(54) Title: SYSTEM, METHOD AND APPARATUS FOR MEASURING BLOOD FLOW AND BLOOD VOLUME
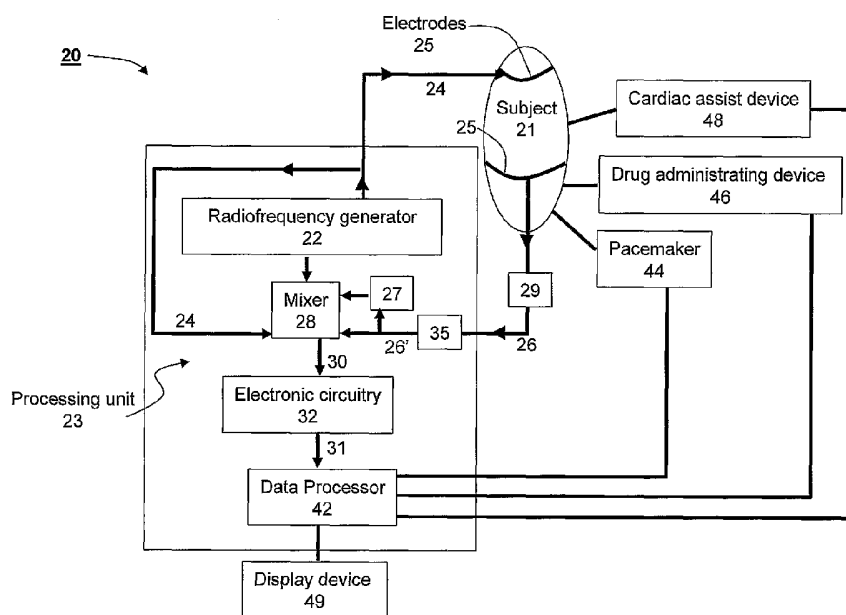
(57) Abstract: A method of calculating blood flow in an organ of a subject using output radiofrequency signals transmitted to
the organ and input radiofrequency signals received from the organ, the method comprises determining a phase shift of the input
radiofrequency signals relative to the output radiofrequency signals and using the phase shift to calculate the blood flow in the organ.

SYSTEM, METHOD AND APPARATUS FOR MEASURING BLOOD FLOW AND BLOOD VOLUME

FIELD AND BACKGROUND OF THE INVENTION

5   The present invention relates to measurement of electrical signals of a body of a subject and, more particularly, to measurement of electrical signals of the body of the subject so as to determine blood volume or blood volume rate, e.g., stroke volume, cardiac output, brain intra luminal blood volume and the like.

Heart diseases are major causes of morbidity and mortality in the modern 10   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 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 15   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.

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.

20   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 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 25   heart rate of 80 beats per minute the resting cardiac output varies between 4.8 and 6.4 L per min.

A common clinical problem is that of hypotension (low blood pressure); this may occur because the cardiac output is low and/or because of low systemic vascular resistance. This problem can occur in a wide range of patients, especially those in 30   intensive care or postoperative high dependency units. In these high risk patients, more detailed monitoring is typically established including measuring central venous pressure via a central venous catheter and continuous display of arterial blood pressure via a peripheral arterial catheter.

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In addition to the above measurements, the measurement of cardiac output is extremely important. For example, when combined with arterial pressure measurements, cardiac output can be used for calculating the systemic vascular resistance. The measurement of cardiac output is useful both for establishing a

5   patient's initial cardiovascular state and for monitoring the response to various therapeutic interventions such as transfusion, infusion of inotropic drugs, infusion of vasoactive drugs (to increase or reduce systemic vascular resistance) or altering heart rate either pharmacologically or by adjusting pacing rate.

Several methods of measuring cardiac output are presently known. One such

10   method is known as the Fick method, described by Adolf Fick in 1870. This method is based on the observation that the amount of oxygen picked up by the blood as it passes through the lungs is equal to the amount of oxygen taken up by the lungs during breathing. In Fick's method, one measures the amount of oxygen taken up by the body during respiration and the difference in oxygen concentration between venous and

15   arterial blood and uses these measurements to calculate the amount of blood pumped through the lungs which is equal to the cardiac output. More specifically, in Fick's method the cardiac output equals the ratio between the oxygen consumption and the arteriovenous oxygen content difference.

Oxygen consumption is typically measured non-invasively at the mouth, while

20   the blood concentrations are measured from mixed venous and peripheral arterial blood drawings. Oxygen consumption is derived by measuring the volume of an expired gas over a certain period of time and the difference in oxygen concentration between the expired gas and the inspired gas.

The Fick method suffers from many drawbacks. First, accurate collection of

25   the gas is difficult unless the patient has an endotracheal tube because of leaks around a facemask or mouthpiece. Second, the analysis of the gas, which is straightforward if the inspired gas is air, is problematic for oxygen enriched air. Third, the arteriovenous oxygen content difference presents a further problem in that the mixed venous (i.e., pulmonary arterial) oxygen content has to be measured and therefore a pulmonary

30   artery catheter is needed to obtain the sample, which may cause complications to the patient.

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The Fick principle can also be applied with CO_2 instead of oxygen, by measuring CO_2 elimination which can be determined more easily as compared to oxygen consumption. With this variant of Fick's method, cardiac output is proportional to the change in CO_2 elimination divided by the change in end tidal CO_2

5   resulting from a brief rebreathing period. These changes are accomplished and measured by a sensor, which periodically adds a rebreathing volume into the breathing . circuit. Although this method improves the ability to perform accurate measurements of gas, it still suffers from most of the above limitations, in particular the limitation related to leaks around the facemask.

10   Another method is by 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

15   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 area and the heart rate to give cardiac output. Besides being very inaccurate, the method has the following disadvantages: (i) the system may only be operated by a skilled operator; (ii) due to the size of the system's probe, heavy sedation

20   or anaesthesia is needed; (iii) the system is expensive; and (iv) the probe cannot be configured to provide continuous cardiac output readings without an expert operator being present.

U.S. Patent No. 6,485,431 discloses a relatively simple method in which the arterial pressure, measured by a pressure cuff or a pressure tonometer, is used for

25   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 output as the product of the mean arterial pressure and compliance divided by a time constant. This method, however, is very inaccurate and it can only provide a rough estimation of the cardiac output.

30   An additional method of measuring cardiac output is called 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

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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

5   atrium of the heart. The saline mixes with the blood in the heart and temporarily depresses the 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

10 area under the curve of temperature depression.

The placement of the catheter into the pulmonary artery is expensive and has associated risk including: death; infection; hemorrhage; arrhythmias; carotid artery; thoracic duct, vena caval, tracheal, right atrial, right ventricular, mitral and tricuspid valvular and pulmonary artery injury. Little evidence suggests that placement of a

15 pulmonary artery catheter improves survival and several suggest an increase in morbidity and mortality.

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 [U.S. Patent Nos. 3,340,867, 4,450,527, 4,852,580, 4,870,578,

20 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; 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.

25 A typical bioimpedance system includes a tetrapolar array of circumferential band electrodes connected to the subject at the base of the neck and surrounding the circumference of the lower chest, at the level of the xiphoid process. When a constant magnitude alternating current flows through the upper cervical and lower thoracic band electrodes, a voltage, proportional to the thoracic electrical impedance (or

30 reciprocally proportional to the admittance), is measured between the inner cervical and thoracic band electrodes. The portion of the cardiac synchronous impedance

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change, temporally concordant with the stroke volume, is ascribed solely and uniquely to volume changes of the aorta during expansion and contraction over the heart cycle.

A major disadvantage of existing bioimpedance systems is that the bioimpedance detectors utilized in such systems require several consecutive levels of amplifier circuits. Each amplifier circuit undesirably amplifies the input noise from signals detected in a body segment, thereby necessitating an increase in the magnitude of the measurement current to maintain a reasonable signal-to-noise ratio. Multiple amplifier circuits require substantial area on printed circuit boards and utilize numerous circuit components thereby increasing the cost and power consumption of the system. The complexity of multiple amplifier systems decreases the reliability of the systems and increases the frequency of required maintenance.

A typical printed circuit board of a bioimpedance system comprises one or more band pass filters, a half-wave rectification circuit and one or more low pass filters. One skilled in the art would appreciate that the noise level is proportional to the bandwidth of the band pass filter. As presently available band pass filters are typically characterized by a frequency ratio of about 5 %, a considerable portion of the noise passes the band pass filter hence being folded into the half-wave rectification circuit. This problem is aggravated by the fact that the typical change in the impedance within the thorax is about 0.1 %, thereby causing a rather low signal-to-noise ratio for such systems.

A recognized problem in bioimpedance measurement is the difficulty in separating and differentiating between cardiovascular bioimpedance signals and respiratory bioimpedance signals, where the latter are typically much larger than the former. An optimization method for increasing the efficiency of the bioimpedance measurement is disclosed in U.S. Patent No. 4,870,578. In this method, changes in the electrical resistance caused by respiration are suppressed by a clamping circuit, synchronized with the electrical activity of the heart. The clamping circuit is timed to clamp the voltages in the measuring equipment to a baseline reference voltage in the time preceding the beginning of mechanical systole. The voltage clamping is released during the mechanical systole of the heart so that the changes in the bioimpedance caused by the pumping action of the heart during mechanical systole are measured.

Although providing a certain degree of improvement to the efficiency of the measurement, this method still suffers from a rather low signal-to-noise ratio.

Additionally, prior art techniques suffer from the limitation of a substantially high level of AM noise which significantly reduces the ability to provide accurate measurement.

There is thus a widely recognized need for and it would be highly advantageous to have, a system, method and apparatus for measuring blood flow devoid of the above limitations.

SUMMARY OF THE INVENTION

According to one aspect of the present invention, there is provided a method of calculating blood flow in an organ of a subject using output radiofrequency signals transmitted to the organ and input radiofrequency signals received from the organ, the method comprises determining a phase shift of the input radiofrequency signals relative to the output radiofrequency signals and using the phase shift to calculate the blood flow in the organ based on a linear relationship between said phase shift and the blood flow.

According to another aspect of the present invention, there is provided an apparatus for calculating blood flow in an organ of a subject from output radiofrequency signals transmitted to the organ and input radiofrequency signals received from the organ, the apparatus comprises a signal processing unit for determining a phase shift of the input radiofrequency signals relative to the output radiofrequency signals, and a blood flow calculator for calculating the blood flow in the organ using a linear relationship between the phase shift and the blood flow.

According to yet another aspect of the present invention, there is provided a system for measuring blood flow in an organ of a subject, the system comprises: a radiofrequency generator for generating output

radiofrequency signals; a plurality of electrodes, designed to be connectable to the skin of the subject, the electrodes being for transmitting the output radiofrequency signals to the organ and for sensing input radiofrequency signals of the organ; and the apparatus described in the preceding paragraph.

5   The signal processing unit may comprise an envelope elimination unit designed and configured to reduce or eliminate amplitude modulation of the input radiofrequency signals so as to provide input radiofrequency signals of substantially constant envelope.

The signal processing unit may comprise: a mixer, electrically

10   communicating with the radiofrequency generator and at least a portion of the plurality of electrodes, the mixer being designed and configured to mix the output radiofrequency signals and the input radiofrequency signals, to provide a mixed radiofrequency signal being indicative of the blood flow; and electronic circuitry for filtering out a portion of the mixed

15   radiofrequency signal so as to substantially increase a signal-to-noise ratio of a remaining portion of the mixed radiofrequency signal.

The system may further comprise a data processor for calculating at least one quantity using the remaining portion of the mixed radiofrequency signal, the at least one quantity being selected from the group consisting of a

20   stroke volume, a cardiac output, a brain intra luminal blood flow and an artery blood flow rate.

The system may further comprise a pacemaker, communicating with the data processor and operable to control a heart rate of the subject, wherein the data processor is programmed to electronically control the

25   pacemaker, in accordance with a value of the at least one quantity.

The system may further comprise a drug administrating device, communicating with the data processor and operable to administrate drugs to the subject, wherein the data processor is programmed to electronically control the drug administrating device, in accordance with a value of the at

30   least one quantity.

The system may further comprise a cardiac assist device, communicating with the data processor and operable to increase the cardiac output.

The cardiac assist device may comprise a reinforcing member
5   designed and configured to restrict an expansion of a portion of a heart tissue, thereby to increase the cardiac output.

At least a portion of the plurality of electrodes may be designed and constructed so as to have a substantial constant sensitivity to electrical signals transmitted through the electrodes, irrespectively of an orientation of
10   the electrodes on the subject.

At least a portion of the plurality of electrodes may comprise an attaching material.

The system may further comprise a detector electrically communicating with at least a portion of the plurality of electrodes for
15   detecting a voltage between a first location and a second location of the subject and for generating the input radiofrequency signals in response to the voltage, wherein the input radiofrequency signals being indicative of impedance and/or hemodynamic reactance of the organ.

The system may further comprise at least one sensor for sensing the
20   voltage, the at least one sensor being designed and constructed for generating signals having a magnitude which is a function of blood flow in, from or to the organ.

The electronic circuitry may comprise a differentiator for performing at least one time-differentiation, to provide a respective derivative of the
25   impedance and/or hemodynamic reactance of the organ.

The differentiator may be selected from the group consisting of a digital differentiator and an analog differentiator.

The system may further comprise a display device for displaying the blood flow.

