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(54) Title: MONITORING OF ACUTE STROKE PATIENTS

(57) Abstract: A method of monitoring an acute stroke patient, comprising: a) obtaining signals of impedance plethysmography (IPG), photoplethysmography (PPG) or both, in the patient, at least once an hour, for at least six hours; b) processing the one or more signals to obtain one or more measures of cerebral hemodynamics of the patient; c) applying a rule about alerting or not alerting medical personnel based on any of values, amount of change, and direction and rate of change of the measures.

MONITORING OF ACUTE STROKE PATIENTS

RELATED APPLICATION/S

This application is related to two other PCT patent applications filed on even date, one titled "Measurement of Cerebral Hemodynamic Parameters," with attorney docket number 47320, and one titled "Diagnosis of Acute Strokes," with attorney docket number 44066.

This application claims benefit under 35 USC 119(e) from US provisional application 61/103,287, filed October 7, 2008. That application is related to PCT patent application PCT/IL2007/001421, filed November 15, 2007, which takes priority from US patent application 11/610,553, filed on December 14, 2006, which claims priority from, and is a continuation-in-part of, PCT patent application PCT/IB2006/050174, filed January 17, 2006, which is a continuation-in-part of two related PCT patent applications PCT/IL2005/000631 and PCT/IL2005/000632, both filed June 15, 2005. Those PCT applications are both continuations-in-part of US patent application 10/893,570, filed July 15, 2004, which is a continuation-in-part of PCT patent application PCT/IL03/00042, filed January 15, 2003, which claims benefit under 35 USC 119(e) from US provisional patent application 60/348,278, filed January 15, 2002.

The contents of all of the above documents are incorporated by reference as if fully set forth herein.

FIELD AND BACKGROUND OF THE INVENTION

The present invention, in some embodiments thereof, relates to a method of monitoring acute stroke patients using impedance plethysmography (IPG) and/or photoplethysmography (PPG) and, more particularly, but not exclusively, to monitoring ischemic stroke patients and sub-arachnoid hemorrhage (SAH) patients for significant changes in cerebral hemodynamic parameters.

A number of cerebral hemodynamic parameters may be clinically useful for diagnosing strokes, trauma, and other conditions that can affect the functioning of the cerebrovascular system. These parameters include regional cerebral blood volume, cerebral blood flow, cerebral perfusion pressure, mean transit time, time to peak, and intracranial pressure. Many methods that are used to measure these parameters, while

giving accurate results, are not practical to use for continuous monitoring, or for initial diagnosis outside a hospital setting, because they are invasive, or because they require expensive and/or non-portable equipment. Such methods include inserting a probe into the cerebrospinal fluid or into an artery, computed tomography (CT), perfusion computed tomography (PCT), positron emission tomography (PET), magnetic resonance imaging (MRI), and transcranial Doppler ultrasound (TCD). Some of this prior art is reviewed in US patent application 11/610,553, published as US2007/0287899 and WO2008/072223, and in the other related applications listed above.

The use of perfusion computed tomography for finding cerebral hemodynamic parameters, and the use of these parameters in evaluating and choosing courses of treatment for stroke patients, is described by Christian Baumgartner et al, "Functional Cluster Analysis of CT Perfusion Maps: A New Tool for Diagnosis of Acute Strokes," J. of Digital Imaging **18**, 219-226 (2005); by Roland Bruening, Axel Kuettner and Thomas Flohr, *Protocols for Multislice CT* (Springer, 2005), especially on page 96; by Ellen G. Hoeffner et al, "Cerebral Perfusion CT: Technique and Clinical Applications," Radiology **231**, 632-644 (2004); and by Hiroshi Hagiwara et al, "Predicting the Fate of Acute Ischemic Lesions Using Perfusion Computed Tomography," J. Comput. Assist. Tomogr. **32**, 645-650 (2008).

A. M. Weindling, N. Murdoch, and P. Rolfe, "Effect of electrode size on the contributions of intracranial and extracranial blood flow to the cerebral electrical impedance plethysmogram," Med. & Biol. Eng. & Comput. **20**, 545-549 (1982) describes measurements of blood flow in the head, using separate current and voltage electrodes on the front and back of the head, and measuring the peak-to-peak change in impedance over a cardiac cycle to find the blood flow. A tourniquet was placed around the head to temporarily stop the scalp blood flow, and then released, in order to determine how much of the measured blood flow was due to scalp blood flow, and how much was due to intracranial blood flow. The scalp blood flow was considered to be completely cut off when there was no detectable variation in the signal from a PPG sensor at the cardiac frequency.

J. Gronlund, J. Jalonen, and I. Valimaki, "Transcephalic electrical impedance provides a means for quantifying pulsatile cerebral blood volume changes following head-up tilt," *Early Human Development* 47 (1997) 11-18, describe electrical impedance

measurements of the head in premature newborn infants. Changes in impedance associated with the cardiac cycle are said to reflect changes in total cerebral blood volume, and earlier papers are referenced which are said to demonstrate this. Variability in impedance, in the range of 1.5 to 4 Hz, was found to decrease by 27%, on average, when the infants' heads were tilted up by 20 degrees. An earlier paper describing related research by the same group is J. Gronlund et al, "High Frequency Variability of Transcephalic Electrical Impedance: A New Parameter for Monitoring of Neonatal Cerebral Circulation?", Proceedings of the Annual International Conference of the Engineering in Medicine and Biology Society, Paris, October 29-November 1, 1992, New York, IEEE, US, Vol. 6 Conf. 14, 29 October 1992, pages 2513-2515.

Rheoencephalography (REG) is a technique that uses bio-impedance measurements of the head to obtain information on about cerebral blood circulation and circulatory problems. Generally, changes in impedance Z across the head, for a particular arrangement of electrodes, are measured as a function of time t over a cardiac cycle, and sometimes over a breathing cycle, due to changes in the volume and distribution of blood in the head. As described by W. Traczewski et al, "The Role of Computerized Rheoencephalography in the Assessment of Normal Pressure Hydrocephalus," *J. Neurotrauma* **22**, 836-843 (2005), REG is commonly used to measure or diagnose problems with circulatory resistance, and problems with arterial elasticity. In patients with normal pressure hydrocephalus, for example, Traczewski et al find two different patterns in Z(t), depending on the elasticity of the small cerebral arteries. The pattern of Z(t) seen in a given patient is said to be useful for making predictions about the likely outcome of different treatments for the hydrocephalus. These patients all had similar, normal values of ICP.

G. Bonmassar and S. Iwaki, "The Shape of Electrical Impedance Spectrosopy (EIS) is altered in Stroke Patients," Proceedings of the 26th Annual Conference of IEEE EMBS, San Francisco, CA, USA, September 1-5, 2004, describes a system that uses electrical impedance to measure an asymmetry in the distribution of cerebral spinal fluid that is present in stroke patients, but not in healthy volunteers. The system uses 10 electrodes placed symmetrically around the subject's head, and passes white noise current at 0 to 25 kHz between any selected pair of electrodes, while measuring the potentials at all the electrodes. The system was found to work best if current was passed

between the front and back of the head, but the paper also describes passing current between symmetrically placed electrodes on the left and right sides of the head.

WO 02/071923 to Bridger et al describes measuring and analyzing pulse waveforms in the head obtained from acoustic signals. Head trauma patients, and to a lesser extent stroke patients, are found to have differences from normal subjects. Trauma and stroke patients are found to have higher amplitudes at harmonics of the heart rate, at 5 to 10 Hz, than normal subjects do.

Yu. E. Moskalenko et al, "Slow Rhythmic Oscillations within the Human Cranium: Phenomenology, Origin, and Informational Significance," *Human Physiology* **27**, 171-178 (2001), describes the use of electrical impedance measurements of the head, and TCD ultrasound measurements, to study slow waves, at frequencies of 0.08 to 0.2 Hz, that are apparently related to regulation of blood supply and oxygen consumption in the brain, and the circulation of cerebrospinal fluid. The studies were done with healthy subjects and with patients suffering from intracranial hypertension. A. Ragauskas et al, "Implementation of non-invasive brain physiological monitoring concepts," *Medical Engineering and Physics* **25**, 667-687 (2003), describe the use of ultrasound to non-invasively monitor such slow waves, as well as pulse waves at the cardiac frequency, in intracranial blood volume, in head injury patients, and find that they can be used to determine intracranial pressure.

Additional background art includes WO 02/087410 to Naisberg et al; Kidwell CS et al, Comparison of MRI and CT for detection of acute intracerebral hemorrhage. JAMA; 2004: 292: 1823-1830; Horowitz SH et al, Computed tomographic-angiographic findings within the first 5 hours of cerebral infarction, Stroke; 1991: 22 1245-1253; The ATLANTIS, ECASS, and NINDS rt-PA study group investigators, Association of outcome with early stroke treatment: Pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials, Lancet; 363: 768-774; Albers G et al, Antithrombotic and thrombolytic therapy for ischemic stroke: The seventh ACCP conference on antithrombotic and thrombolytic therapy, Chest 2004; 126: 483-512; Kohrmann M et a,. MRI versus CT-based thrombolysis treatment within and beyond the 3 hour time window after stroke onset: a cohort study, Lancet Neurol 2006; 5:661-667; Albers GW et al, Magnetic resonance imaging profiles predict clinical response to early reperfusion: The diffusion and perfusion imaging evaluation for understanding stroke

evolution (DEFUSE) study, Ann Neurol 2006; 60: 508-517; Johnston SC et al, National stroke association guidelines for the management of transient ischemic attacks, Ann Neurol 2006; 60: 301-313.

