动力学。