According to still another aspect of the present invention, there is provided a method of measuring blood flow in an organ of a subject, the method comprises: generating output radiofrequency signals; transmitting the output radiofrequency signals to the organ and sensing input radiofrequency signals of the organ; and determining a phase shift of the input radiofrequency signals relative to the output radiofrequency signals and using the phase shift to calculate the blood flow in the organ, based on a linear relationship between said phase shift and the blood flow.

The method may further comprise reducing or eliminating amplitude modulation of the input radiofrequency signals, so as to provide input radiofrequency signals of substantially constant envelope.

The reducing or eliminating of the amplitude modulation may comprise maintaining a phase modulation of the input radiofrequency signals of substantially constant envelope.

The method may further comprise mixing the output radiofrequency signals and the input radiofrequency signals so as to provide a mixed radiofrequency signal being indicative of the blood flow, and filtering out a portion of the mixed radiofrequency signal so as to substantially increase a signal-to-noise ratio of a remaining portion of the mixed radiofrequency signal.

The mixing may comprise providing a radiofrequency sum and a radiofrequency difference.

The filtering of the portion of the mixed radiofrequency signal may be carried out by a low pass filter designed and constructed for filtering out the radiofrequency sum.

The method may further comprise analogically amplifying the remaining portion of the mixed radiofrequency signal.

The method may further comprise digitizing the remaining portion of the mixed radiofrequency signal.

The method may further comprise calculating at least one quantity using the remaining portion of the mixed radiofrequency signal, the at least one quantity being selected from the group consisting of a stroke volume, a cardiac output and a brain intra luminal blood volume and an artery blood

5   flow rate.

The artery blood flow rate may be selected from the group consisting of an external carotid blood flow rate, an internal carotid blood flow rate, an ulnar blood flow rate, a radial blood flow rate, a brachial blood flow rate, a common iliac blood flow rate, an external iliac blood flow rate, a posterior

10   tibial blood flow rate, an anterior tibial blood flow rate, a peroneal blood flow rate, a lateral plantar blood flow rate, a medial plantar blood flow rate, a deep plantar blood flow rate.

The method may further comprise controlling a heart rate of the subject in accordance with a value of the at least one quantity.

15   The controlling of a heart rate of the subject may be carried out by a pacemaker.

The method may further comprise using a value of the at least one quantity for selecting an amount and a type of drugs and administrating the amount and the type of drugs to the subject.

20   The method may further comprise providing a site of surgical access to a portion of a heart of a subject and maintaining the reduction of cardiac expansion of the portion of the heart a substantial amount of time so as to increase the cardiac output.

The transmitting of the output radiofrequency signals to the organ

25   and sensing the input radiofrequency signals of the organ may be carried out by connecting a plurality of electrodes to the skin of the subject.

A number of the plurality of electrodes may be selected so as to substantially decouple the input radiofrequency signals from at least one effect selected from the group consisting of a posture changes effect, a

30   respiration effect and a motion effect.

The plurality of electrodes may comprise two, three or four electrodes.

The connecting of the plurality of electrodes may be done so as to have a substantial constant sensitivity to electrical signals transmitted through the electrodes, irrespectively of an orientation of the electrodes on the subject.

At least a portion of the plurality of electrodes may comprise at least one elongated conducting material designed and constructed to wind at least a portion of an external organ of the subject, so as to have a substantial constant sensitivity to electrical signals transmitted through the electrodes, irrespectively of an orientation of the electrodes on the external organ.

The external organ may be selected from the group consisting of a chest, a hip, a thigh, a neck, a head, an arm, a forearm, an abdomen, a gluteus, a leg and a foot.

The method may further comprise detecting a voltage between a first location and a second location of the subject and generating the input radiofrequency signals in response to the voltage, wherein the input radiofrequency signals being indicative of impedance and/or hemodynamic reactance of the organ.

The method may further comprise performing at least one time-differentiation thereby providing a respective derivative of the impedance and/or hemodynamic reactance of the organ.

The derivative may be selected from the group consisting of a first derivative and a second derivative.

The performing of the time-differentiation may be effected by a procedure selected from the group consisting of a digital differentiation and an analog differentiation.

The method may further comprise displaying the blood flow using a display device.

The display device may be capable of displaying the blood flow as a function of time.

There is also disclosed herein, an apparatus for determining blood flow in an organ of a subject from output radiofrequency signals transmitted to the organ and input radiofrequency signals received from the organ, the apparatus comprises: electronic circuitry having an envelope elimination unit designed and configured to reduce or eliminate amplitude modulation of the input radiofrequency signals thereby to provide input radiofrequency signals of substantially constant envelope; and a signal processing unit for determining the blood flow in the organ using the input radiofrequency signals of substantially constant envelope.

The signal processing unit may be designed and configured to determine a phase shift of the input radiofrequency signals relative to the output radiofrequency signals of substantially constant envelope, the phase shift being indicative of the blood flow in the organ.

The envelope elimination unit may be designed and configured to maintain a phase modulation of the input radiofrequency signals.

The envelope elimination unit may comprise a limiter amplifier.

The apparatus may further comprise a mixer, for mixing the output radiofrequency signals and the input radiofrequency signals of substantially constant envelope thereby to provide a mixed radiofrequency signal.

The electronic circuitry may be designed and configured to filter out a portion of the mixed radiofrequency signal so as to substantially increase a signal-to-noise ratio of a remaining portion of the mixed radiofrequency signal.

The mixer may be operable to provide a radiofrequency sum and a radiofrequency difference.

The electronic circuitry may comprise a low pass filter for filtering out the radiofrequency sum. The electronic circuitry may comprise an

analog amplification circuit for amplifying the remaining portion of the mixed radiofrequency signal.

The electronic circuitry may comprise a digitizer for digitizing the remaining portion of the mixed radiofrequency signal. The electronic circuitry may be designed and constructed so as to minimize sensitivity of the input radiofrequency signals to impedance differences between the plurality of electrodes and the organ of the subject.

The electronic circuitry may comprise at least one differential amplifier characterized by an impedance being substantially larger than the impedance differences between the plurality of electrodes and the organ of the subject.

Preferably, the signal-to-noise ratio is increased by at least 1OdB, more preferably by at least 2OdB, most preferably by at least 3OdB.

The present invention successfully addresses the shortcomings of the presently known configurations by providing a system, method and apparatus for measuring and/or calculating blood flow, far exceeding prior art technologies.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and 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 not intended to be limiting.

Implementation of the method and system of the present invention involves performing or completing selected tasks or steps manually, automatically, or a combination thereof. Moreover, according to actual instrumentation and equipment of preferred embodiments of the method and system of the present invention, several selected steps could be implemented

by hardware or by software on any operating system of any firmware or a combination thereof. For example, as hardware, selected steps of the invention could be implemented as a chip or a circuit. As software, selected steps of the invention could be implemented as a plurality of software instructions being executed by a computer using any suitable operating system. In any case, selected steps of the method and system of the invention could be described as being performed by a data processor, such as a computing platform for executing a plurality of instructions.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is 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 purposes of illustrative discussion of the preferred embodiments of the present invention only and are presented in the cause of providing what is believed to be the most useful and readily understood description of the principles and conceptual aspects of the invention. In this regard, no attempt is made to show structural details of the invention in more detail than is necessary for a fundamental understanding of the invention, the_____

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description taken with the drawings making apparent to those skilled in the art how the several forms of the invention may be embodied in practice.

In the drawings:

FIG. 1 is a schematic illustration of a conventional bioimpedance system, according to prior art teachings;

FIG. 2 is a schematic illustration of a system for measuring blood flow in an organ of a subject, according to a preferred embodiment of the present invention;

FIG. 3 is a schematic illustration of electronic circuitry for filtering out a portion of a signal so that a remaining portion of the signal is characterized by a substantially increased signal-to-noise ratio;

FIGs. 4a-h are schematic illustrations of electrodes (c, d, g and h) and the respective positions to which the electrodes are attached (a, b, e and f), according to a preferred embodiment of the present invention;

FIGs. 4i-L are schematic illustrations of electrode stickers, according to a preferred embodiment of the present invention;

FIG. 5 is a schematic illustration of an apparatus for determining blood flow in an organ of a subject, according to a preferred embodiment of the present invention;

FIG. 6 is a schematic illustration of an apparatus for calculating blood flow, according to a preferred embodiment of the present invention;

FIG. 7 is a flowchart diagram of a method of calculating blood flow, according to a preferred embodiment of the present invention;

FIG. 8 is a flowchart diagram of a method of measuring blood flow in an organ of a subject, according to a preferred embodiment of the present invention;

FIG. 9a is a block diagram of a printed circuit board for measuring blood flow, using three electrodes;

FIG. 9b is a block diagram of a printed circuit board for measuring blood flow, using two electrodes;

FIG. 9c is a block diagram of a printed circuit board for measuring blood flow, using four electrodes;

FIG. 9d is a block diagram of an analog amplification circuit for amplifying the radiofrequency signal;

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FIGs. 10a-b show monitoring results of the change in the hemodynamic reactance and its measured derivative, obtained using a prototype system with three electrodes built according to a preferred embodiment of the present invention, for the purpose of determining stroke volume and cardiac output;

FIG. 10c shows monitoring results of the ECG signal, change in the bioimpedance, its first derivative and its second derivative, obtained using a conventional (prior art) system;

FIGs. 11a-b show monitoring results of the change in the hemodynamic reactance and its measured derivative obtained using the prototype system with two electrodes, built for the purpose of measuring brain intra luminal blood volume change and flow rate.

FIG. 12a shows monitoring results of the change in the hemodynamic reactance and its measured derivative, obtained using a prototype system with four electrodes built according to a preferred embodiment of the present invention, for the purpose of determining stroke volume and cardiac output;

FIG. 12b shows a comparison between data acquired from ECG (two leads), blood wave front (left and right) and CO signal including its first and second derivatives, according to a preferred embodiment of the present invention; and

FIG. 13 show monitoring results of the change in the hemodynamic reactance and its measured derivative obtained using the prototype system with four electrodes, for the purpose of measuring brain intra luminal blood volume change and flow rate.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is of a system, method and apparatus for measuring blood flow in an organ of a subject, which can be used for determining many blood-flow related parameters for the purpose of medical diagnosis and/or treatment. Specifically, the present invention can be used for determining stroke volume, cardiac output, brain intra luminal blood volume and blood flow in other arteries of the body such as, but not limited to, arteries in the chest, hip, thigh, neck, head, arm, forearm, abdomen, gluteus, leg and foot.

For purposes of better understanding the present invention, as illustrated in Figures 2-9b of the drawings, reference is first made to the construction and operation

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of a conventional (*i.e.*, prior art) system for determining blood flow as illustrated in Figure 1.

Before explaining at least one embodiment of the invention in detail, it is to be understood that the invention is not limited in its application to the details of construction and the arrangement of the components set forth in the following description or illustrated in the drawings. The invention is capable of other embodiments or of being practiced or carried out in various ways. Also, it is to be understood that the phraseology and terminology employed herein is for the purpose of description and should not be regarded as limiting.

Referring now to the drawings, Figure 1 illustrates the conventional system, generally referred to herein as system **10**, which includes a radiofrequency generator **12** for generating a periodic high frequency current output in response to a periodic control input signal. System **10** further includes output spot electrodes **14** for carrying current output from radiofrequency generator **12**. Electrodes **14** are connected to locations of a human body **13** above and below the heart. Shown in Figure 1 are two output spot electrodes, connected to two pairs of locations, a first pair **A** and a second pair **D**, hence form a tetrapolar array of electrodes. Current, generated by radiofrequency generator **12**, flows between location pairs **A** and **D** and causes a voltage drop on the segment **A-D**, due to the impedance of body **13**.

System **10** further includes an electrical bioimpedance detector **15** and four additional electrodes for detecting a voltage signal, between two additional location pairs designated **B** and **C**, located respectively in proximity to pairs **A** and **D** and, similarly to electrodes **14**, form a tetrapolar array of electrodes. Bioimpedance detector **15** is connected to body **13** through two input spot electrodes **17**. Detector **15** generates an output signal indicative of the impedance of segment **B-C**, in response to the voltage signal received by electrodes **17**.

The voltage signal is proportional to the magnitude of the periodic current and also proportional to the electrical bioimpedance of the tissue between the pairs **A** and **D** (or pairs **B** and **C**).

The radiofrequency generator typically generates a high frequency current a few milliamperes Root Mean Square in magnitude and a few tens of kilohertz in frequency.

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The amplitude of the voltage signal is modulated by changes in conductivity in the body segment. In the thorax, such changes are due to changes in the volume of blood within the thorax and by orientation of erythrocytes as a function of blood flow velocity in major arteries. The voltage signal modulation envelope is a superimposed

5   sum of conductivity changes caused by changes in posture, respiration, cardiac cycle, motion artifacts and electrical noise.

The determination of the blood flow is thus by measuring the impedance change, ΔZ and calculating the blood flow therefrom. The ability of system 10 and similar prior art systems to measure blood flow depends on several assumptions which

10   model the dependence of the blood flow on the impedance, Z. More specifically, it is assumed that the change in thoracic impedance is due to the pulsatile nature of blood flow and that effect of ventilation (changes in chest size) can be neglected.