SUMMARY OF THE INVENTION

An aspect of some embodiments of the invention concerns a method of continuously or frequently monitoring acute stroke patients, using IPG and/or PPG, to estimate cerebral hemodynamic parameters, and to detect changes in these parameters that might require immediate medical intervention.

There is thus provided, in accordance with an exemplary embodiment of the invention, method of monitoring an acute stroke patient, comprising:

a) obtaining signals of impedance plethysmography (IPG), photoplethysmography (PPG) or both, in the patient, at least once an hour, for at least six hours;

b) processing the one or more signals to obtain one or more measures of cerebral hemodynamics of the patient;

c) applying a rule about alerting or not alerting medical personnel based on any of values, amount of change, and direction and rate of change of the measures.

Optionally measuring and applying the rule are done automatically without human intervention.

Optionally, the method also includes performing medical tests or treatment or both, in response to the alerting of medical personnel.

Optionally, the patient is an ischemic stroke patient.

Alternatively, the patient is a sub-arachnoid hemorrhage (SAH) patient.

In an embodiment of the invention, the measures comprise an estimate of one or more of global, hemispheric and regional measures of cerebral blood flow (CBF), of cerebral blood volume (CBV), of mean transit time (MTT), and of time to peak (TTP), and mathematical functions of the foregoing parameters singly or in any combination.

Optionally, the signals comprise at least a first signal obtained from a measurement primarily of the left side of the head, and a second signal obtained from a measurement primarily on the right side of the head that is substantially a mirror image of the first measurement, and processing comprises comparing the first and second signals.

Optionally, the one or more signals comprise at least one signal obtained from an impedance measurement made substantially symmetrically or anti-symmetrically with respect to a bilateral symmetry plane of the patient's head.

In an embodiment of the invention, processing the one or more signals comprises finding an effective rise time interval of a cardiac cycle.

Optionally, the effective rise time interval begins when the signal first reaches a fixed percentage of the full range of the signal, above a minimum value of the signal.

Additionally or alternatively, the effective rise time interval ends when the signal first reaches a fixed percentage of the full range of the signal, below a maximum value of the signal.

Alternatively, the effective rise time interval ends at a maximum slope of the signal, or at a first inflection point of the signal with positive third derivative, or at a first local maximum of the signal, after the beginning of the effective rise time interval.

Optionally, processing the one or more signals comprises finding an integral of the signal over the effective rise time interval.

Optionally, processing the one or more signals comprises comparing the integral of said signal over the effective rise time interval to an integral of said signal over an effective fall time interval of a cardiac cycle.

Alternatively or additionally, processing the one or more signals comprises finding a curvature of the signal during the effective rise time interval.

Optionally, processing comprises normalizing a signal to obtain a measure that does not depend on a degree of amplification of the signal.

Optionally, processing comprises normalizing a time interval to a cardiac cycle period.

Optionally, the method also includes obtaining an electrocardiogram (ECG) signal of the patient, and processing comprises using the ECG signal to calibrate the timing of a feature of an IPG or PPG signal in a cardiac cycle.

Optionally, the measures comprise an estimate of cerebral blood flow, and medical personnel are alerted when the estimate of cerebral blood flow falls by a predetermined relative amount that is at least 10% of an initial value of the estimate of cerebral blood flow.

Additionally or alternatively, the predetermined relative amount is not more than 30% of an initial value of the estimate of cerebral blood flow.

Optionally, the measures comprise an estimate of cerebral blood flow, and medical personnel are alerted when the estimate of cerebral blood flow increases by a predetermined relative or absolute amount.

Optionally, the one or more signals comprise a signal obtained from a measurement made primarily of one side of the head, and processing comprises using at least said signal to find a measure that is an estimate of a hemispheric or regional cerebral hemodynamic parameter on the same side of the head, or on the opposite side of the head.

Optionally, the hemispheric or regional cerebral hemodynamic parameter is on a side of the head in which clinical evidence indicates a stroke occurred.

In an embodiment of the invention, processing comprises:

a) applying a first algorithm to a first one of the signals to calculate a first measure;

b) applying a second algorithm, the same or substantially the same as the first algorithm, to a second one of the signals, to calculate a second measure; and

c) comparing the first measure and the second measure.

Optionally, the first one of the signals is obtained from a measurement made substantially symmetrically on the head with respect to the bilateral symmetry plane, and the second one of the signals is obtained from a measurement made primarily on one side of the head.

Alternatively, the first and second of the signals are both obtained from measurements made primarily on a same side of the head.

Optionally, one of the first and second of the signals is an IPG signal, and the other one is a PPG signal.

There is further provided, according to an exemplary embodiment of the invention, a method of evaluating patients suspected of suffering from an acute stroke, the method comprising:

a) obtaining signals of impedance plethysmography (IPG), photoplethysmography (PPG) or both, in the patient;

b) processing the one or more signals to obtain one or more measures of cerebral hemodynamics of the patient;

c) utilizing at least said measures to evaluate whether the patient suffered from an ischemic stroke for which the patient would be likely to benefit from thrombolytic therapy;

d) treating the patient with thrombolytic therapy if the patient is evaluated to be likely to benefit from it; and

e) monitoring the patient according to the method of claim 1, following the thrombolytic therapy.

There is further provided, in accordance with an exemplary embodiment of the invention, a system for monitoring an acute stroke patient, comprising:

a) an electric current source;

b) at least two sensors adapted to be placed on the patient's head, each sensor comprising an IPG electrode structure adapted to pass current from the current source through the head to measure impedance, or comprising a PPG sensor powered by the current source, or both;

c) a controller which receives one or more waveforms of one or more signals from the sensors, processes the waveforms to obtain one or more measures of cerebral hemodynamics of the patient, and applies a rule to decide when to issue a medical alert based on the measures; and

d) an alert device, activated by the controller when the controller issues a medical alert, which alerts medical personnel when it is activated.

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.

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 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. 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 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 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:

FIG. 1 schematically shows a cerebral perfusion monitoring system, monitoring an acute stroke patient in a hospital, according to an exemplary embodiment of the invention ;

FIG. 2 is a flowchart showing a method of monitoring a patient using the system in FIG. 1;

FIG. 3 is a more detailed view schematically showing an exemplary IPG electrode structure and PPG sensor that can be used in the system in FIG. 1, placed on the head of a patient;

FIG. 4 is a more detailed schematic view of the IPG electrode structure shown in FIG. 3;

FIG. 5 is a more detailed schematic view of the PPG sensor shown in FIG. 3; and

FIG. 6A schematically shows IPG and PPG signals for a patient with high global CBV, and FIG. 6B schematically shows IPG and PPG signals for a patient with low global CBV, illustrating a method of analyzing IPG and PPG signals according to an exemplary embodiment of the invention.

DESCRIPTION OF EMBODIMENTS OF THE INVENTION

The present invention, in some embodiments thereof, relates to a method of monitoring acute stroke patients using impedance plethysmography (IPG) and/or photoplethysmography (PPG) and, more particularly, but not exclusively, to monitoring ischemic stroke patients and sub-arachnoid hemorrhage (SAH) patients for significant changes in cerebral hemodynamic parameters.

An aspect of some embodiments of the invention concerns a method of monitoring an acute stroke patient using impedance plethysmography (IPG) and/or photoplethysmography (PPG), to detect significant changes in cerebral hemodynamic parameters that might require medical intervention, and to alert medical personnel when such changes are detected. The patient is monitored continuously, or at least at frequent intervals, for example data is obtained at least once an hour, or at least twice an hour, or at least once every 10 minutes, or every 5 minutes, or every minute. Monitoring at least once an hour may allow medical intervention to be performed successfully, even with a few unsuccessful attempts, within the typical time window of 3 hours before penumbral brain tissue is permanently damaged, and more frequent monitoring is inexpensive and improves the safety margin. The duration of monitoring is at least six hours, or at least 12 hours, or at least 24 hours, or at least 48 hours. Monitoring for these durations covers the periods when patients are most likely to develop complications, following an initial stroke, or following thrombolytic therapy or endovascular procedures for treating a stroke. The longer the time, the less likely complications are to develop.

Continuous monitoring means that once enough IPG and/or PPG data has been accumulated to analyze in order to estimate the cerebral hemodynamic parameters, for example several cardiac cycles worth of data, more data begins to be accumulated

without interruption, in order to make the next estimate of the cerebral hemodynamic parameters.

In an exemplary embodiment of the invention, continuous or frequent monitoring is made practical by the non-invasive nature, lack of ionizing radiation, relatively small size, and/or relatively low cost of the equipment for IPG and PPG measurements, in contrast to prior art methods of measuring cerebral hemodynamic parameters, such as perfusion CT and perfusion MRI, which are not suitable to use for continuous or very frequent monitoring. The timely medical intervention, for example within an hour or less, made possible by such continuous or frequent monitoring can be critical to preventing or minimizing brain damage in the patient. For example, the patient may be an ischemic stroke patient, and a change in cerebral hemodynamic parameters may indicate a hemorrhagic transformation on the ischemia, which is a common complication especially if the patient has received thrombolytic therapy. Other changes in hemodynamic parameters may indicate a new ischemia, or edema, or high blood pressure which can increase the risk of cerebral hemorrhage. Alternatively, the patient is a sub-archnoid hemorrhage (SAH) patient, and a change in cerebral hemodynamic parameters may indicate vasospasm, which is a major cause of mortality and morbidity in SAH patients.