It is further assumed is that all impedance changes are due to the variation of aortic blood volume, while pulmonary circulation are neglected and venous return are

15   considered as constant. Thus, the total impedance Z is typically approximated to $Z = \rho L/A$, where ρ is the resistivity of the blood, L is the distance between the electrodes and A is its cross-sectional area. Assuming that the aorta has a cylindrical shape and that the changes in the blood resistivity are small, the time dependence of the aortic volume V can be written as $V(t) = \rho\, L^2/Z(t)$, where $Z(t) = \rho\, L/A(t)$. It is

20   recognized, however, that a non-invasive measurement of the explicit time-dependence of $Z(t)$ is not achievable and one can only measure a static thoracic impedance, Z_0.

Under the assumptions that (i) the resistivity of the blood is similar to the resistivity of the thoracic tissues, and (ii) the thorax has a cylindrical shape with a

25   single chamber in parallel with the aorta, Z_0 satisfies, $1/Z_0 = 1/Z_c + 1/Z_a$, where Z_c and Z_a are the impedances of the thorax and the aorta, respectively. Assuming further that $|Z_0 - Z_c| < 1\ \%$, the pulsatile change in the aortic volume ΔV change is volume can be approximated to $\Delta V = \rho\, L^2/Z_0^2\ \Delta Z$. As the relation between ΔV and the stroke volume, SV depends on the net flux of blood (SV $= V_0 +$ input flow $-$ output flow), additional

30   modeling have to be made in order to extrapolate SV. These models can include independent assessment of aortic valve closure or the substitution of the maximal

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time-derivative of the aortic impedance, $(dZ/dt)_{max}$ and the systolic ejection time, T, into the derivative of ΔV: $SV = d(\Delta V)/dt = \rho L^2/Z_0^2\ T\ (dZ/dt)_{max}$.

The time-derivative of the impedance is proportional to the impedance change, ΔZ. Typically, however, the value of the impedance change, ΔZ, is smaller than the value of the impedance, Z, by 2-4 orders of magnitude, thus affecting the quality of the measurement in terms of signal-to-noise ratio. The noise content of the received signal can be reduced by the use of one or more band pass filters, filtering out frequencies below a low threshold and above a high threshold. Nevertheless, the efficiency of known band pass filters is insufficient and the resulting signal still has a substantial amount of the noise content folded therein.

Additionally, the above formula for calculating SV includes many measurement-dependent coefficients which contribute to the aggregated error of the total measurement. Specifically, errors in the measurements of the static impedance Z_0, the distance between the electrodes L and/or the systolic ejection time T, significantly increase the uncertainty in the stroke volume.

Still additionally, impedance measurement as performed by system 10 and other prior art systems suffer from considerable AM noise which further increases the uncertainty in the stroke volume.

The present embodiments successfully overcome the above shortcomings by providing system for measuring blood flow in an organ of a subject, generally referred to herein as system 20.

Reference is now made to Figure 2, which is a schematic illustration of system 20, according to a preferred embodiment of the present invention. System 20 preferably comprises a radiofrequency generator 22, for generating output radiofrequency signals. Generator 22 may be embodied as any radiofrequency generator, such as, but not limited to, radiofrequency generator 12 of system 10. System 20 further comprises a plurality of electrodes 25, which are connected to the skin of subject 21. Electrodes 25 transmit output radiofrequency signals 24, generated by generator 22 and sense input radiofrequency signals 26 originated from the organ of subject 21.

System 20 preferably comprises a signal processing unit 23 for determining a phase shift $\Delta\varphi$ of signals 26 relative to signals 24. It was discovered by the Inventor

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of the present invention that the phase shift of the input signals, as received from the organ, relative to the output signals as generated by generator 22, is indicative of the blood flow in the organ. Thus, according to the presently preferred embodiment of the invention the blood flow is determined using the phase shift.

5   The advantage of using $\Delta\varphi$ for determining the blood flow is that the relation between the blood flow and $\Delta\varphi$ depends on fewer measurement-dependent quantities as compared to prior art determination techniques (e.g., system 10 above) in which the impedance is used. Specifically, it was found by the Inventor of the present invention that there is a linear relationship between $\Delta\varphi$ and the blood flow, with a proportion 10 coefficient comprising the systolic ejection time, T. For example, the stroke volume SV can be calculated using the relation SV = const.$\times T \times \Delta\varphi$, and the cardiac output CO can be calculated using the relation CO = const.$\times T \times \Delta\varphi \times$HR, where HR is the heart rate of the subject (e.g., in units of beats per minutes), and "const." a constant which can be found, for example, using a calibration curve. As will be appreciated by one 15 ordinarily skilled in the art, the absence of L and Z_0 from the formulae for SV and CO significantly reduces the uncertainty in the obtained values because there is no entanglement between the obtained values and errors associated with the measurement of L and Z_0.

         According to a preferred embodiment of the present invention signal 20 processing unit 23 comprises an envelope elimination unit 35 which reduces or, more preferably, eliminates amplitude modulation of signals 26. Optionally and preferably unit 35 maintains the phase modulation of signals 26. Signals generated by unit 23 are designated in Figure 2 by numeral 26'. The input to envelope elimination unit 35 (signals 26) typically carries a substantial amount of AM noise, which can be 25 described, without limitation as a signal $v_{26} = v(t)\cos(\omega t + \varphi(t))$, which contains both phase and amplitude modulation. According to a preferred embodiment of the present invention unit 35 generates signals (signals 26') having a substantial constant envelope, e.g., $v_{26'} = v_0\cos(\omega t + \varphi(t))$, where v_0 is substantially a constant. Signals 26' thus represent the phase (or frequency) modulation of signal 26. Signal 26' may be 30 created, for example, using a limiter amplifier which amplifies signals 26 and limits their amplitude such that the amplitude modulation is removed. The advantage of the

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removal of the amplitude modulation is that it allows a better determination of the phase shift $\Delta\varphi$ between the input and output signals.

The phase shift can be determined for any frequency component of the spectrum of radiofrequency signals received from the organ. For example, in one embodiment, the phase shift is preferably determined from the base frequency component, in another embodiment the phase shift is preferably determined from the second frequency component, and so on. Alternatively the phase shift can be determined using several frequency components, e.g., using an appropriate averaging algorithm.

Processing unit 23 preferably comprises a mixer 28, electrically communicating with generator 22 and at least a portion of electrodes 25, for mixing signals 24 and signals 26', so as to provide a mixed radiofrequency signal 30 being indicative of the blood flow. Signals 24 and 26' may be inputted into mixer 28 through more than one channel, depending on optional analog processing procedures (e.g., amplification) which may be performed prior to the mixing.

For example, in one embodiment, both signals 24 and 26 may be inputted into mixer 28 directly from the terminals that are used for transmitting the signals to and from electrodes 25. In another embodiment, signal 26 may be inputted via an additional unit 27, which is designed for processing signal 26. In an additional embodiment, signal 24 may be inputted from generator 22 where certain analog processing procedures are performed prior to the mixing.

Mixer 28 may be any known radiofrequency mixer, such as, but not limited to, double-balanced radiofrequency mixer and unbalanced radiofrequency mixer. According to a preferred embodiment of the present invention, mixed radiofrequency signal 30 is composed of a plurality of radiofrequency signals, which may be, in one embodiment, a radiofrequency sum and a radiofrequency difference. A sum and a difference may be achieved, e.g., by selecting mixer 28 so that signals 24 and signals 26 are multiplied thereby. Since a multiplication between two frequencies is equivalent to a frequency sum and a frequency difference, mixer 28 outputs a signal which is composed of the desired radiofrequency sum and radiofrequency difference.

One ordinarily skilled in the art would appreciate that the advantage in the production of a radiofrequency sum and a radiofrequency difference is that whereas

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the radiofrequency sum includes both the signal, which is indicative of the blood flow and a considerable amount of electrical noise, the radiofrequency difference is approximately noise-free.

Thus, the present invention provides an efficient technique for minimizing the electrical noise being associated with such an involved measurement in which the effect of interest is smaller than the measured quantity by about 2-4 orders of magnitude.

According to a preferred embodiment of the present invention system 20 further comprises electronic circuitry 32, which filters out a portion of signal 30 so that a remaining portion 31 of signal 30 is characterized by a substantially increased signal-to-noise ratio.

Reference is now made to Figure 3, which is a schematic illustration of circuitry 32. According to a preferred embodiment of the present invention circuitry 32 comprises a low pass filter 34 to filter out the high frequency content of signal 30. Low pass filter 34 is particularly useful in the embodiment in which mixer 28 outputs a sum and a difference, where low pass filter filters out the radiofrequency sum and leaves the radiofrequency difference, which, as stated, is approximately noise-free.

Low pass filter 34 may be designed and constructed in accordance with the radiofrequency difference of a particular system which employs system 20. A judicious design of filter 34 substantially reduces the noise content of remaining portion 31. In a conventional bioimpedance system, for example, a substantial amount of the noise of the received signal is folded into the remaining signal, which is thus characterized by a bandwidth of about 2 kilohertz. It has been found by the inventors of the present invention that by including output radiofrequency signal 24 and by mixing it with input radiofrequency signal 26, the noise in the resulting signal is characterized by a bandwidth that is at least one order of magnitude below the noise bandwidth of conventional systems.

According to a preferred embodiment of the present invention, mixer 28 and circuitry 32 are designed and constructed for increasing the signal-to-noise ratio by at least 20 dB, more preferably by 25 dB, most preferably by 30 dB.

Circuitry 32 preferably comprises an analog amplification circuit 36 for amplifying remaining portion 31 of signal 30. The construction and design of analog

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amplification circuit **36** is not limited, provided circuit **36** is capable of amplifying signal **31**. A non limiting example of amplification circuit **36** is further detailed herein below in the Examples section that follows.

According to a preferred embodiment of the present invention circuitry **32** further comprises a digitizer **38** for digitizing signal **31**. The digitization of signal **31** is useful for further digital processing of the digitized signal, *e.g.*, by a microprocessor.

Additionally and preferably, circuitry comprises a differentiator **40** (either a digital differentiator or an analog differentiator) for performing at least one time-differentiation of the measured impedance to obtain a respective derivative (*e.g.*, a first derivative, a second derivative, *etc.*) of the impedance and/or hemodynamic reactance. Differentiator **40** may comprise any known electronic functionality (*e.g.*, a chip) that is capable of performing analog or digital differentiation. The time-derivative of the impedance is useful, for example, for measuring stroke volume or cardiac output, as further detailed hereinafter.

Referring now again to Figure 2, according to a preferred embodiment of the present invention system **20** further comprises a data processor **42** for calculating at least one quantity using signal **31**. Many blood-volume related quantities may be calculated, such as, but not limited to, a stroke volume, a cardiac output and a brain intra luminal blood volume. System **20** may further comprise a display device **49** for displaying the blood flow and other information, preferably as a function of time.

According to a preferred embodiment of the present invention system **20** further comprises a detector **29** for detecting a voltage drop on a portion of the body of subject **21** defined by the positions of electrodes **25**. In response to the detected voltage, detector **29** preferably generates signals which are indicative of impedance of the respective portion of the body. In this embodiment, the stroke volume can be calculated using $(dZ/dt)_{max}$, as further detailed hereinabove. Knowing the stroke volume, the cardiac output is calculated by multiplying the stroke volume by the heart rate of the subject. More preferably, detector **29** generates signals which are indicative of a hemodynamic reactance, X.

As used herein, "hemodynamic reactance" refers to the imaginary part of the impedance. Techniques for extracting the imaginary part from the total impedance are known in the art. Typically, such extraction is performed at hardware level but the use

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of algorithm at a software level is not excluded from the scope of the present invention. As will be appreciated by one of ordinary skill in the art, the hemodynamic reactance can be used for determining the aforementioned phase shift $\Delta\varphi$.

The blood flow determination provided by system 20 may be used both for diagnostic and for treatment. Hence, according to a preferred embodiment of the present invention, system 20 may further comprise a pacemaker 44, communicating with data processor 42. In this embodiment, data processor 42 is preferably programmed to electronically control pacemaker 44 in accordance with the calculated quantity. For example, in one embodiment, data processor 42 calculates the cardiac output and sends signals to pacemaker 44 which controls, substantially in real-time, the heart rate of subject 21, so as to improve the cardiac output.

Additionally or alternatively, system 20 may also comprise a cardiac assist device 48, preferably constructed and design for increasing the cardiac output. Cardiac assist devices are known in the art and typically comprise a reinforcing member which restricts an expansion of a portion of the heart tissue, so that the cardiac output is increased. In this embodiment, data processor 42 is preferably programmed to electronically control device 48 in accordance with the calculated cardiac output, so that both the determination and the improvement of the cardiac output are automatically performed by system 20.

According to a preferred embodiment of the present invention system 20 may comprise a drug administrating device 46, communicating with data processor 42. Device 46 serves for administrating drugs to subject 21. In this embodiment, data processor 42 is preferably programmed to electronically control device 46, in accordance with the value of the calculated quantity. For example, if the calculated quantity is the brain intra luminal blood volume, then depending on the value of the blood volume, data processor 42 sends signal to device 46 and thereby controls the amount and/or type of medications administered to subject 21.

The number of electrodes which are connected to subject 21 is preferably selected so as to substantially decouple the input radiofrequency signals from undesired effects, such as, but not limited to, a posture changes effect, a respiration effect, a motion effect and the like.

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For any number of electrodes which are used in accordance with a preferred embodiment of the present invention, at least a portion of the electrodes are designed and constructed to so as to have a substantial constant sensitivity to electrical signals transmitted through electrodes, irrespectively of an orientation of the electrodes on the
5   subject.

Reference is now made to Figures 4a-h, which are schematic illustrations of electrodes 25 (Figures 4c, 4d, 4g and 4h) and the respective positions to which electrodes 25 are attached (Figures 4a, 4b, 4e and 4f), according to a preferred embodiment of the present invention. Figures 4c and 4g shows the inner side of
10   electrode 25 and Figures 4d and 4h shows the outer side of electrode 25.

Hence, electrodes 25 preferably comprise at least one elongated conducting material 50 designed and constructed to wind at least a portion of an external organ, which may be, for example, a chest, a hip, a thigh, a neck, a head, an arm, a forearm, an abdomen, a gluteus, a leg, a foot and the like. Optionally, electrode 25 may also
15   comprise an attaching material 52 (e.g., velcro, glue and the like) for facilitating the attachment of electrode 25 to subject 21.

It is recognized that conventional spot electrodes, which are used, e.g., in bioimpedance systems (see, e.g., Figure 1), are sensitive to the particular position to which the electrodes are attached. This sensitivity is particularly disadvantageous in
20   bioimpedance systems where the signal-to-noise ratio is intrinsically small and the fluctuations caused by such artifacts may be comparable to the entire effect which is to be measured. It is further recognized that the problems associated with the sensitivity to small displacements are aggravated when the number of spot electrodes increases. Specifically, with a tetrapolar array of Figure 1, there are eight spot electrodes each of
25   which contribute to the sensitivity to small displacements, hence increasing the uncertainty of the final measurement.

The advantage of the use of electrodes 25, according to the presently preferred embodiment of the invention, is that the signal which is received from the body of subject 21 does not depend on small displacements of the electrodes. In addition, as
30   further detailed herein below, the number of electrodes which are used is substantially smaller than the number which is used in conventional systems. It will be appreciated

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that smaller number of electrodes (i) reduces the uncertainty factor; (ii) is more easy to attach; and (iii) more comfortable to the patient.

Referring to Figures 4a, in one embodiment, one electrode is attached to the neck of subject 21 and two electrodes are attached below the heart. This embodiment may be used, for example, for measuring and determining stroke volume and cardiac output. It is it be understood, however, that other configurations are not excluded for the purpose of determining stroke volume and cardiac output. Specifically, two electrodes may be used. Nevertheless, it was found by the inventors of the present invention, that the motion effects with the use of three electrodes were less pronounced than with the use of two electrodes. The preferred electrodes to be used in this embodiment are shown in Figures 4c (inner side) and 4d (outer side).

Referring to Figure 4b, in another embodiment, two electrodes are attached to the neck of subject 21 and two electrodes are attached below the heart. This embodiment may be used, for example, for measuring and determining stroke volume and cardiac output. As demonstrated in the Examples section that follows, the quality of the results is significantly enhanced with the use of four electrodes. The preferred electrodes to be used in this embodiment are shown in Figures 4c (inner side) and 4d (outer side).

Referring to Figures 4e-h, in an additional embodiment, two electrodes formed on a single elongated strip may be used for the purpose of determining brain intra luminal blood volume. Specifically, as shown in Figure 4e, a single strip (thus, two electrodes) may be wound around the forehead of subject 21, or alternatively and preferably, two strips (thus, four electrodes) may be adjacently wound around the forehead of subject 21.

It is to be understood that any number of electrodes or connection configurations are not excluded from the present invention. For example, the electrodes shown in Figure 4c-d, the electrodes shown in Figure 4g-h or any other electrodes may be used, in any combination, for measuring blood flow in any artery of the body, such as, but not limited to, the external carotid artery, the internal carotid artery, the ulnar artery, the radial artery, the brachial artery, the common iliac artery, the external iliac artery, the posterior tibial artery, the anterior tibial artery, the

peroneal artery, the lateral plantar artery, the medial plantar artery and the deep plantar artery.

When system 20 is used together with other systems it is desired to minimize the area occupied by electrodes 25 so as not to interfere the operation of the other systems. For example, in intensive care units, the subjects are oftentimes connected to ECG leads, arterial line, central venous line, brain stem evoked response equipment, chest tubes, GI tube, intravenous and the like. In such or similar situations system 20 preferably comprises smaller electrodes, which are illustrated in Figures 4i-L.

Figures 4i-j show a back side (Figure 4i) and a front side (Figure 4j) of a sticker which can be used for transmitting and sensing the radiofrequency signals, according to a preferred embodiment of the present invention. The sticker comprises electrical contacts 45 being as fixed and predetermined distance therebetween, thus reducing any the effect of variable inter-electrode distance on the measurement.

Figures 4K-L show a front side (Figure 4K) and a back side (Figure 4L) of another sticker which is similar to the sticker shown in Figures 4i-j, with the exception that the sticker of Figures 4K-L can be connected to system 20 using a single line because the electrical contacts on the sticker are interconnected by an internal line 47.

According to another aspect of the present invention there is provided an apparatus for determining blood flow in an organ of a subject, generally referred to herein as apparatus 60. Apparatus 60 enjoys the property of an enhanced signal-to-noise ratio and, as such, apparatus 60 may be used in combination with any blood flow measuring system, e.g., system 20.

Reference is now made to Figure 5, which is a schematic illustration of apparatus 60. Apparatus 60 preferably comprises electronic circuitry having an envelope elimination unit (e.g., unit 35) for reducing or eliminate amplitude modulation of the input radiofrequency signals as further detailed hereinabove. Apparatus further comprises a signal processing unit (e.g., unit 23) for determining the blood flow in the organ. According to a preferred embodiment of the present invention the signal processing unit determines the phase shift of the input signals relative to the output signals as further detailed hereinabove.

Apparatus 60 may further comprise mixer 28 for mixing signals 24 and signals 26', so as to provide a mixed radiofrequency signal as further detailed hereinabove.

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As illustrated in Figure 5, signals 24 and 26 may be inputted into mixer 28 either directly from the terminals, which are used for transmitting the signals to and from the organ, or via unit 22. The electronic circuitry of apparatus 60 preferably filters out a portion of the mixed radiofrequency signal such that the remaining portion of the

5   signal is characterized by a substantially increased signal-to-noise ratio as detailed above.

According to an additional aspect of the present invention there is provided an apparatus 90 for calculating blood flow in an organ of a subject from the output and input radiofrequency signals.

10   Reference is now made to Figure 6 which is a simplified illustration of apparatus 90. Apparatus 90 preferably comprising a signal processing unit (e.g., unit 23) for determining a phase shift of the input radiofrequency signals relative to the output radiofrequency signals, and a blood flow calculator 92 which calculates the blood flow using the phase shift. Calculator 92 preferably calculates the blood flow

15   using a linear relation between the blood flow and the phase shift, as further detailed hereinabove.

According to yet another aspect of the present invention there is provided a method of calculating the blood flow blood. The method comprises the following steps, which are illustrated in the flowchart of Figure 7. In a first step of the method,

20   designated by Block 94, the phase shift of the input signals relative to the output signals is determined, and in a second step, designated by Block 96 the phase shift is used for calculating the blood flow, e.g., using a linear relationship between the phase shift and the blood flow.

According to still another aspect of the present invention there is provided a

25   method of measuring blood flow in an organ of a subject, the method comprising the following steps, which are illustrated in the flowchart of Figure 8. Hence, in a first step, designated by Block 72, output radiofrequency signals are generated, e.g., by a radiofrequency generator. In a second step, designated by Block 74, the output radiofrequency signals are transmitting to the organ and input radiofrequency signals

30   are sensed of the organ, e.g., by an array of electrodes.

In a third step, designated by Block 75, a phase shift of the input signals relative to said output signals is determined and used for calculating the blood flow as

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further detailed hereinabove. In optional steps, designated in Figure 8 by Blocks 76 and 78, the output radiofrequency signals and the input radiofrequency signals are mixed (Block 76) to provide a mixed signal, and a portion of the mixed signal is filtered out (Block 78) so as to substantially increase the signal-to-noise ratio of a
5   remaining portion thereof as further detailed hereinabove.

According to a preferred embodiment of the present invention, the method may further comprise the following optional steps, where each optional step may be performed independently of the other optional steps in any combination or order. Hence, in one optional step the remaining portion of the mixed radiofrequency signal
10   is analogically amplified; in another optional step, the remaining portion of mixed radiofrequency signal is digitized; in an additional optional step at least one quantity (e.g., a stroke volume, a cardiac output and a brain intra luminal blood volume) is calculated; in still an additional step at least one time-differentiation is performed, as further detailed hereinabove.

15   Following are technical preferred values which may be used for selective steps and parts of the embodiments described above.

As used herein the term "about" refers to ± 10 %.

The output radiofrequency signals are preferably from about ·10KHz to about 200KHz in frequency and from about 10mV to about 50mV in magnitude; the input
20   radiofrequency signals are preferably about 70KHz in frequency and about 20mV in magnitude; a typical impedance which can be measured by the present embodiments is from about 25Ohms to about 35Ohms; the resulting signal-to-noise ratio of the present embodiments is at least 40dB; low pass filter 34 is preferably characterized by a cutoff frequency of about 35Hz and digitizer 38 preferably samples the signals at a rate of
25   about 1000 samples per second.

Additional objects, advantages and novel features of the present invention will become apparent to one ordinarily skilled in the art upon examination of the following examples, which are not intended to be limiting. Additionally, each of the various
30   embodiments and aspects of the present invention as delineated herein above and as claimed in the claims section below finds experimental support in the following examples.

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EXAMPLES

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

A prototype of a system for measuring blood flow in an organ of a subject
5   according to the above description was constructed.

The prototype system includes:

(a)   a self made radiofrequency generator generating output radiofrequency signals, 70Khz in frequency and 20mV in magnitude;

(b)   a plurality of electrodes, as described in Figures 4b, 4c, 4e and 4f; and
10   (c)   a double balanced mixer, purchased from Mini-Circuits, used for providing a radiofrequency sum and a radiofrequency difference, as detailed above.

The prototype system further includes electronic circuitry formed in a printed circuit board. Several electronic circuitries were designed and manufactured, so as to investigate the correlation between the quality of the results, the design of the
15   electronic circuitry and the number of electrodes. The various electronic circuitries are schematically illustrated in Figures 9a-d.

Figure 9a shows a block diagram of electronic circuitry to be used with three electrodes (see results of cardiac-output measurements in Example 1, below). The electrodes leads are designated in Figure 9a by E_1, E_2 and I_1, where the output
20   radiofrequency signals, generated by the radiofrequency generator (designated OSC), are outputted through E_1 and E_2 and the input radiofrequency signals, as measured of the body are inputted through I_1.

The input signals and are channeled through a differential amplifier G_1, a band pass filter BPF and a differential amplifier G_2. The input signals are channeled
25   through a differential amplifier G_3, a band pass filter BPF and an envelope elimination unit EEU. The EEU eliminates the amplitude modulation from the input signal. Both input and output signals are mixed by mixer DMB, to form, as stated, a frequency sum and a frequency difference. A low pass filter LPF filters out the frequency sum and the resulting signal (carrying the frequency difference) is further amplified by
30   additional differential amplifiers G_5, G_6 and G_7. Once amplified, the signal is digitized by an analog to digital digitizer and passed, via a USB communication interface to a processing and display unit.

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Figure 9b shows a block diagram of electronic circuitry to be used with two electrodes of brain intra-luminal blood volume measurements in Example 2, below). As there are only two electrodes E_2 and I_1 are combined to a single lead I_1.

Thus, the output signals and are channeled through a differential amplifier G_1,

5   a band pass filter BPF and a differential amplifier G_2. The input signals are channeled through a differential amplifier G_2, a band pass filter BPF and an envelope elimination unit EEU which eliminates the amplitude modulation from the input signal. Both input and output signals are mixed by mixer DMB, to form the frequency sum and difference. The low pass filter LPF filters out the frequency sum and the resulting

10   signal is further amplified by additional differential amplifiers G_4, G_5 and G_6. As in the case of three electrodes, the signal is digitized by an analog to digital digitizer and passed, via a USB communication interface to a processing and display unit.

Figure 9c shows a block diagram of electronic circuitry to be used with four electrodes (see results of cardiac-output measurements in Example 3 and brain intra-

15   luminal blood volume measurement in Example 4, below). The four leads, designated E_1, E_2, I_1 and I_2,   where the output radiofrequency signals, generated by radiofrequency generator OSC, are outputted through E_1 and E_2 and the input radiofrequency signals, as measured of the body are inputted through I_1 and I_2. In addition, the four leads, E_1, E_2, I_1 and I_2 are connected to the body through capacitors

20   designated C_1, C_2, C_3 and C_4.

The principles of the circuitry of Figure 9c are similar to the principles of the circuitry of Figure 9a with three electrodes. The advantage of the circuitry of Figure 9c is that by using both input leads I_1 and I_2 (as opposed to one input lead I_1 of Figure 9a), effects of impedance differences between the electrodes and the body can be

25   minimized. Specifically, the influence of the voltage drop I_1 and I_2 is controlled by the characteristic impedance of the differential amplifier G_3, which is selected to be sufficiently large so that any impedance changes due to the contact between the body and the electrode is negligible, compared to the impedance of G_3.

Figure 9d shows a block diagram of the analog amplification circuit, which

30   was used to amplify the radiofrequency signal after the low pass filtering in which the radiofrequency sum was filtered out.

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EXAMPLE 1

Measurement of Stroke Volume and Cardiac Output Using Three Electrodes

Three electrodes were connected to a human subject, as shown in Figure 4a. The hemodynamic reactance was measured and was used for determining and
5   monitoring (i) stroke volume; and (ii) cardiac output.