Optionally, values of one or more standard cerebral hemodynamic parameters in clinical use, such as cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit (MTT), and time to peak (TTP), are estimated from IPG and/or PPG signals, and medical personnel are alerted if one or a combination of these standard parameters changes, or fails to change when it was expected to, in a way that indicates medical intervention is needed. Alternatively or additionally, a condition for alerting medical personnel is formulated directly in terms of characteristics of the IPG and/or PPG signals. In either case, this is referred to herein as alerting medical personnel in response to changes in one or more measures of cerebral hemodynamics.

A variety of methods of analyzing IPG and PPG signals may optionally be used to obtain estimate standard parameters or to obtain other measures of cerebral hemodynamics. Typically the measures depend on the behavior of the signal as a function of phase of the cardiac cycle, although measures based on behavior over longer time scales, such as a slow wave amplitude, may also be found. A correlation between

slow wave amplitude and volume of stroke lesion is described, for example, in related provisional application 61/103,287, and in the co-filed application titled "Measurement of Cerebral Hemodynamic Parameters." The signals may be smoothed, or averaged over multiple cardiac cycles, or transformed in other ways, and noisy or outlying cardiac cycles may be excluded. The measures may pertain to an effective rise time interval of the signal during a cardiac cycle, defined in various ways, or to an effective fall time interval. The measures may depend on integrals of the signal, for example integrals over an effective rise time or over the whole cardiac cycle, and may depend on weighted integrals, in which, for example, the signal is weighed with a function that falls off smoothly at the limits of the integral, before performing the integration. Obtaining the measures may involve comparing measures found from substantially the same algorithm applied to different signals, for example comparing IPG and PPG signals, or comparing signals based on data pertaining to different sides of the head, or comparing a signal from data pertaining symmetrically to both sides of the head to a signal from data pertaining to only one side of the head. The measures may be dimensionless, not depending on an amplification gain of the signals. In some embodiments of the invention, ECG data is used in obtaining the measures, for example ECG data is used to calibrate the timing of a feature of the signal relative to the cardiac cycle.

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 set forth in the following description or exemplified by the Examples. The invention is capable of other embodiments or of being practiced or carried out in various ways.

Referring now to the drawings, FIG. 1 illustrates a cerebral perfusion monitoring system 100, being used to monitor an acute stroke patient 102, optionally continuously, while lying on a bed 104, for example in a hospital. Patient 102 is, for example, an ischemic stroke patient, optionally a patient who has received thrombolytic therapy and is particularly prone to developing a cerebral hemorrhage. Alternatively, patient 102 is an SAH patient, who may be prone to vasospasm. A controller 106 is connected to sensors 108, placed on the patient's head, by cables 110. The controller is, for example, a general-purpose computer, or a specially dedicated circuit. The sensors include

electrodes for IPG, and/or PPG sensors, which generate IPG and PPG signals analyzed by controller 106. An example of suitable sensors is shown in more detail below, in FIGS. 3-5. Optionally, an ECG device 112 is connected to ECG electrodes placed on the patient's chest, and ECG data is used by controller 106 in analyzing the signals from sensors 108. Optionally, a display screen 114 displays one or more cerebral hemodynamic parameters or other measures, as a function of time, calculated by controller 106 from the sensor data. Controller 106 activates one or more alert devices 116, for example a flashing light or an audible alarm, to alert medical personnel, if one or more measures of cerebral hemodynamics, calculated by controller 106, change by an amount and in a direction to indicate that the patient requires medical intervention, according to a rule programmed into controller 106. A person responding to the alert may be able to see at a glance the change in the patient's condition that caused the alert, by looking at display screen 114. Optionally, the alert device comprises an on-screen icon or similar element that appears, for example, on a display screen at a nurses' station. Optionally, the on-screen element also provides information about the values of the measures of cerebral hemodynamics that triggered the alert.

Although patient 102 is shown lying down in FIG. 1, system 100 may also be used to monitor patients who are ambulatory.

FIG. 2 shows a flowchart 200 of a method of monitoring a patient, used by system 100. At 202, IPG electrodes and/or PPG sensors are placed on the patient's head. In some embodiments of the invention, electrodes and/or PPG sensors may also be placed on the patient's neck, for example to measure a signal of blood flow in the carotid artery or another artery in the neck. The electrodes and sensors are optionally placed on the patient after admission to the hospital, and optionally after any initial tests are done, such as perfusion CT or MRI imaging, and after any initial treatment is administered, for example thrombolytic therapy. As described in the co-filed application "Diagnosis of Acute Strokes," a cerebral perfusion monitoring system similar to system 100 may also be used to evaluate stroke patients initially, before or upon admission to the hospital, and optionally electrodes and sensors already placed on the patient's head for that purpose are left in place when the patient is transferred to a hospital ward and monitored by system 100. Details of how electrodes and sensors are placed on the patient's head are described below in connection with FIG. 3.

At 204, one or more IPG signals from the IPG electrodes, and/or one or more PPG signals from the PPG sensors, are obtained by controller 106, and are processed by the controller at 206. Exemplary details of how this may be done are given below, under the heading "Exemplary methods of analyzing IPG and PPG signals." Controller 106 calculates from the signals one or more estimated cerebral hemodynamic parameters, such as CBF, CBV, MTT, and TTP, or other measures of cerebral hemodynamics, which can be used to detect medically significant changes in the patient's condition. The inventors have found, in clinical tests, that estimates of regional, hemispheric and global cerebral hemodynamic parameters, calculated from IPG and PPG signals, have correlations of about 0.5 to 0.7 with the same cerebral hemodynamic parameters measured by perfusion CT, across a sample of many different patients, with the parameters varying over a range of a factor of 2 or 3. It is likely that even higher correlations would be found between the estimates and the parameters for a given patient, if the parameters were to change over time.

The estimated cerebral hemodynamic parameters or other measures are optionally recorded at 208. This is done, for example, at regular frequent intervals, and the recorded data is used, for example, to create plots of the measures over time, for display screen 114.

At 210, the current estimates of the parameters or other measures are compared with past values, recorded at 208. If one or more of the measures have changed by too great an amount, either relatively or absolutely, then an alert is optionally given to medical personnel at 212, for example by sounding an alarm. The alert is optionally triggered automatically by controller 106, according to one or more criteria stored in a memory of controller 106, in the form of an algorithm, or a table, or a fuzzy logic condition, etc. The criteria may be personalized for different patients, depending for example on a diagnosis of their condition, or on clinical symptoms, and may be programmable by a physician. For example, an alert may be given if an estimate of CBF, CBV, MTT, or TTP changes by more than 10% of its initial value, or by more than 20%, or by more than 30%, optionally only in a direction that indicates a worsening of the patient's condition, for example a drop in CBF or CBV, or an increase in MTT or TTP. Optionally, the alert is only given if the change persists for a minimum period, for example for at least 1 minute, or at least 5 minutes, or at least 10 minutes, or at least 20

minutes, or at least 30 minutes. Requiring such a waiting period may reduce false alarms, while still allowing a timely medical response when one is needed. An alert may also be given if a cerebral hemodynamic parameter fails to show an improvement in the patient's condition when it is expected to, for example if CBF fails to increase within one hour, or another period, after thrombolytic therapy is administered. An alert may also be given if a cerebral hemodynamic parameter jumps around in value more than usual, for example with at least twice its usual standard deviation, even without showing a trend in one direction, since this may indicate instability and incipient change in cerebral blood circulation.

For some parameters, a change in either direction may be a reason to give an alert. For example, a decrease in CBF may indicate an ischemic stroke, while an increase in CBF may indicate an increase in blood pressure that could increase the chance of a cerebral hemorrhage. Alternatively, an alert is given even for a change in a measure that indicates an improvement in the patient's condition. For example, if the patient received thrombolytic therapy, then an alert may be given if CBF increases to normal levels, indicating that the blocked artery recanalized due to the therapy. In response, perhaps after verifying the recanalization with other tests, the patient may be moved out of the Intensive Care Unit, or his treatment regimen may be changed to reflect the change in risks and tradeoffs.

Optionally, the threshold of change needed to trigger an alert is smaller if the change occurs over a shorter time. Optionally, an alert is given whenever a parameter goes beyond an absolute threshold, regardless of the amount change. Or, an alert is given whenever the parameter either goes beyond an absolute threshold or changes by a certain relative or absolute amount. For example, if an estimated value of regional CBF falls below a certain value, such as 20 milliliters per 100 grams per minute, this may indicate a need for medical intervention, even if the change in regional CBF was not very great. The values of parameters or changes in parameters that trigger an alert optionally depend on the values of one or more other measures of cerebral hemodynamics, or on other medical parameters that are monitored, such as pulse rate, blood pressure, or body temperature.

FIG. 3 shows a combination sensor 300 for a cerebral perfusion monitor system, in place on the head of a patient 302. Another combination sensor 310, optionally a

mirror image of sensor 300, is optionally used on the other side the patient's head, and is mostly hidden in FIG. 3. This sensor design is optionally used for sensors 108 in FIG. 1. Sensor 300 comprises an IPG electrode structure 304, optionally elliptical in shape, and optionally placed at a corner of the patient's forehead, optionally with an electrically conductive gel to assure good electrical contact with the skin. A PPG sensor 306, optionally circular, is optionally placed on the patient's temple. A cable 308 connects sensor 300 to the controller of the cerebral fusion monitor, for example controller 106 in FIG. 1. The cable optionally contains eight wires, including two wires used for electrode 304, and four wires used for PPG sensor 306 (two wires each for a light source and a light detector). Two of the wires in the cable are not used in sensor 300, but are included for use in a new design, under development, that will use two IPG electrodes on each side of the head.

Alternatively, any other design of IPG electrodes and/or PPG sensors, combined in one structure or separate, may be used, including any prior art design or off-the-shelf design for IPG electrodes and/or PPG sensors. The system need not use both IPG electrodes and PPG sensors, but optionally only uses one or the other.

The combination sensors used on the two sides of the patient's head are optionally placed at positions and orientations that are mirror images of each other, or nearly mirror images of each other, with respect to the bilateral symmetry plane of the head. Similarly, the two combination sensors are constructed to be mirror images of each other, or nearly mirror images of each other. Using sensors with such symmetry in design and location has the potential advantage that, by comparing measurements that are substantially mirror images of each other, they can be used to detect even small asymmetries in blood circulation in the head, which could be indicative of a stroke. In cases where the electrode and sensor configurations are said to be "nearly mirror images," the corresponding electrodes and sensors on the two sides of the head are all placed at locations that are mirror images of each other, to within 2 cm, or 1 cm, or 5 mm, or 2 mm, or 1 mm, or to within whatever precision the head is bilaterally symmetric. Alternatively, the corresponding electrodes and sensors are close enough to being placed in mirror image positions, that any differences in left and right hemisphere cerebral hemodynamic parameters inferred from the IPG and PPG signals from those misplaced sensors and electrodes will be small, by at least a factor of 2, or 5, or 10, or

20, compared to real differences in left and right hemisphere cerebral hemodynamic parameters typically found in ischemic stroke patients, or compared to the ranges in the values of these parameters typically seen among a random sample of ischemic stroke patients. Two measurements are "substantially mirror images of each other" if they are made with corresponding sensors and/or electrodes that are nearly mirror images in their configuration. Two measurements that are mirror images of each other, but are not identical, because each of the measurements is asymmetrical with respect to the bilateral symmetry of the head, should produce identical signals if the blood circulation in the head is bilaterally symmetric, as it normally is in a healthy subject. Any differences in such pairs of signals can reveal asymmetries in blood circulation in the head.

In some patients, previous trauma to the scalp or the brain, or previous brain surgery, may cause large asymmetries in the impedance of the head, so that asymmetry in cerebral blood circulation cannot be inferred simply from differences in the impedance signals from two mirror image measurements. Similarly, massive and asymmetric scarring from a burn or other trauma may cause asymmetries in PPG signals from symmetrically placed sensors on opposite sides of the head. Even in these patients, it might be possible to detect changes in the asymmetry of cerebral blood circulation, from changes in a difference between mirror image IPG or PPG signals, if the initial differences are properly calibrated.

In some embodiments of the invention, additional electrodes and/or PPG sensors are used. For example, there may be two electrodes on each side of the head, allowing impedance measurements to be made asymmetrically, for example locally on each side of the head. A number of such options are described in the co-filed application titled "Measurement of Cerebral Hemodynamic Parameters," cited above. As used herein, an impedance measurement is called "asymmetric" if it is neither symmetric (such as current going from the middle of the forehead to the back of the head) or antisymmetric (such as current going from the right temple to the left temple).

FIG. 4 shows electrode structure 304 in more detail. An elliptical ring-shaped current electrode 400 surrounds an elliptical voltage electrode 402. One of the wires in cable 308 connects to the current electrode, which passes current through the head, and one of the wires connects to the voltage electrode, which measures electric potential through a high impedance circuit, and passes very little current. Both are imbedded in an

insulating holder 404, and a connector 406 snaps into a connector on the end of cable 308, shown in FIG. 3. Some of the potential advantages of using a ring-shaped current electrode surrounding a central voltage electrode are described in two related patent applications cited above, US patent application 10/893,570, published as US2005/0054939, and PCT application PCT/IL2005/000632, published as WO2006/011128, although in those applications the electrodes are circular rather than elliptical. The ring-shaped current electrode may produce a broader distribution of current, resulting in more current going through the brain and less current going through the scalp, than if a more compact current electrode of the same area were used. The separate high-impedance voltage electrode, insulated from the current electrode, may effectively measure the voltage drop across the interior of the skull, with relatively little less contribution from the high impedance skin and skull, than if the same electrode were used for passing current and measuring voltage. For safety reasons, the electrodes use a frequency of at least a few kHz, and currents no greater than 2.5 mA. For the test data shown below in the Examples, a frequency of 25 kHz and current of 1 mA or less was used.

FIG. 5 shows a more detailed view PPG sensor 306, showing the surface of the sensor that is in contact with the skin. The sensor comprises a red LED 500, and a photodiode 502, imbedded in an opaque holder 504 that keeps out stray light. A suitable LED is, for example, model TF281-200, sold by III-V Compounds. A suitable photodiode is, for example, model TFMD5000R, also sold by III-V Compounds. Red light from the LED scatters from blood in the skin, with relatively little absorption compared to blue or green light. The amplitude of scattered light detected by the photodiode, which is optionally further shielded from stray light by a red filter that covers it, increases with increasing blood volume in the skin in the immediate vicinity of the LED and photodiode, and exhibits a characteristic rising and falling pattern over a cardiac cycle.

Conditions that can be detected by cerebral perfusion monitor

Among the conditions that system 100 could be used to detect, using the method of flowchart 200, are:

1) New ischemic stroke in an ischemic stroke patient. A new ischemic stroke can cause a sudden decrease in regional and hemispheric CBF, and a corresponding increase in regional and hemispheric TTP, both in the central core of the ischemia where tissue is likely to progress to an infarction, and in the penumbra where blood flow is reduced, but the tissue could recover if the blood clot can be removed. CBV, on the other hand, tends to be low only in the central core of the ischemia, but at near normal levels in the penumbra. A sudden decrease in CBF and increase in TTP, detected by system 100, could indicate a new ischemic stroke, and the magnitude of the decrease in CBV could indicate the relative size of the core and the penumbra. Once medical personnel have been alerted to this possibility in timely fashion, for example within an hour of the occurrence of the ischemia, or within 30 minutes, or 15 minutes, the nature of the event can be verified, and its precise location can be found, by techniques such as perfusion CT and MRI. Particularly if there is a large penumbra, prompt intervention can prevent further damage. For example, an endovascular procedure such as an embolectomy can be used to attempt to remove the blockage. The window of opportunity to remove the blockage, in order to prevent permanent damage to the penumbra, may be about 3 hours.

2) Vasospasm in a SAH patient. Vasospasm, a common complication of SAH, is expected to produce similar effects on cerebral hemodynamic parameters as an ischemic stroke, and its occurrence can be verified, and location found, using CT-Angio imaging, for example. Prompt medical intervention can save viable brain tissue. Possible treatment includes triple H therapy, vasodilator drugs, and endovascular angioplasty.

3) Hyperperfusion in an ischemic stroke patient. An increase in CBF, above normal values, for example by 10%, 20%, 30%, 50% or 100%, may indicate an increase in blood pressure, which can increase the risk of a hemorrhagic transformation of the ischemia, or of a new cerebral hemorrhage. If detected by system 100, and verified by other tests, it can be treated by blood pressure lowering medication.

4) Hemorrhagic transformation of ischemic stroke, or edema. It is expected that a cerebral hemorrhage may gradually decrease CBF, as intracranial pressure builds up, over an hour or several hours for example. Edema may have a similar effect. Any sufficiently large decrease in CBF could be detected by system 100, and once medical personnel are alerted, imaging techniques such as CT or MRI could be used to find the cause, and it can be treated in timely fashion, within an hour or a few hours.

5) Success or failure of thrombolytic therapy in first few hours. Thrombolytic therapy is normally administered intravenously. A patient receiving thrombolytic therapy can be monitored immediately afterward using system 100, to see if the blood clot has dissolved, as indicated by a recovery of CBF for example. If the blood clot fails to dissolve in an hour or two, thrombolytic therapy can be administered again, through a femoral artery, while continuing to monitor the patient by system 100. If the blood clot still fails to dissolve, an endovascular procedure can be used to try to remove the blood clot. This kind of monitoring is sometimes done for very high risk patients, using CT-Angio imaging instead of using system 100 to determine whether the blood clot has dissolved, but that is too expensive to do routinely for most patients. Monitoring using system 100 is much less expensive and can be done routinely for all patients receiving thrombolytic therapy.

Exemplary methods of analyzing IPG and PPG signals

A number of methods of analyzing IPG and PPG signals have been found by the inventors to be useful for estimating standard cerebral hemodynamic parameters, as shown by results of a clinical study described below in the Examples. Most of these methods involve analysis of features of the signal that approximately repeat each cardiac cycle. For those features, noise can optionally be reduced by detrending the signal, so that it is always at the same level at the diastolic point of each cycle, by throwing out noisy or unusual cardiac cycles, and by taking a running average of the signals from multiple cardiac cycles in phase with each other, for example taking a running average over 9 cardiac cycles. As described in related PCT application PCT/IL2007/001421,

cited above, published as WO2008/072223, the result is a relatively low noise signal as a function of cardiac phase, which rises over a relatively short rise time from its minimum value at the diastolic point to a maximum value at the systolic point, and then falls over a longer fall time back to its minimum value at the next diastolic point. Examples of such detrended and averaged IPG and PPG signals are shown below in FIGS. 6A and 6B. The signal used for the analysis need not be a linearly amplified signal coming directly from the IPG electrodes and PPG sensors, but may be nonlinearly distorted in any manner.