Figures 10a-b shows the monitoring results obtained using the prototype system (using the circuitry of Figure 9a) on a time scale of 250 ms/div. Two waveforms are displayed in each of Figures 10a-b, the change in the hemodynamic reactance and its measured time derivative. The waveforms shown in Figure 10b are
10   in reverse magnification compared to the waveforms shown in Figure 10a.

For comparison, Figure 10c shows monitoring results obtained using a conventional system (GE/Cardiodynamic). The waveforms displayed in Figure 10c, are, from top to bottom, the ECG signal, the change in the bioimpedance, ΔZ, its first derivative, dZ/dt and its second derivative d^2Z/dt^2.

15   The improvement of the signal-to noise ratio of the present invention (Figures 10a-b) over the conventional system (Figure 10c) is vivid. In the prototype system the signal-to-noise ratio was 50dB, whereas in the conventional system the signal-to-noise ratio was 20dB.

20   ## EXAMPLE 2

Measurement of Brain Intra Luminal Blood Volume Change and Flow Rate Using Two Electrodes

Two electrodes were connected to a human subject, as shown in Figure 4e. The hemodynamic reactance was measured and was used for determining and
25   monitoring brain intra luminal blood volume change and flow rate.

Figures 11a-b show the monitoring results obtained using the prototype system (using the circuitry of Figure 9b) on a time scale of 250 ms/div. Two waveforms are displayed in each of Figures 11a-b, the change in the hemodynamic reactance and its measured derivative, where in Figure 11b, the vertical scale for the curve of the
30   change in the hemodynamic reactance is twice larger than the respective curve in Figure 11a.

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As shown in Figures 11a-b, a good signal-to noise ratio of 50dB was obtained for both quantities. The curves of the present example acquire a sharper peak, as compared to Example 1. This phenomenon is consistent with physiological findings, according to which the resistance to blood flow in the brain is substantially lower than
5   the resistance in the thorax. Thus, in the brain, there is only a small delay in the response to the change of blood flow, as compared to the thorax. The quick response to blood flow is manifested by the measured quantities hence the sharp peaks in the curves of Figure 11a-b.

10   *EXAMPLE 3*

Measurement of Stroke Volume and Cardiac Output Using Four Electrodes

Four electrodes were connected to a human subject, as shown in Figure 4b. The hemodynamic reactance was measured and was used for determining and monitoring (i) stroke volume; and (ii) cardiac output.
15   Figure 12a shows the monitoring results obtained using the prototype system (using the circuitry of Figure 9c) on a time scale of 500 ms/div. Two waveforms are displayed in Figure 12, the change in the change in the hemodynamic reactance and its measured time derivative.

Figure 12b shows a comparison between the CO signal as calculated from the
20   phase shift $\Delta\varphi$ according to the embodiments of the invention, and data acquired from other channels. From top to bottom, Figure 12b shows, as a function of time: ECG lead I (designated I In Figure 12b), ECG lead II (designated II), left blood wave front (L), right blood wave front (R), CO signal (N), first derivative of the CO signal (dN) and second derivative of the CO signal (ddN). As shown in Figure 12b, the
25   embodiments of the present invention provide a high quality signal which enjoys an enhance signal-to-noise ratio and is indicative of the blood flow.

Comparing Figures 12a-b and Figures 10a-b, the use of four electrodes (and the electronic circuitry of Figure 9c) significantly improves of the quality of the results.
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EXAMPLE 4

Measurement of Brain Intra Luminal Blood Volume Change and Flow Rate Using Four Electrodes

Two electrodes were connected to a human subject, as shown in Figure 4f. The hemodynamic reactance was measured and was used for determining and monitoring brain intra luminal blood volume change and flow rate.

Figure 13 show the monitoring results obtained using the prototype system (using the circuitry of Figure 9c) on a time scale of 500 ms/div. Two waveforms are displayed in Figure 13, the change in the hemodynamic reactance and its measured derivative.

As shown in Figures 13, a good signal-to noise ratio of 50dB was obtained for both quantities. As in Example 3 above, a comparison between Figures 13 and 9a-b, reveal a significant improvement of the present example (four electrodes and the circuitry of Figure 9c) over Example 2 (two electrodes and the circuitry of Figure 9b).

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.

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. 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.

The term "comprise" and variants of that term such as "comprises" or "comprising" are used herein to denote the inclusion of a stated integer or integers but not to exclude any other integer or any other integers, unless in the context or usage an exclusive interpretation of the term is required.

Reference to prior art disclosures in this specification is not an admission that the disclosures constitute common general knowledge in Australia.

The claims defining the invention are as follows:

1.   A method of calculating blood flow in an organ of a subject using output radiofrequency signals transmitted to the organ and input radiofrequency signals received from the organ, the method comprising determining a phase shift of the input radiofrequency signals relative to the output radiofrequency signals and using said phase shift to calculate the blood flow in the organ based on a linear relationship between said phase shift and the blood flow.

2.   The method of claim 1, wherein a proportion coefficient of said linear relationship comprises a systolic ejection time of a heart of the subject.

3.   An apparatus for calculating blood flow in an organ of a subject from output radiofrequency signals transmitted to the organ and input radiofrequency signals received from the organ, the apparatus comprising a signal processing unit for determining a phase shift of the input radiofrequency signals relative to the output radiofrequency signals, and a blood flow calculator for calculating the blood flow in the organ using a linear relationship between said phase shift and the blood flow.

4.   The apparatus of claim 3, wherein a proportion coefficient of said linear relationship comprises a systolic ejection time of a heart of the subject.

5.   A system for measuring blood flow in an organ of a subject, the system comprising:

a radiofrequency generator for generating output radiofrequency signals;

a plurality of electrodes, designed to be connectable to the skin of the subject, said electrodes being for transmitting said output radiofrequency signals to the organ and for sensing input radiofrequency signals of the organ; and

the apparatus of claim 3.

6.   The system of claim 5, wherein said signal processing unit comprises an envelope elimination unit designed and configured to reduce or eliminate amplitude modulation of said input radiofrequency signals so as to provide input radiofrequency signals of substantially constant envelope.

7.   The system of claim 6, wherein said envelope elimination unit is designed and configured to maintain a phase modulation of said input radiofrequency signals.

8.   The system of claim 6, wherein said envelope elimination unit comprises a limiter amplifier.

9.   The system of claim 5, wherein said signal processing unit comprises:

a mixer, electrically communicating with said radiofrequency generator and at least a portion of said plurality of electrodes, said mixer being designed and configured to mix said output radiofrequency signals and said input radiofrequency signals, to provide a mixed radiofrequency signal being indicative of the blood flow; and

electronic circuitry for filtering out a portion of said mixed radiofrequency signal so as to substantially increase a signal-to-noise ratio of a remaining portion of said mixed radiofrequency signal.

10.   The system of claim 9, wherein said mixer is operable to provide a radiofrequency sum and a radiofrequency difference and said electronic circuitry comprises a low pass filter for filtering out said radiofrequency sum.

11.   The system of claim 9, wherein said electronic circuitry comprises an analog amplification circuit for amplifying said remaining portion of said mixed radiofrequency signal.

12.   The system of claim 9, wherein said electronic circuitry comprises a digitizer for digitizing said remaining portion of said mixed radiofrequency signal.

13. The system of claim 9, further comprising a data processor for calculating at least one quantity using said remaining portion of said mixed radiofrequency signal, said at least one quantity being selected from the group consisting of a stroke volume, a cardiac output, a brain intra luminal blood flow and an artery blood flow rate.

14. The system of claim 13, wherein said artery blood flow rate is selected from the group consisting of an external carotid blood flow rate, an internal carotid blood flow rate, an ulnar blood flow rate, a radial blood flow rate, a brachial blood flow rate, a common iliac blood flow rate, an external iliac blood flow rate, a posterior tibial blood flow rate, an anterior tibial blood flow rate, a peroneal blood flow rate, a lateral plantar blood flow rate, a medial plantar blood flow rate, a deep plantar blood flow rate.

15. A method of measuring blood flow in an organ of a subject, the method comprising:

generating output radiofrequency signals;

transmitting said output radiofrequency signals to the organ and sensing input radiofrequency signals of the organ; and

determining a phase shift of said input radiofrequency signals relative to said output radiofrequency signals and using said phase shift to calculate the blood flow in the organ, based on a linear relationship between said phase shift and the blood flow.

16. The method of claim 15, wherein a proportion coefficient of said linear relationship comprises a systolic ejection time of a heart of the subject.

17. The method of claim 15, further comprising reducing or eliminating amplitude modulation of said input radiofrequency signals, so as to provide input radiofrequency signals of substantially constant envelope.

18. The method of claim 15, further comprising mixing said output radiofrequency signals and said input radiofrequency signals so as to provide a mixed radiofrequency signal being indicative of the blood flow, and filtering out a portion of

said mixed radiofrequency signal so as to substantially increase a signal-to-noise ratio of a remaining portion of said mixed radiofrequency signal.

19.   The method of claim 18, wherein said mixing comprises providing a radiofrequency sum and a radiofrequency difference.