An effective robust rise time interval may be defined, which may further reduce the effect of noise on the signal analysis. For example, the robust rise time interval begins when the signal is a certain fraction of its total range (maximum minus minimum) above the minimum value, for example 5% or 10% or 15% or 20% above the minimum. The robust rise time interval optionally ends when the signal first reaches a point a certain fraction of its total range below the maximum, for example 5%, 10%, 15%, 20%, 25% or 30% below the maximum. For the data analyzed below in the Examples, the robust rise time interval is defined as extended from a point 10% above the minimum to a point 20% below the maximum.

Other effective rise times are defined as ending at the point of maximum slope, or at the first local peak. With these definitions of the end of the effective rise time, the rise time interval, and other quantities which depend on it, may be less subject to being changed by noise, than if the rise time were defined as ending at the global maximum of the signal.

Characteristics of the signal in an effective rise time interval may be compared to similar characteristics of the signal in an effective fall time interval, which may optionally be defined as any part of the cardiac cycle excluding the effective rise time interval. For example, a ratio of the effective rise time interval to the effective fall time interval may be calculated, or a ratio of the signal integrated over the effective rise time interval to a ratio of the signal over the effective fall time interval. Such ratios are respectively related in a simple way to the effective rise time normalized to the whole cardiac period, and to the signal integrated over the effective rise time, normalized to the signal integrated over the whole cardiac period. The latter measure has been found to be particularly useful for estimating some standard cerebral hemodynamic parameters, as is described below in the Examples.

Another measure used in the Examples is a normalized curvature of the signal during an effective rise time interval. The curvature is defined, for example, by first fitting the signal during the rise time interval to a straight line, then fitting the signal during the rise time interval to a parabola, and taking the difference in the cardiac phase, or time, where the two fits cross a level halfway between the minimum and maximum of the signal. This difference may be normalized to the length of the rise time interval. This definition of curvature may be less sensitive to noise than simply taking the average second derivative of the signal during an effective rise time interval.

It may be useful to compare measures calculated by the same or substantially the same algorithm from two different signals, and this can serve as a measure based on both signals. (Two algorithms may be considered substantially the same if they yield similar results from a given signal, at least for most signals that are likely to occur.) For example, if the measure for each signal is an effective rise time defined in a particular way, then a measure based on two signals could be the ratio of the effective rise time for the first signal, to the effective rise time defined in the same way, or substantially the same way, for the second signal. Similarly, if the measure for each signal is the normalized signal integrated over the robust rise time described above, then the measure based on both signals could be the ratio of that normalized integral for the first signal, to the normalized integral from the second signal, defined in the same way, or substantially the same way. The two signals could be, for example, an IPG signal and a PPG signal measured on the same side of the head, or an IPG signal measured symmetrically across the head and a PPG signal measured on one side of the head, or two signals of the same modality measured on opposite sides of the head. If the measure only uses a signal measured on one side of the head, then the signal may be on the same side of the head as the suspected stroke, based on clinical data such as hemiplegia, or it may be on the opposite side of the head from the suspected stroke. It should be noted that blood circulation patterns on the side of the head opposite to a stroke are also generally affected by the stroke, because, for example, an ischemia on one side of the head may cause greater than normal blood flow on the other side of the head.

As used herein, a procedure is said to comprise comparing two signals when the procedure comprises calculating a difference between the two signals, or calculating a

ratio of the two signals, or calculating any quantity that depends on how the two signals are different from each other.

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

The terms "comprises", "comprising", "includes", "including", “having” and their conjugates mean "including but not limited to". This term encompasses the terms "consisting of" and "consisting essentially of".

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

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.

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.

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.

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.

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

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.

A clinical study was performed, using stroke patients, in which certain standard cerebral hemodynamic parameters were measured by perfusion CT, and were also estimated using various dimensionless measures based on IPG and PPG signals as functions of cardiac cycle phase. The IPG electrodes and PPG sensors were configured as shown in FIG. 3, and the IPG signals were found using up to 1 mA of current, at about 25 kHz. The signals were detrended, setting their minimum for each cardiac cycle to the same level, and in some but not all cases several consecutive cardiac cycles were averaged together, in phase, to reduce noise while retaining the shape of the signal as a function of cardiac cycle phase. A best linear fit and correlation were calculated for the dimensionless measures based on the IPG and PPG signals, and the values of the

parameters measured by perfusion CT. Correlations found ranged from approximately 0.5 to 0.7, with values of the parameters generally ranging over a factor of about 2 or 3, or occasionally more, among the different patients in the sample. The best linear fits listed here could be used as a starting point for providing estimates of these cerebral hemodynamic parameters from IPG and PPG data. For example, if the normalized integral over the robust rise time is found to be exactly the same for the IPG signal and the PPG signal on the same side of the head as the stroke, then measure #2, in the list below, would be equal to 1.0, and substituting this value for the measure into the best linear fit for measure #2, Measure = –Parameter/6.9 + 1.49, would imply that the value of the parameter, in this case global CBV, is probably about 3.5. Standard units are used for the parameters: milliliters per 100 grams of tissue for CBV, milliliters per 100 grams of tissue per minute for CBF, and seconds for TTP.

1) This measure was the ratio of a measure based on the IPG signal across the head, to a measure based on the PPG signal on the side of the head opposite to the stroke. For each of these signals, the measure was a rise time interval starting at the diastolic point, and ending at the point of maximum slope. This measure was used to estimate the parameter hemispheric CBV on the stroke side. The correlation was R^2 = 0.54, and the best linear fit was:

$$\text{Measure} = \text{Parameter}/4.8 + 0.06$$

with the hemispheric CBV ranging from about 2 to 4.5 milliliters per 100 grams, for the bulk of the patients in the sample.

2) This measure was the ratio of a measure based on the IPG signal across the head, to a measure based on the PPG signal on the same side of the head as the stroke. For each of these signals, the measure was the normalized integral of the signal over the robust rise time interval, defined above. This measure was used to estimate the parameter global CBV. The correlation was $R^2 = 0.72$, and the best linear fit was:

$$\text{Measure} = -\text{Parameter}/6.9 + 1.49$$

with the global CBV ranging from about 2 to 4.5 milliliters per 100 grams, for the bulk of the patients in the sample.

3) This measure was the ratio of a measure based on the IPG signal across the head, to a measure based on the PPG signal on the opposite side of the head from the stroke. For each of these signals, the measure was the normalized integral of the signal

over the robust rise time interval, defined above. This measure was used to estimate the parameter global CBV. The correlation was $R^2 = 0.59$, and the best linear fit was:

$$\text{Measure} = -\text{Parameter}/8.3 + 1.4$$

4) This measure was the normalized integral of the signal over the robust rise time interval, defined above, for the PPG signal on the same side of the head as the stroke. This measure was used to estimate hemispheric CBF on the same side of the head as the stroke. The correlation was $R^2 = 0.56$, and the best linear fit was:

$$\text{Measure} = \text{Parameter}/650 + 0.12$$

with the hemispheric CBF ranging from 13 to 40 milliliters per 100 grams per minute, for the bulk of the patients in the sample.

5) This measure was the normalized integral of the signal over the robust rise time interval, defined above, for the PPG signal on the same side of the head as the stroke. This measure was used to estimate hemispheric TTP on the same side of the head as the stroke. The correlation was $R^2 = 0.56$, and the best linear fit was:

$$\text{Measure} = \text{Parameter}/420 + 0.08$$

with the hemispheric TTP ranging from 20 to 40 seconds, for the bulk of patients in the sample.

6) This measure was the normalized integral of the signal over the robust rise time interval, defined above, for the IPG signal across the head. This measure was used to estimate global TTP. The correlation was $R^2 = 0.46$, and the best linear fit was:

$$\text{Measure} = \text{Parameter}/280 + 0.04$$

with the global TTP ranging from 25 to 35 seconds, for the bulk of the patients in the sample.

7) This measure was the normalized rise time curvature of the signal, defined above, for the PPG signal on the same side of the head as the stroke. This measure was used to estimate the ratio of regional CBF on the same side of the head as the stroke, to global CBF, a quantity with a range of about a factor of 8 over the patients in the sample. The correlation was $R^2 = 0.53$, and the best linear fit was:

$$\text{Measure} = \text{Parameter}/21.6 + 0.017$$

with the ratio of regional to global CBF ranging from 0.1 to 0.8 for the bulk of the patients in the sample.

The relatively high correlations found between the measures of the IPG and PPG signals, and the cerebral hemodynamic parameters, show that it is already feasible to obtain useful estimates of cerebral hemodynamic parameters from IPG and PPG signals. In the near future, when more refined techniques for measuring IPG and PPG signals, and better measures derived from those signals, may be available, even more precise estimates of cerebral hemodynamic parameters may be possible.