20.   The method of claim 19, wherein said filtering said portion of said mixed radiofrequency signal is by a low pass filter designed and constructed for filtering out said radiofrequency sum.
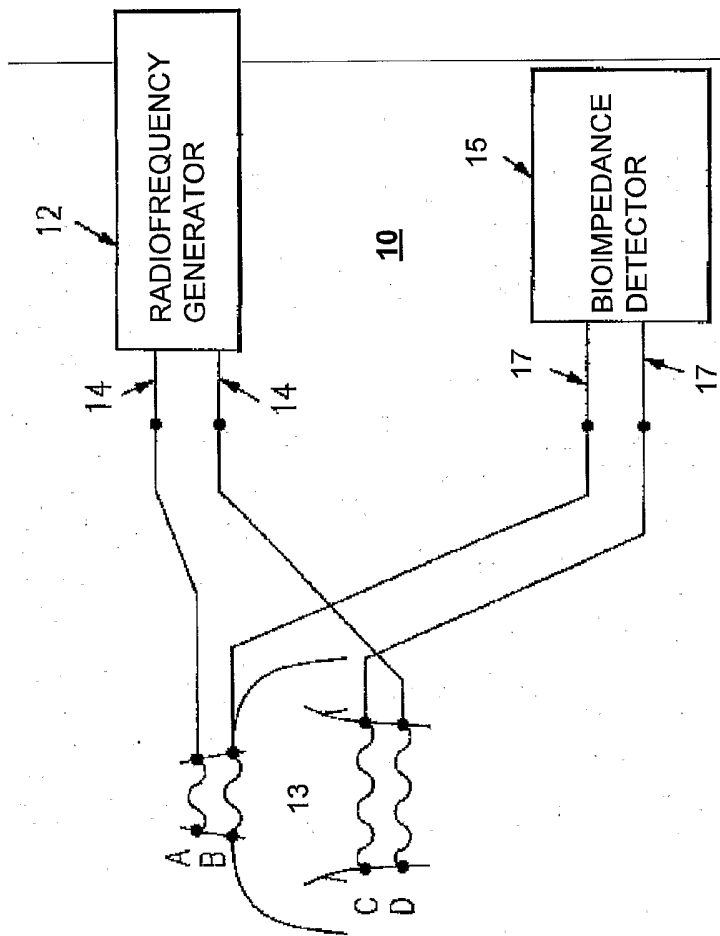
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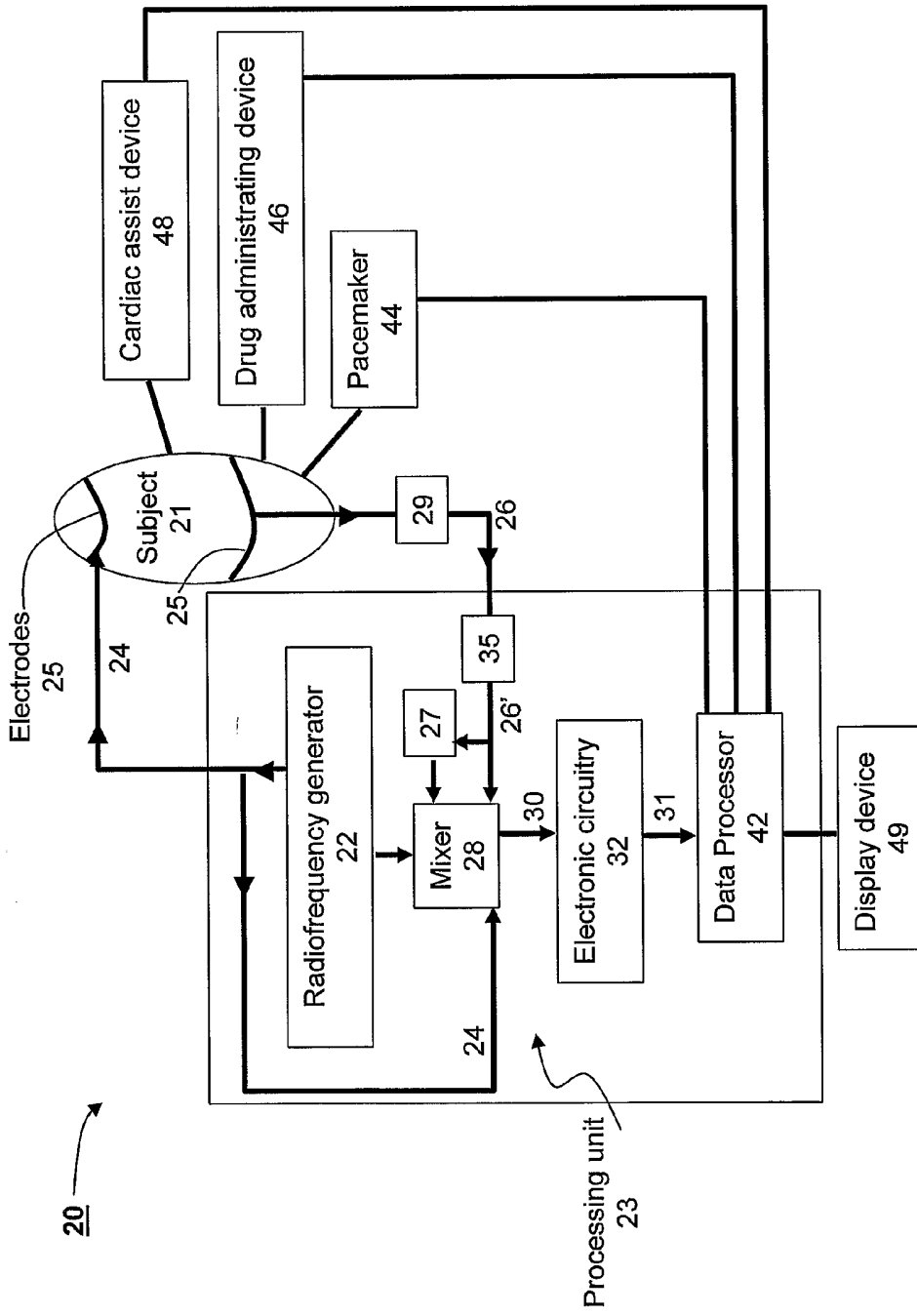
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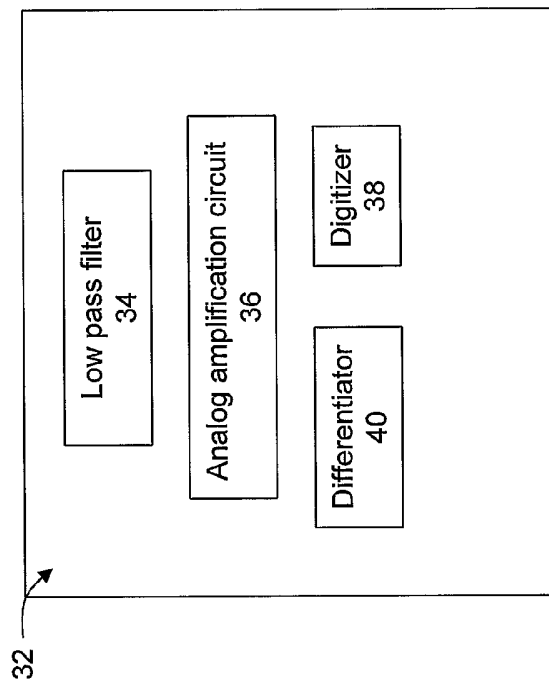
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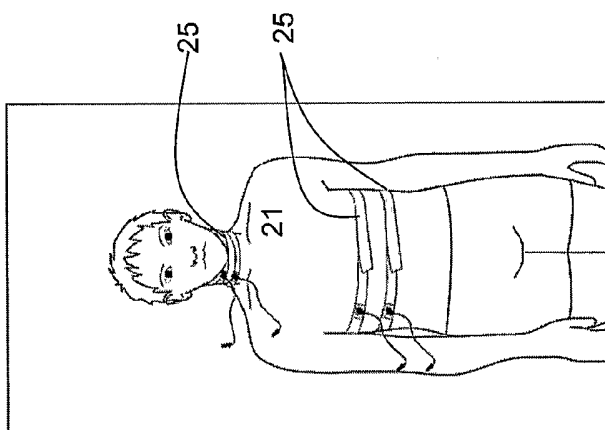
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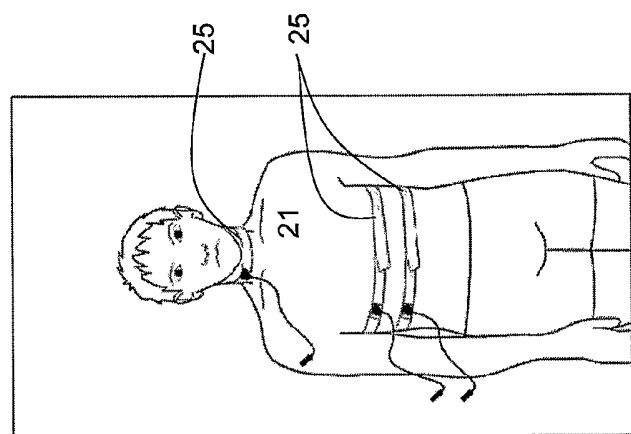
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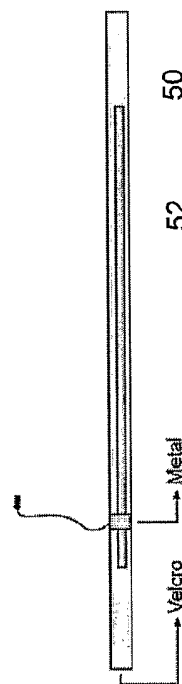
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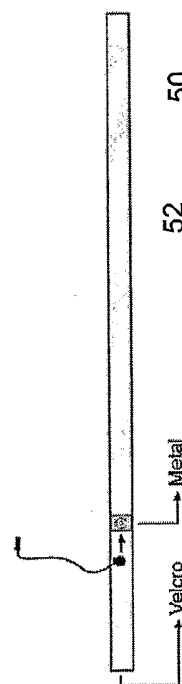
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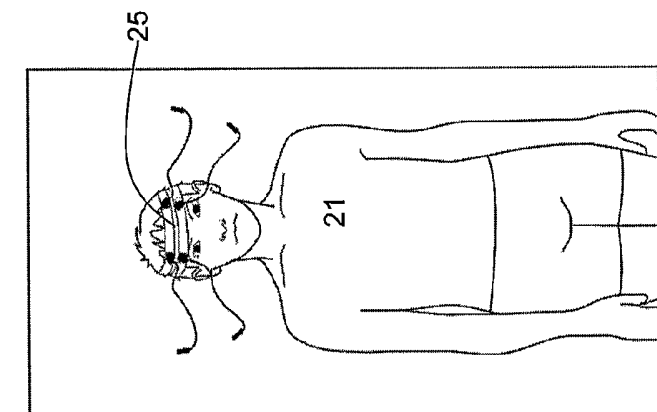
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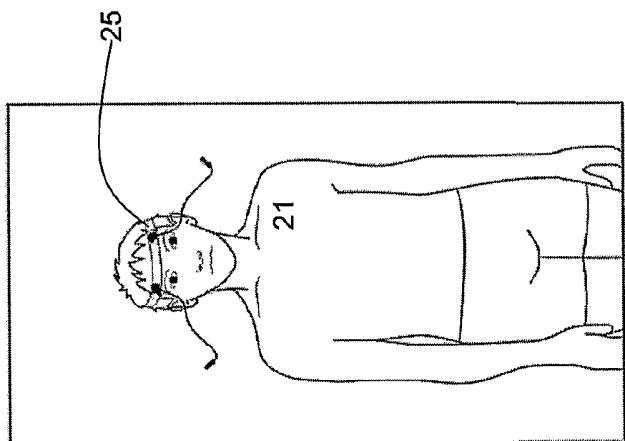
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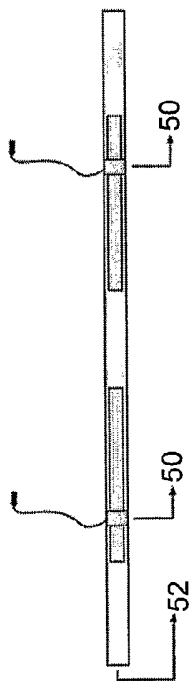
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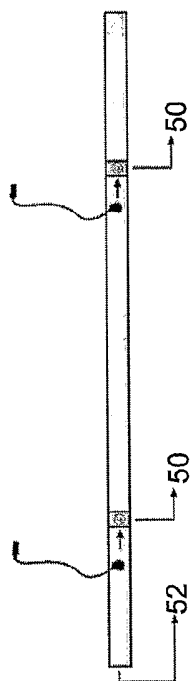
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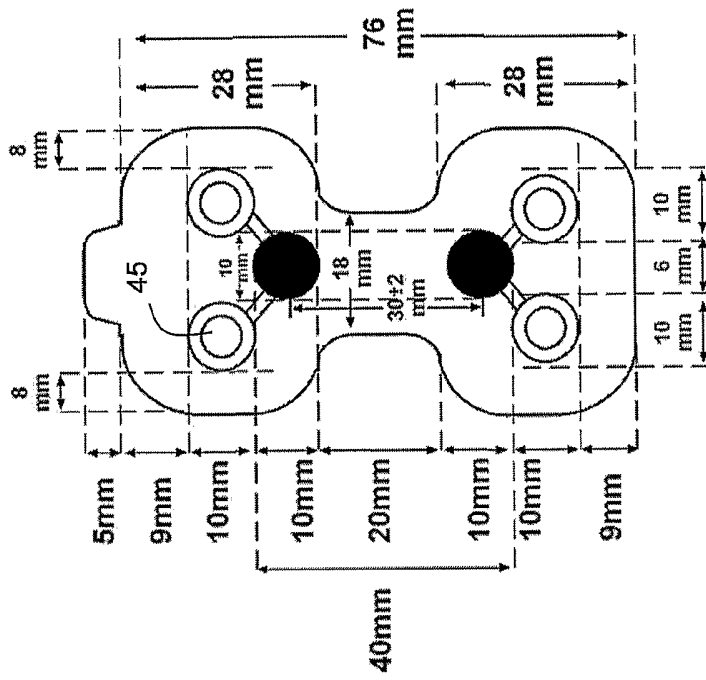
Fig. 4j

Fig. 4i

Fig. 4L

Fig. 4K

Fig. 5

signal processing unit
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Blood flow calculator
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Fig. 6

Fig. 7

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72
Generating output radiofrequency signals

74
Transmitting the output signals and sensing input signals of the organ

76
Mixing the output signals and the input signals

78
Filtering out a portion of the mixed signal

75
Determining a phase shift
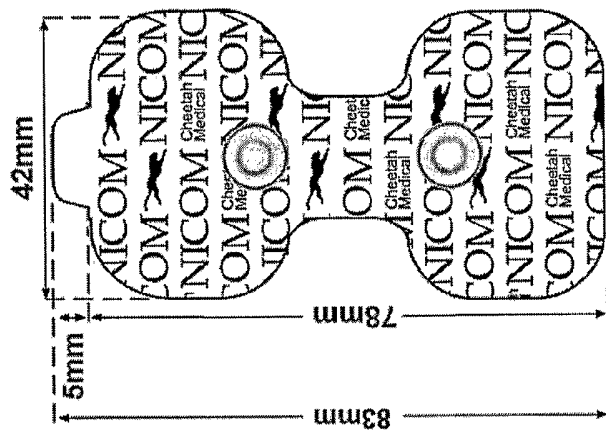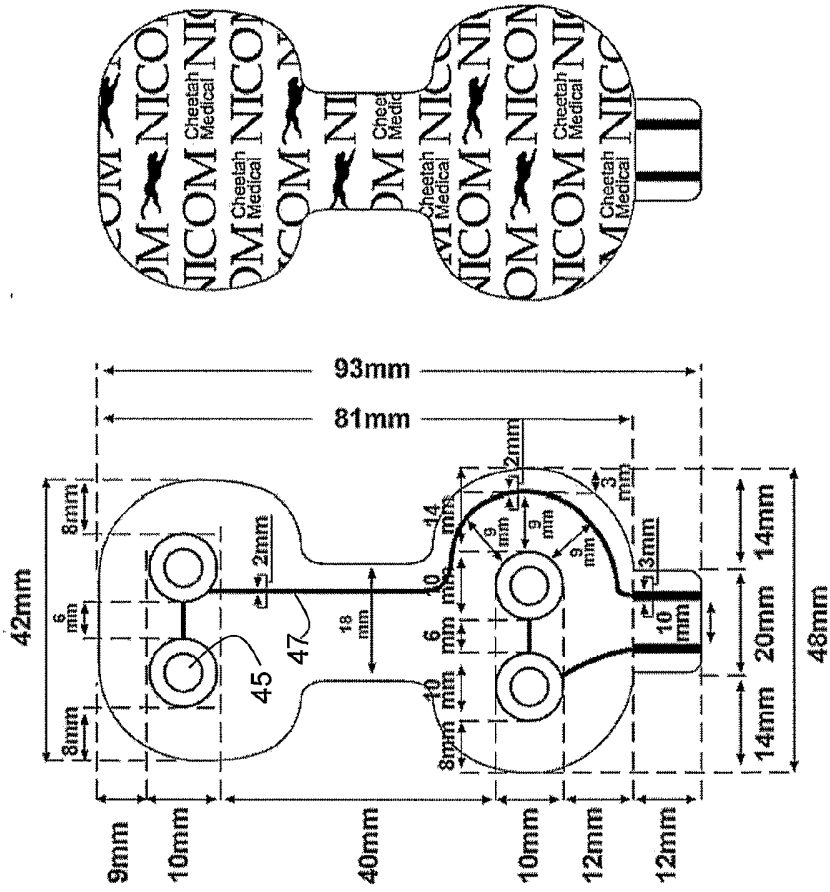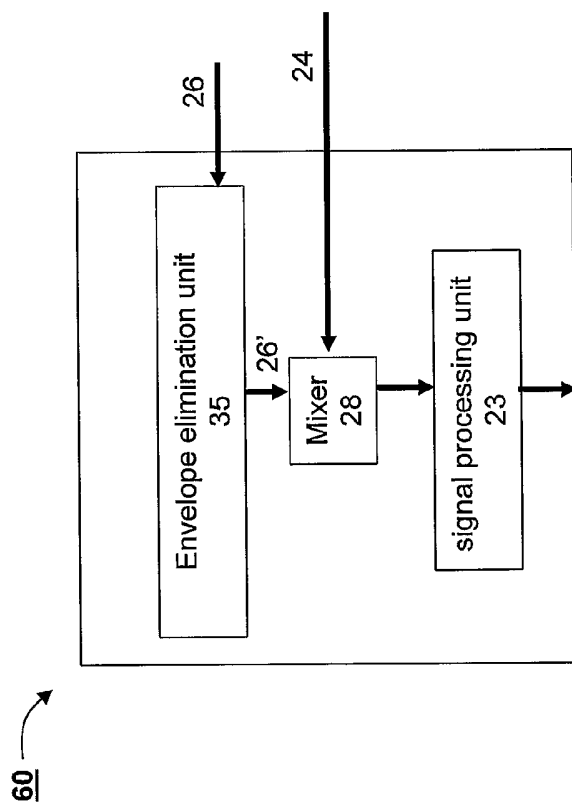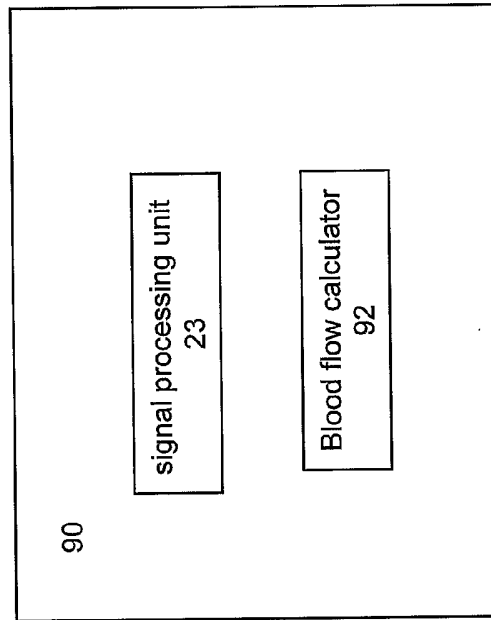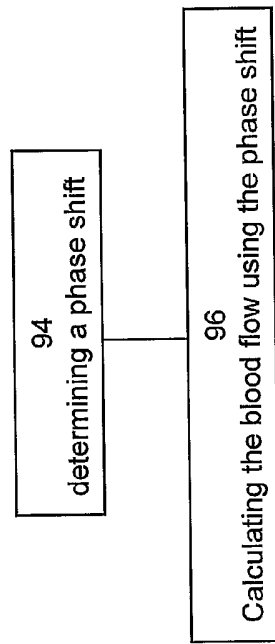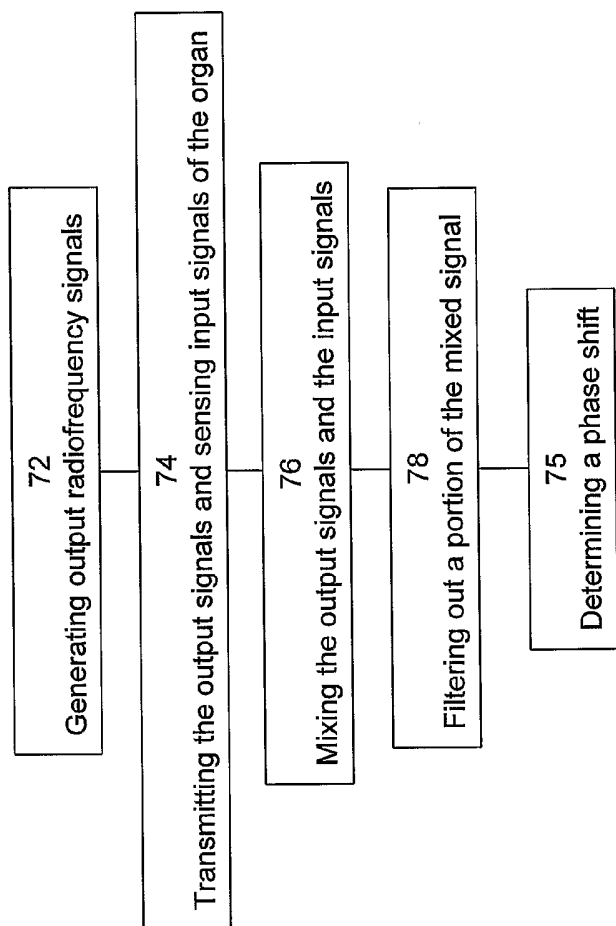
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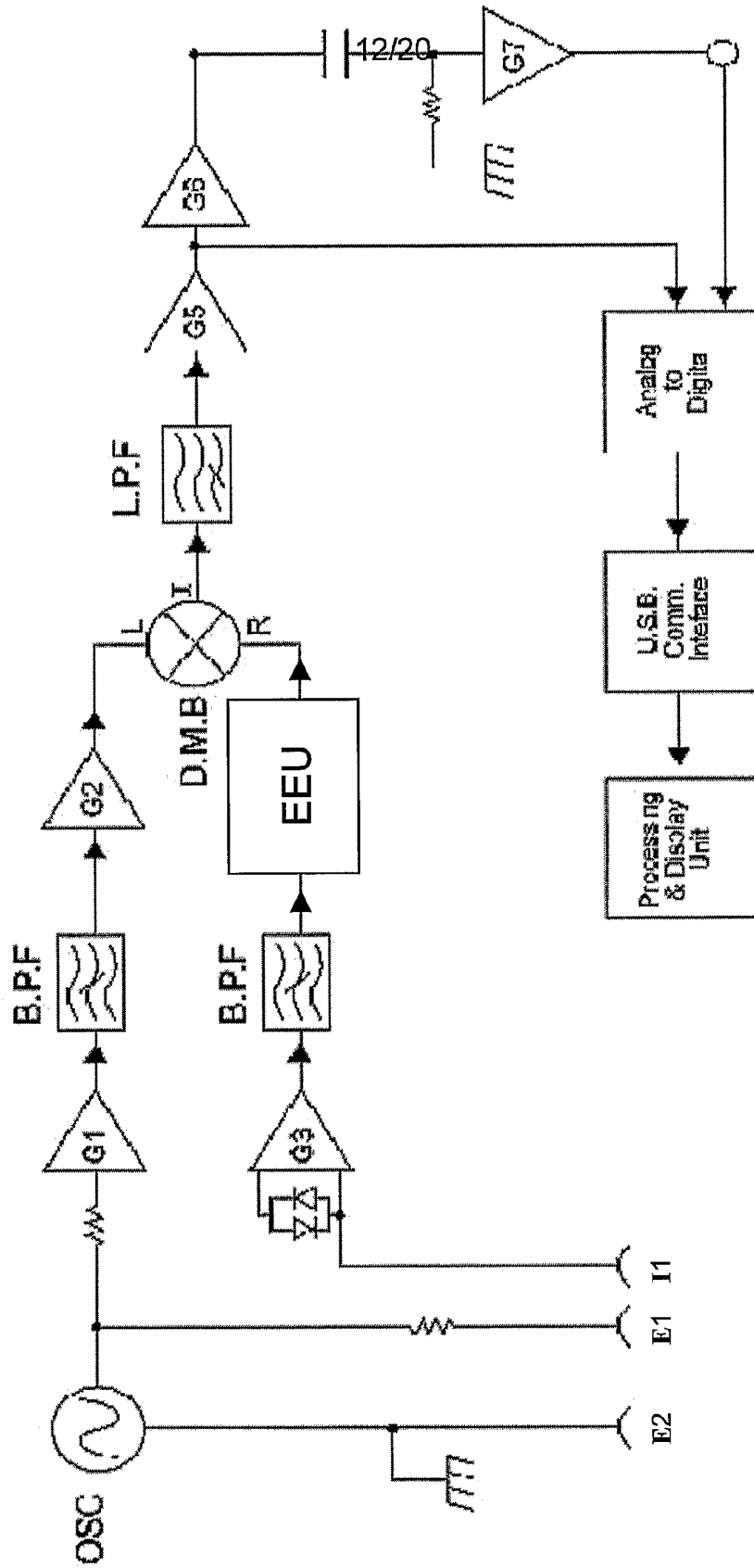
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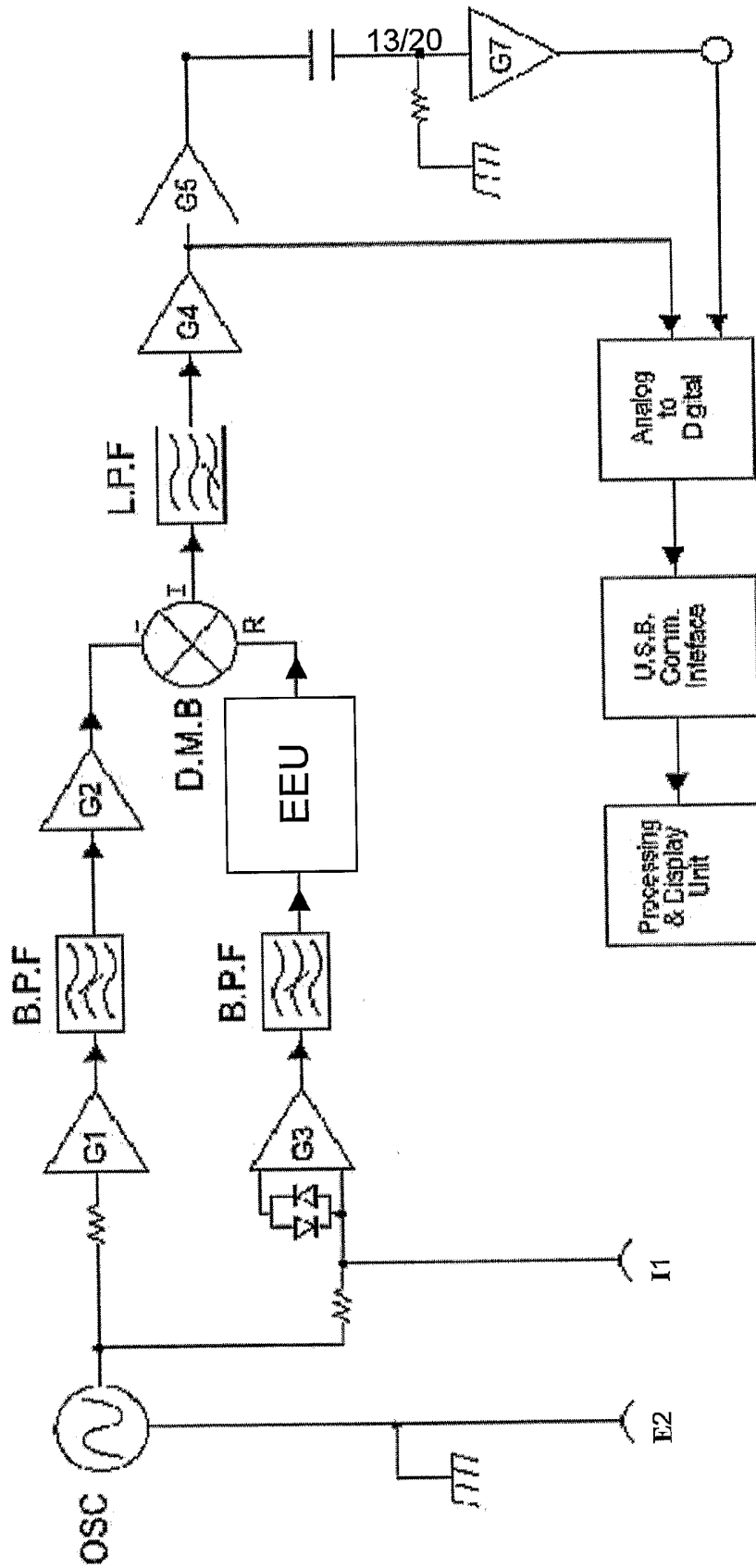
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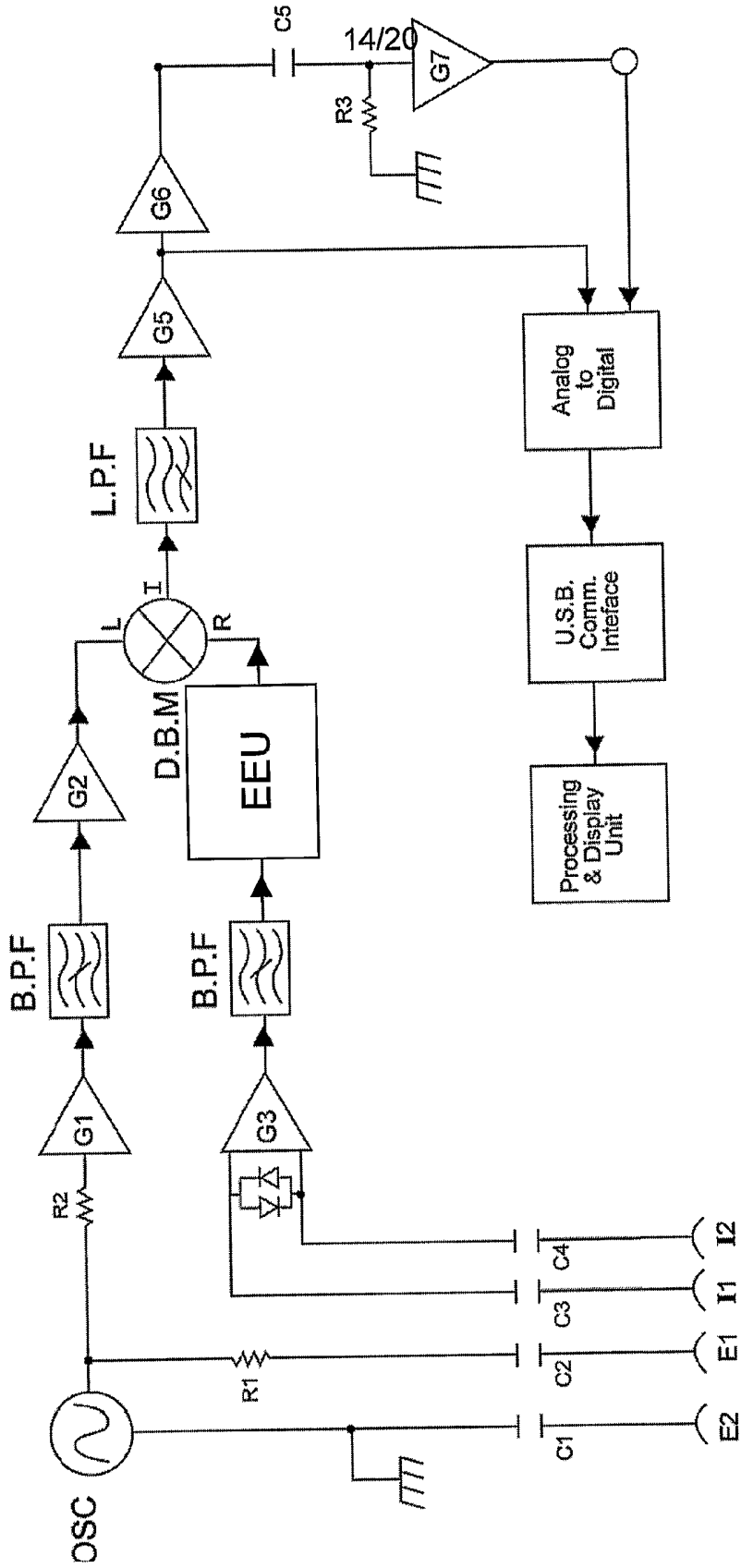
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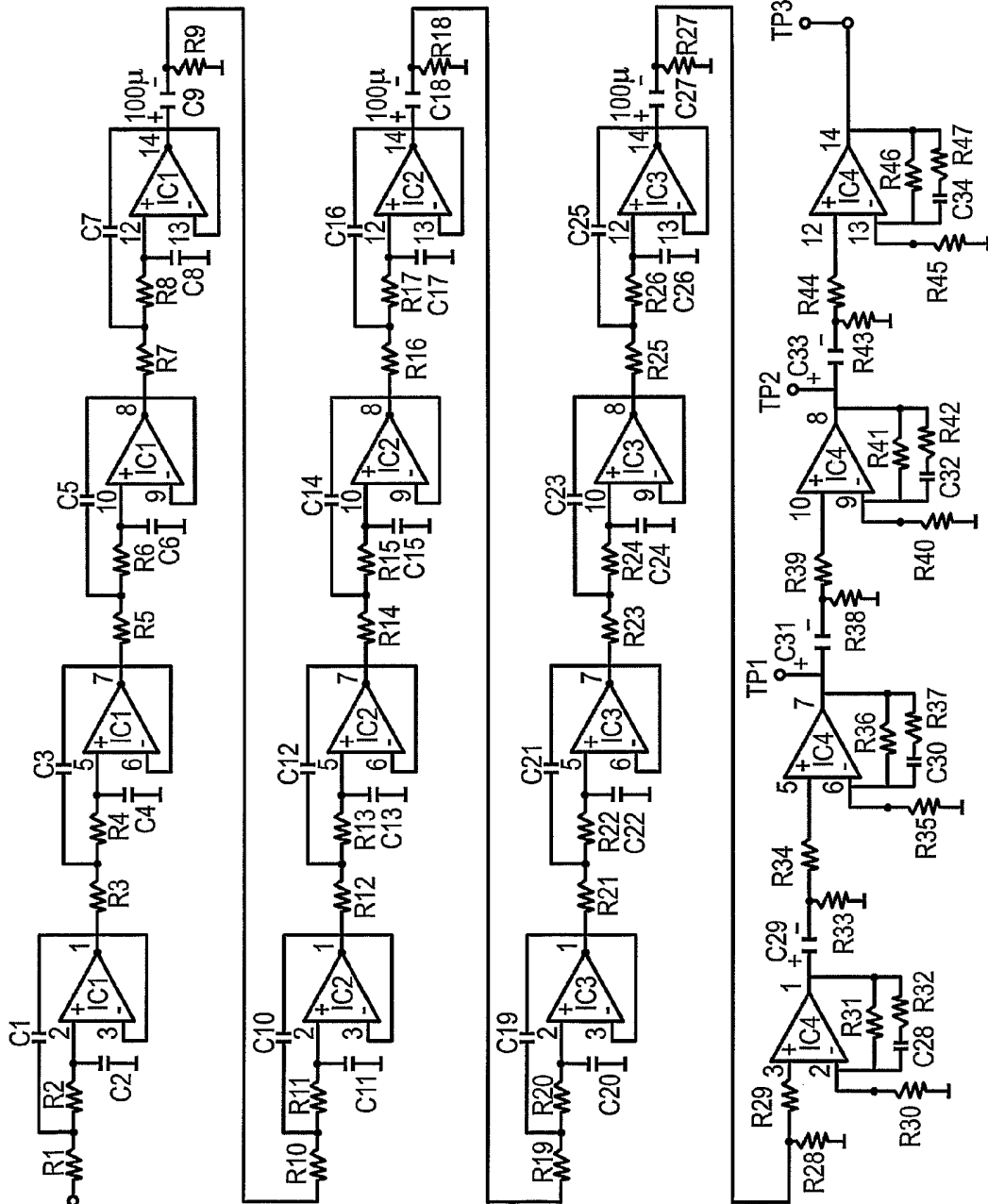
Fig. 9d