FIGS. 6A and 6B show plots of IPG and PPG signals for two ischemic stroke patients who participated in the clinical study. FIG. 6A shows a plot 600 of the IPG signal measured across the head, and a plot 602 of the PPG signal measured on the same side of the head as the stroke, for a patient with unusually high global CBV, 5.3 milliliters per 100 grams of tissue, as measured by perfusion CT. The time is given in minutes, and the amplitudes of the signals are in arbitrary units. Noise has been reduced by taking a running average over 9 cardiac cycles, adding up the different cardiac cycles in phase. FIG. 6B shows a plot 604 of an IPG signal, and a plot 606 of a PPG signal, measured in the same way for a patient with unusually low global CBV, only 2.1 milliliters per 100 grams of tissue. The signals, especially the IPG signal, are visibly very different in the two patients, reflecting the large differences in their global CBV. The differences may be quantified by taking the normalized integral of the signal over a robust rise time, as described above. This quantity is 0.08 for the signal in plot 600, because the signal rises very quickly; 0.14 for the signal in plot 602; 0.21 for the signal in plot 604, which rises much more slowly than the signal in plot 600; and 0.19 for the signal in plot 606. The ratio of this quantity for the two signals provides a measure of 0.6 for the first patient, with global CBV parameter equal to 5.3, and a measure of 1.1 for the second patient, with global CBV parameter equal to 2.1. These quantities fit fairly well with the best linear fit, Measure = –Parameter/6.9 + 1.49, found for this parameter and measure in the clinical study, and one could have inferred the global CBV for these patients to fairly good approximation based on this relationship and on the IPG and PPG signals, even without making the much more expensive perfusion CT measurement.

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. To the extent that section headings are used, they should not be construed as necessarily limiting.

WHAT IS CLAIMED IS:

1. A method of monitoring an acute stroke patient, comprising:
   a) obtaining signals of impedance plethysmography (IPG), photoplethysmography (PPG) or both, in the patient, at least once an hour, for at least six hours;
   b) processing the one or more signals to obtain one or more measures of cerebral hemodynamics of the patient;
   c) applying a rule about alerting or not alerting medical personnel based on any of values, amount of change, and direction and rate of change of the measures.

2. A method according to claim 1, wherein measuring and applying the rule are done automatically without human intervention.

3. A method according to claim 1 or claim 2, also including performing medical tests or treatment or both, in response to the alerting of medical personnel.

4. A method according to any of the preceding claims, wherein the patient is an ischemic stroke patient.

5. A method according to any of claims 1-3, wherein the patient is a sub-arachnoid hemorrhage (SAH) patient.

6. A method according to any of the preceding claims, wherein the measures comprise an estimate of one or more of global, hemispheric and regional measures of cerebral blood flow (CBF), of cerebral blood volume (CBV), of mean transit time (MTT), and of time to peak (TTP), and mathematical functions of the foregoing parameters singly or in any combination.

7. A method according to any of the preceding claims, wherein the signals comprise at least a first signal obtained from a measurement primarily of the left side of the head, and a second signal obtained from a measurement primarily on the right side of the head

that is substantially a mirror image of the first measurement, and processing comprises comparing the first and second signals.

8. A method according to any of the preceding claims, wherein the one or more signals comprise at least one signal obtained from an impedance measurement made substantially symmetrically or anti-symmetrically with respect to a bilateral symmetry plane of the patient's head.

9. A method according to any of the preceding claims, wherein processing the one or more signals comprises finding an effective rise time interval of a cardiac cycle.

10. A method according to claim 9, wherein the effective rise time interval begins when the signal first reaches a fixed percentage of the full range of the signal, above a minimum value of the signal.

11. A method according to claim 9 or claim 10, wherein the effective rise time interval ends when the signal first reaches a fixed percentage of the full range of the signal, below a maximum value of the signal.

12. A method according to claim 9 or claim 10, wherein the effective rise time interval ends at a maximum slope of the signal, or at a first inflection point of the signal with positive third derivative, or at a first local maximum of the signal, after the beginning of the effective rise time interval.

13. A method according to any of claims 9-12, wherein processing the one or more signals comprises finding an integral of the signal over the effective rise time interval.

14. A method according to claim 13, wherein processing the one or more signals comprises comparing the integral of said signal over the effective rise time interval to an integral of said signal over an effective fall time interval of a cardiac cycle.

15. A method according to any of claims 9-14, wherein processing the one or more signals comprises finding a curvature of the signal during the effective rise time interval.

16. A method according to any of the preceding claims, wherein processing comprises normalizing a signal to obtain a measure that does not depend on a degree of amplification of the signal.

17. A method according to any of the preceding claims, wherein processing comprises normalizing a time interval to a cardiac cycle period.

18. A method according to any of the preceding claims, also including obtaining an electrocardiogram (ECG) signal of the patient, wherein processing comprises using the ECG signal to calibrate the timing of a feature of an IPG or PPG signal in a cardiac cycle.

19. A method according to any of the preceding claims, wherein the measures comprise an estimate of cerebral blood flow, and medical personnel are alerted when the estimate of cerebral blood flow falls by a predetermined relative amount that is at least 10% of an initial value of the estimate of cerebral blood flow.

20. A method according to claim 19, wherein the predetermined relative amount is not more than 30% of an initial value of the estimate of cerebral blood flow.

21. A method according to any of the preceding claims, wherein the measures comprise an estimate of cerebral blood flow, and medical personnel are alerted when the estimate of cerebral blood flow increases by a predetermined relative or absolute amount.

22. A method according to any of the preceding claims, wherein the one or more signals comprise a signal obtained from a measurement made primarily of one side of the head, and processing comprises using at least said signal to find a measure that is an

estimate of a hemispheric or regional cerebral hemodynamic parameter on the same side of the head, or on the opposite side of the head.

23. A method according to claim 22, wherein the hemispheric or regional cerebral hemodynamic parameter is on a side of the head in which clinical evidence indicates a stroke occurred.

24. A method according to any of the preceding claims, wherein processing comprises:

a) applying a first algorithm to a first one of the signals to calculate a first measure;

b) applying a second algorithm, the same or substantially the same as the first algorithm, to a second one of the signals, to calculate a second measure; and

c) comparing the first measure and the second measure.

25. A method according to claim 24, wherein the first one of the signals is obtained from a measurement made substantially symmetrically on the head with respect to the bilateral symmetry plane, and the second one of the signals is obtained from a measurement made primarily on one side of the head.

26. A method according to claim 24, wherein the first and second of the signals are both obtained from measurements made primarily on a same side of the head.

27. A method according to any of claims 24-26, wherein one of the first and second of the signals is an IPG signal, and the other one is a PPG signal.

28. A method of evaluating patients suspected of suffering from an acute stroke, the method comprising:

a) obtaining signals of impedance plethysmography (IPG), photoplethysmography (PPG) or both, in the patient;

b) processing the one or more signals to obtain one or more measures of cerebral hemodynamics of the patient;

c) utilizing at least said measures to evaluate whether the patient suffered from an ischemic stroke for which the patient would be likely to benefit from thrombolytic therapy;

d) treating the patient with thrombolytic therapy if the patient is evaluated to be likely to benefit from it; and

e) monitoring the patient according to the method of claim 1, following the thrombolytic therapy.

29. A system for monitoring an acute stroke patient, comprising:

a) an electric current source;

b) at least two sensors adapted to be placed on the patient's head, each sensor comprising an IPG electrode structure adapted to pass current from the current source through the head to measure impedance, or comprising a PPG sensor powered by the current source, or both;

c) a controller which receives one or more waveforms of one or more signals from the sensors, processes the waveforms to obtain one or more measures of cerebral hemodynamics of the patient, and applies a rule to decide when to issue a medical alert based on the measures; and

d) an alert device, activated by the controller when the controller issues a medical alert, which alerts medical personnel when it is activated.

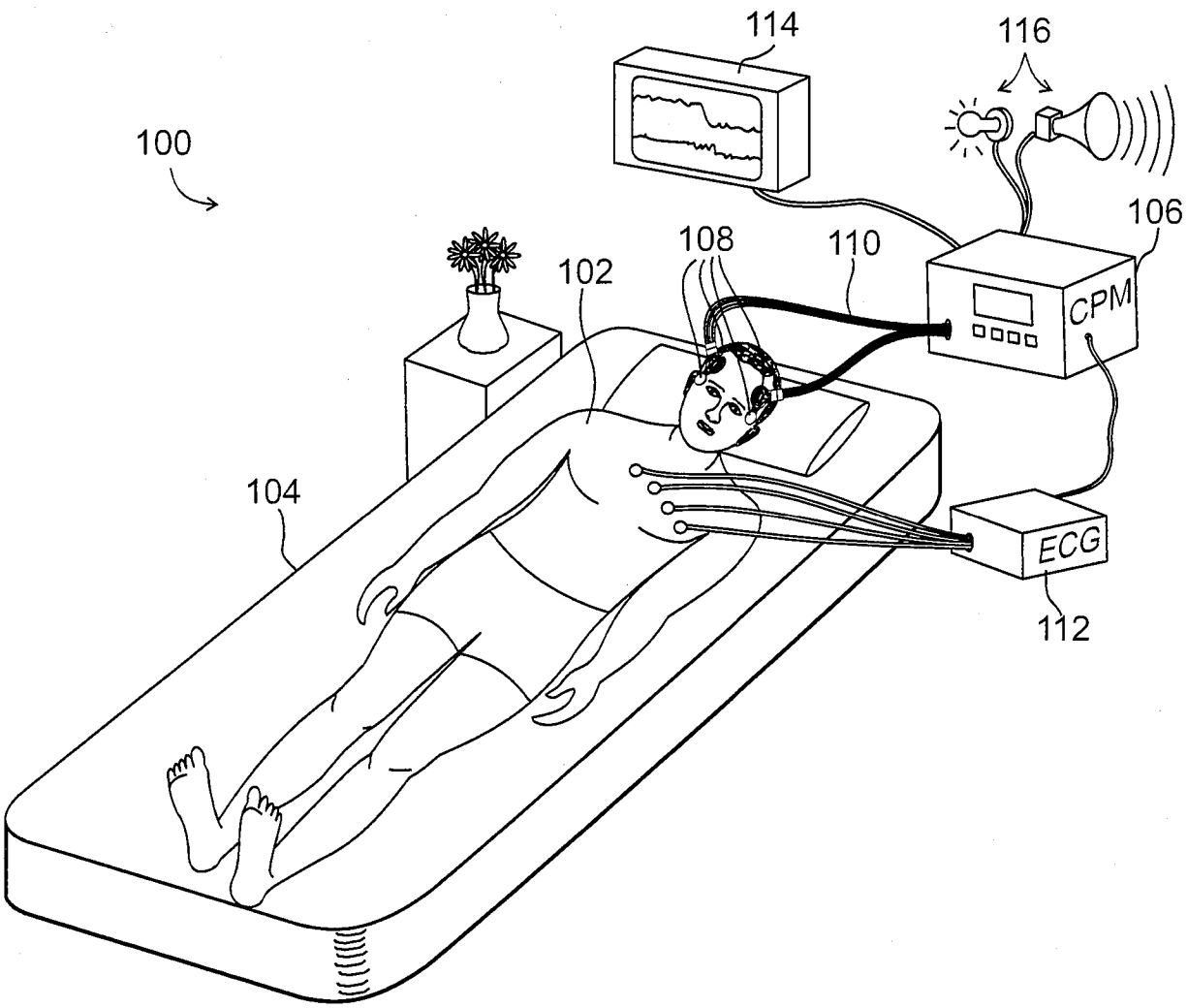


FIG. 1

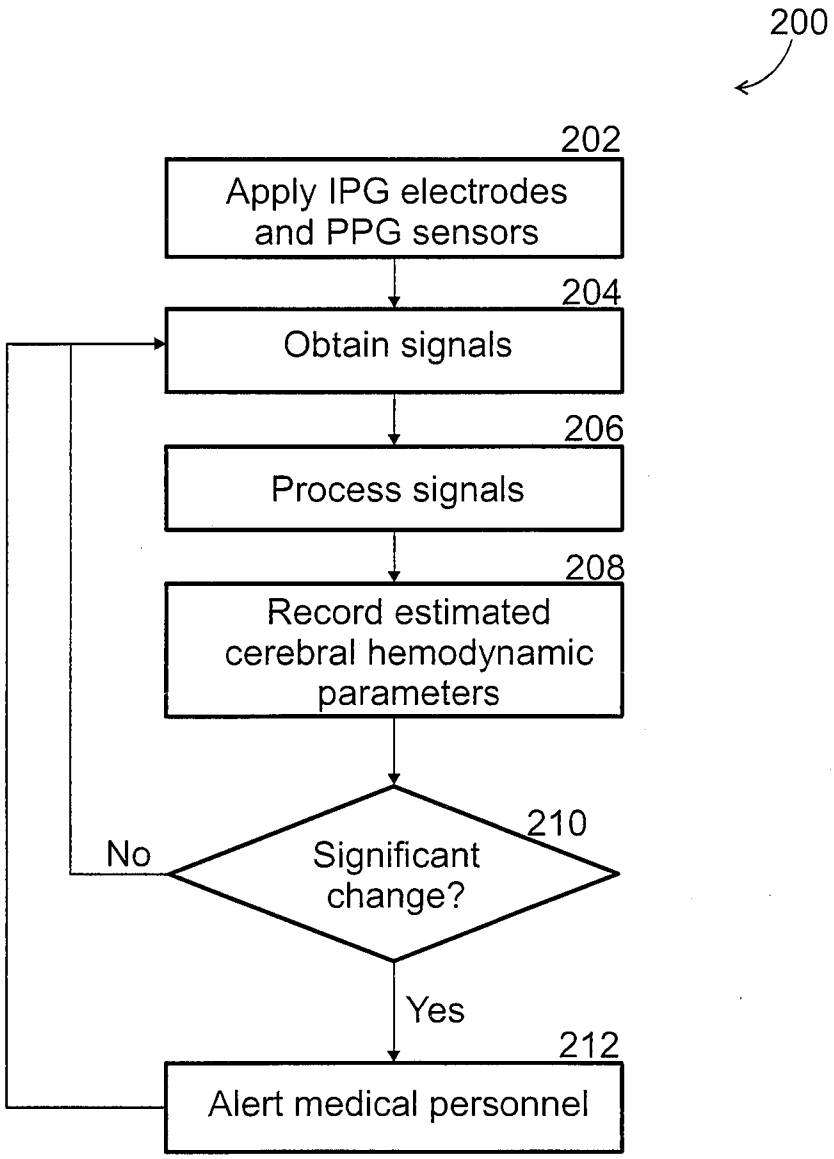

200
202
Apply IPG electrodes and PPG sensors
204
Obtain signals
206
Process signals
208
Record estimated cerebral hemodynamic parameters
210
Significant change?
No
Yes
212
Alert medical personnel