Fig. 10a

Fig. 10b

Fig. 10c

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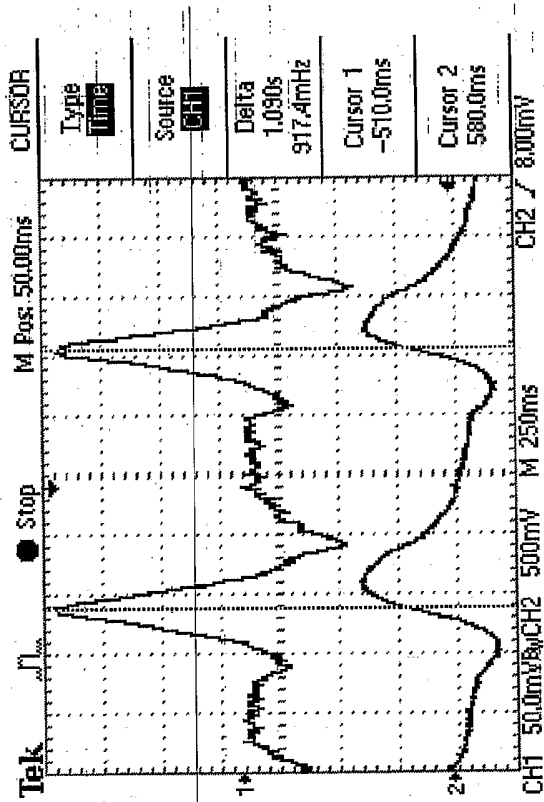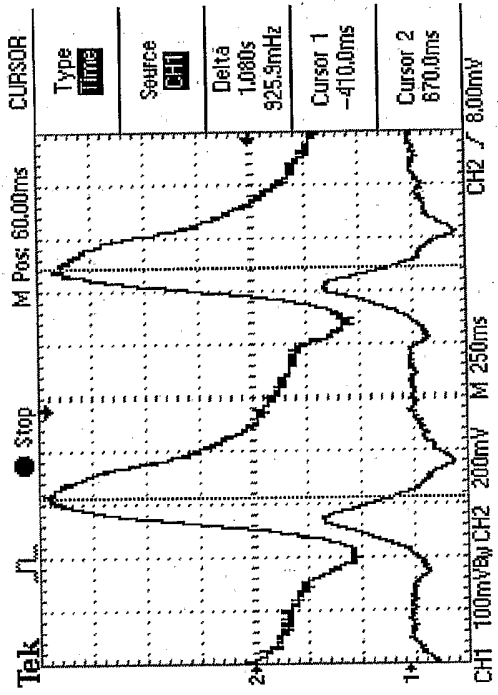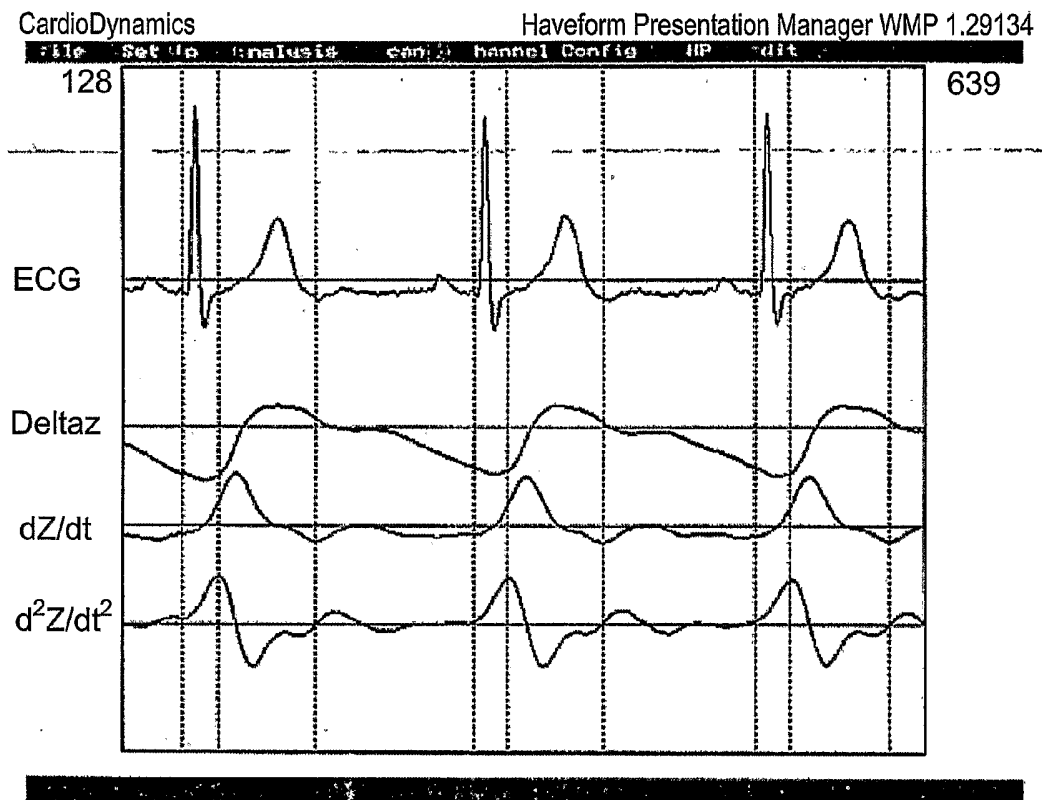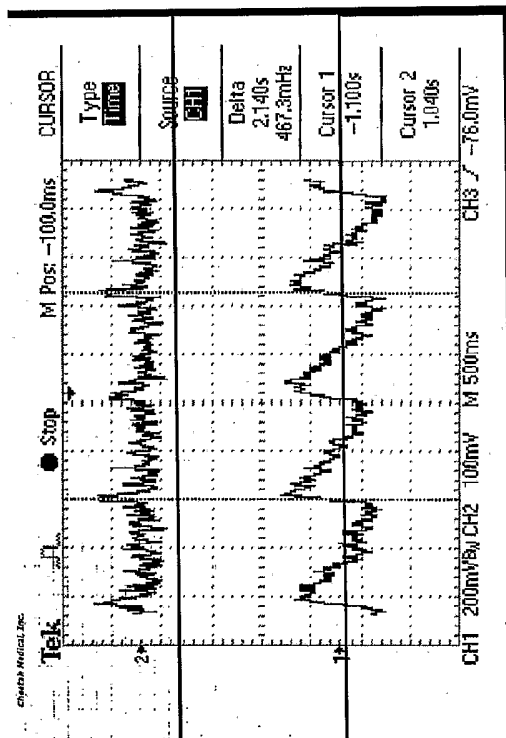
Fig. 11a

Fig. 11b

Fig. 12a

Fig. 12b

Fig. 13