FIG. 2

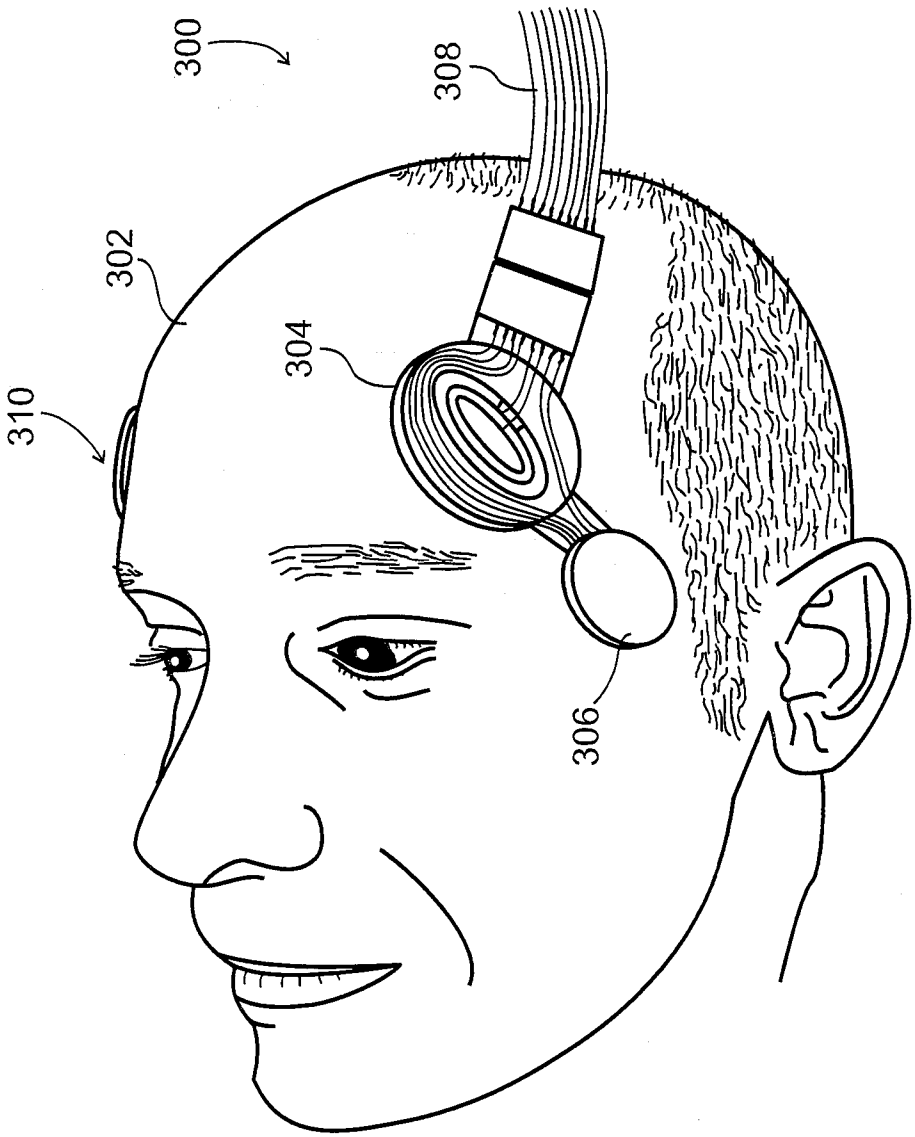


FIG. 3

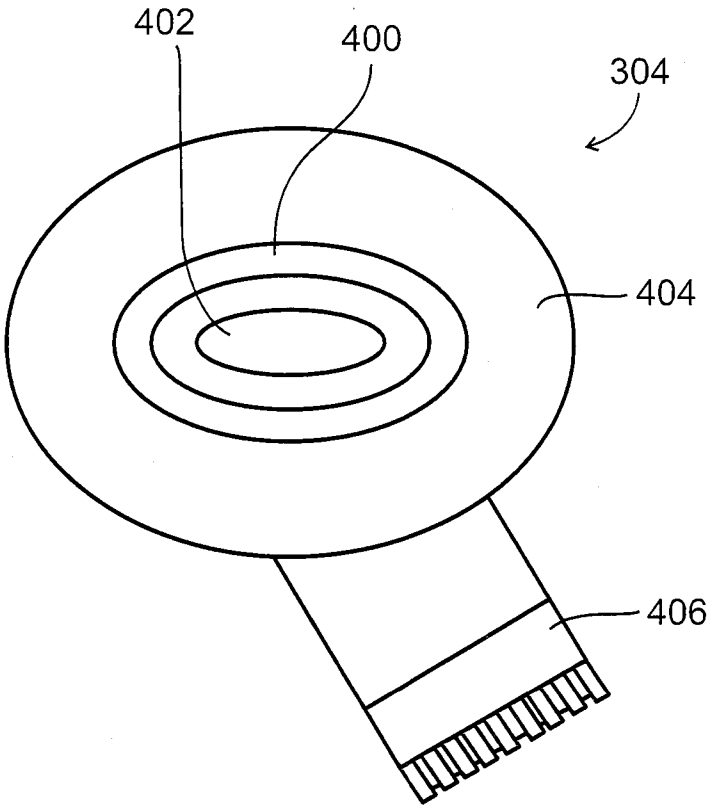


FIG. 4

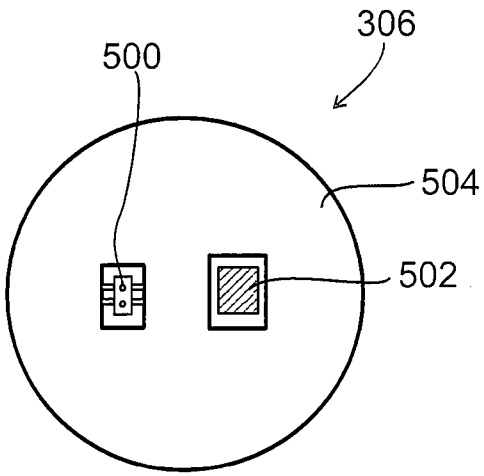
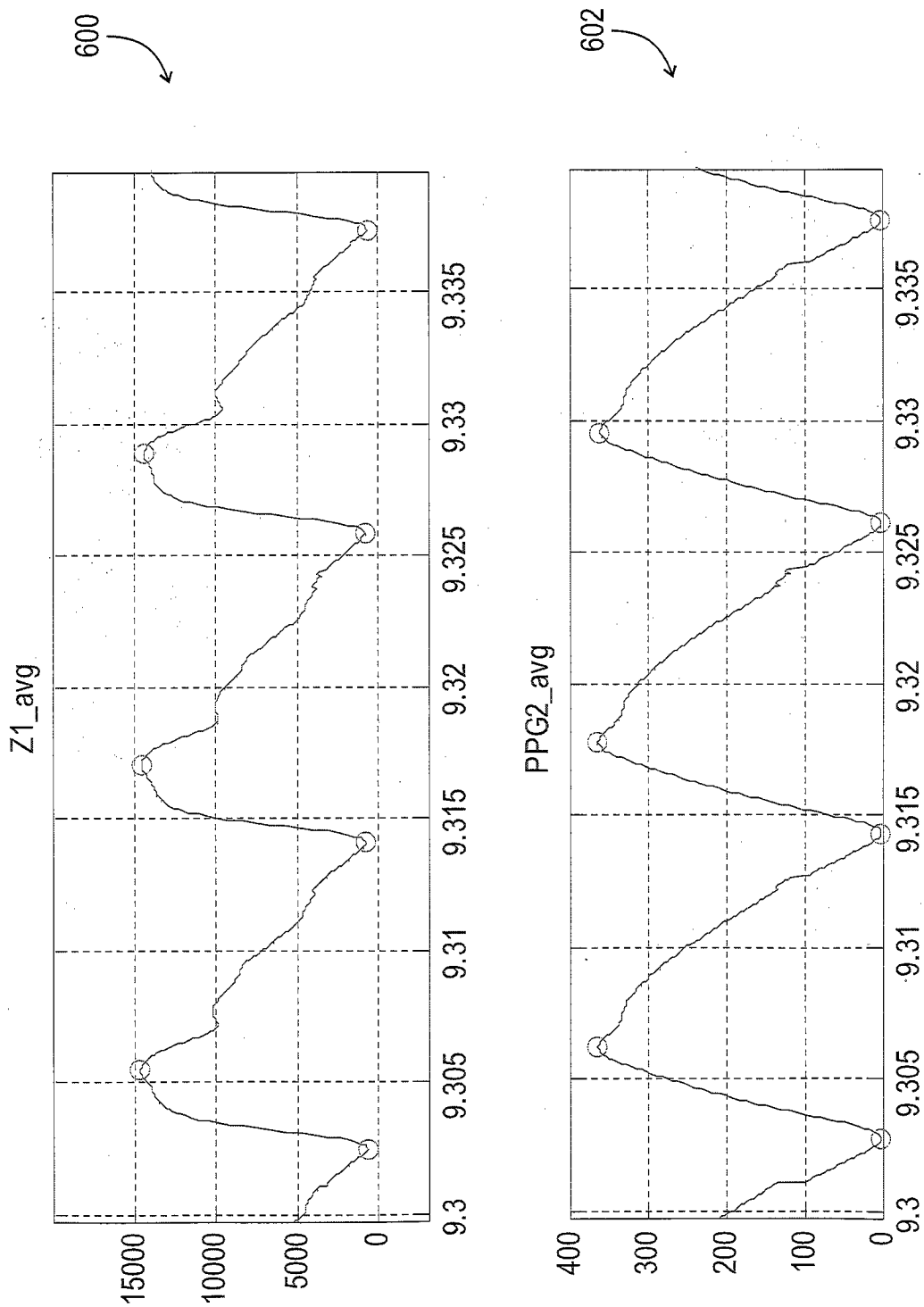


FIG. 5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Z1_avg
15000
10000
5000
0
9.3
9.305
9.31
9.315
9.32
9.325
9.33
9.335
602
PPG2_avg
400
300
200
100
0
9.3
9.305
9.31
9.315
9.32
9.325
9.33
9.335

FIG. 6A

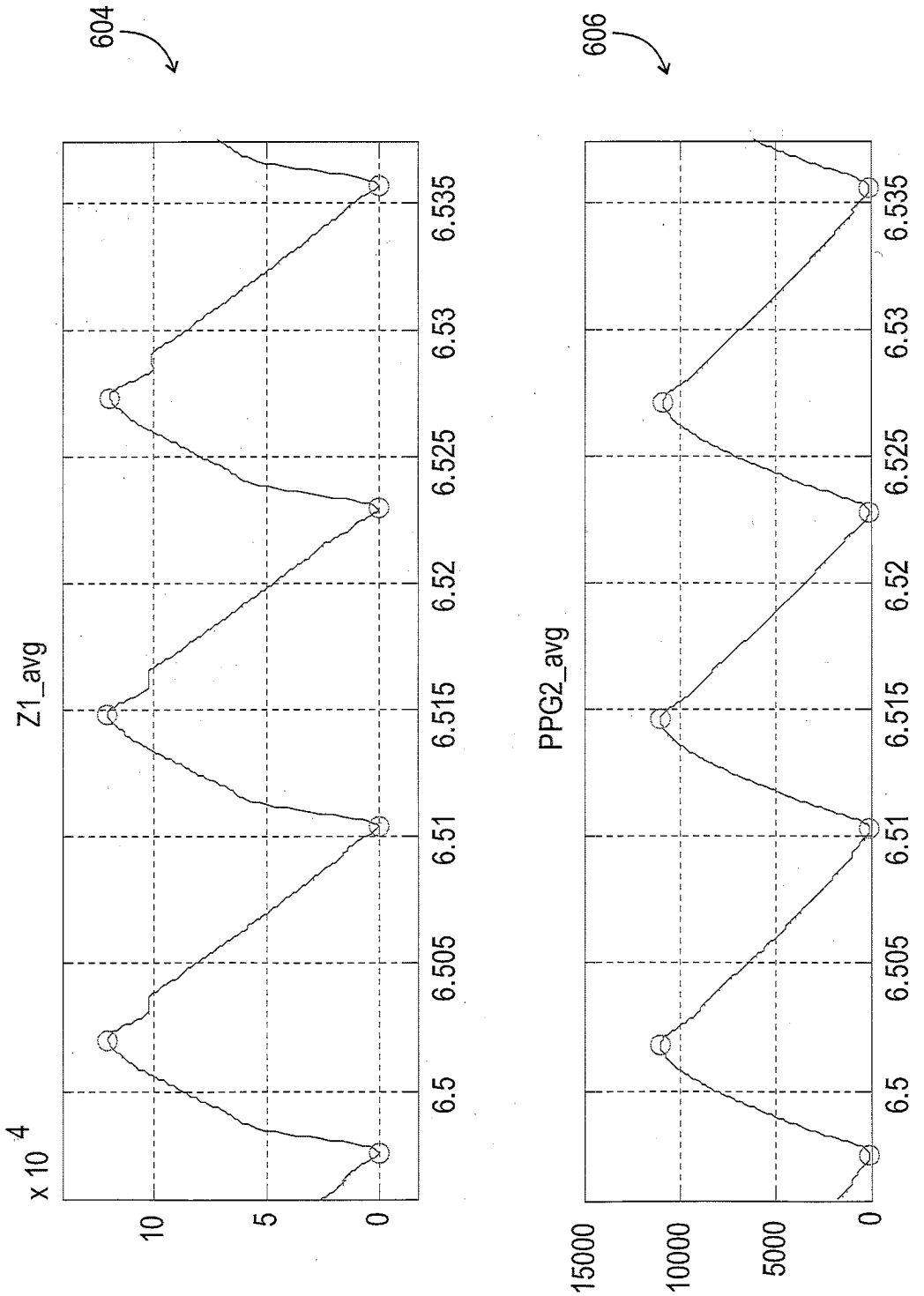
604
606
Z1_avg
x 10^4
10
5
0
6.5
6.505
6.51
6.515
6.52
6.525
6.53
6.535
PPG2_avg
15000
10000
5000
0

FIG. 6B