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(54) Title: METHOD AND DEVICE FOR NON-INVASIVE MEASUREMENTS IN A SUBJECT

(57) Abstract: A method and system are presented for use in non-invasive measurements in a subject (e.g. patient's body). According to this technique, measurements are performed on a measurement location in the subject by applying an external electromagnetic field to the measurement location and detecting at least two responses of the measurement location, and generating data indicative of the detected response. These at least two responses are characterized by at least two different values of a certain controllable parameter. The measurements include measurements carried out under a normal blood flow condition in the measurement location enabling generation of first measured data indicative of a first time variation of the response for each of the at least two parameter values, and include measurements sessions carried out under a condition of artificial kinetics in the measurement location enabling generation of second measured data indicative of a second time variation of the response for each of said at least two parameter values. The first and second measured data are processed to determine a first relation between the first time variations for the different parameter values and a second relation between the second time variations for said different parameter values. The first and second relations are utilized to determine the at least one blood and/or tissue related parameter.

METHOD AND DEVICE FOR NON-INVASIVE MEASUREMENTS IN A SUBJECT

FIELD OF THE INVENTION

This invention is generally in the field of non-invasive measuring techniques and relates to a method and device for non-invasive measurements in a subject (e.g. human body). The invention is particularly useful for measuring blood parameters, such as the concentration of a substance in blood (e.g., hemoglobin, glucose, drugs or cholesterol), or other important blood parameters such as oxygen saturation.

BACKGROUND OF THE INVENTION

Various non-invasive techniques have been developed for determining blood-related parameters such as hemoglobin, hematocrit, oxygen saturation, etc. These techniques are disclosed for example in the following publications:

A pulse oxymetry based hemoglobin measurement technique is described in the article *"Noninvasive total hemoglobin measurement"*, by Kye Jin Jeon et al., Journal of Biomedical Optics 7(1), 45–50, January 2002. This technique consists of a wavelength selection and prediction algorithm for determining total hemoglobin concentration. A model has been developed, based on the difference in optical density induced by the pulsation of the heartbeat, by taking an approximation of Twersky's theory on the assumption that the variation of blood vessel size is small during arterial pulsing. The device utilizes a five wavelength light emitting diode array as the light source. The selected wavelengths are two isobestic points and three in compensation for tissue scattering. Data are collected from 129 outpatients who are randomly grouped as calibration and prediction sets. The ratio of the variations of optical density between systole and

diastole at two different wavelengths is used as a variable. Several such variables have been selected that show high reproducibility among all variables. Multiple linear regression analysis has been made in order to predict total hemoglobin concentration. The correlation coefficient is 0.804 and the standard deviation is 0.864 g/dL for the calibration set. The relative percent error and standard deviation of the prediction set are 8.5% and 1.142 g/dL, respectively. These investigations demonstrate the possibility of noninvasive hemoglobin measurement, particularly, using the wavelengths below 1000 nm.

U.S. Patent No. 5,277,181 discloses noninvasive measurement of hematocrit and hemoglobin content by differential optical analysis. This technique utilizes differential optical absorption of two or more wavelengths of light during blood volume changes. The method is also useful for noninvasive measurements of other blood analytes, such as glucose, where variations in hematocrit or blood hemoglobin concentration cause errors in the measurement.

U.S. Patent No. 4,927,264 discloses a non-invasive measuring method and apparatus of blood constituents. Here, in order to measure the oxygen saturation in venous blood, a venous blood stream is made time-variant by applying pressure with a peak value of the minimum blood pressure to a proximal portion from a measuring part. Light beams with different wavelengths are transmitted from the measuring part and detected by photodiodes. Photodetected signals are logarithm-converted and venous signal components are separated from logarithm-converted signals with a filter circuit. The oxygen saturation of venous blood is calculated on the basis of separated venous signal components.

U.S. Patent No. 5,827,181 describes noninvasive blood chemistry measurement method and system that isolate measurement contributions due to a patient's blood to accurately measure blood chemistry. According to one embodiment, a noninvasive blood chemistry measurement method decreases the blood volume within a patient's body part relative to the normal blood volume in the body part and performs a baseline measurement. Blood volume is then increased and a second measurement is performed. Comparison of the second

measurement to the baseline measurement isolates the measurement attributes of the patient's blood. In accordance with another embodiment, a noninvasive blood chemistry measurement system decreases blood volume by applying mechanical pressure to a body part. According to yet another embodiment, blood volume in the body part is decreased using a pressure cuff. In a further embodiment, a noninvasive probe accurately measures blood chemistry and uses a suction cup to increase blood volume at the blood chemistry measurement site.

U.S. Patent No. 6,606,509 discloses a method and apparatus for improving the accuracy of noninvasive hematocrit measurements. According to this technique, the changes in the intensities of light of multiple wavelengths transmitted through or reflected light from the tissue location are recorded immediately before and after occluding the flow of venous blood from the tissue location with an occlusion device positioned near the tissue location. As the venous return stops and the incoming arterial blood expands the blood vessels, the light intensities measured within a particular band of near-infrared wavelengths decrease in proportion to the volume of hemoglobin in the tissue location; those intensities measured within a separate band of wavelengths in which water absorbs respond to the difference between the water fractions within the blood and the displaced tissue volume. A mathematical algorithm applied to the time-varying intensities yields a quantitative estimate of the absolute concentration of hemoglobin in the blood. To compensate for the effect of the unknown fraction of water in the extravascular tissue on the hematocrit measurement, the tissue water fraction is determined before the occlusion cycle begins by measuring the diffuse transmittance or reflectance spectra of the tissue at selected wavelengths.

A different approach is disclosed in various patents assigned to the assignee of the present application, such as for example US 6,400,972; US 6,587,704; US 6,711,424; US 6,804,002 and US 6,804,002. These techniques provide for measurement of various parameters of the patient's blood, based on the creation of a condition of artificial kinetics at a measurement location, and

maintaining this condition during a certain time. Measurements are carried out during a time period including this certain time by applying an external electromagnetic field to the measurement location and detecting a response to the applied field. Measured data is in the form of time evolutions of the responses of the medium corresponding to the different parameters of the applied field. By analyzing the measured data, at least one blood parameter is extracted.

SUMMARY OF THE INVENTION

There is a need in the art to facilitate non-invasive measurements of various blood parameters, by providing a novel method and device capable of providing the improved accuracy of measurements.

The inventors have found a certain problem associated with the fact that the methodology of each of the known approaches is based on a different kind of blood related signal. More specifically, pulsatile measurements (e.g., the above-indicated article *"Noninvasive total hemoglobin measurement"*, by Kye Jin Jeon et al., Journal of Biomedical Optics 7(1), 45–50, January 2002; US 5,277,181) are based on the arterial blood natural volumetric changes. Under-systolic volume manipulation based measurements (e.g., the above-indicated patents US 4,927,264; US 5,827,181; US 6,606,509) deal with venous blood. Over-systolic occlusion based measurements (disclosed in the above-indicated patents US 6,400,972; US 6,587,704; US 6,711,424 and US 6,804,002) are based on the arterial blood artificial kinetics. The physical and physiological principles underlying the pulsatile signal, under-systolic volumetric signal and post occlusion signals might be different.

The inventors have found that the accuracy of measurements could be improved by appropriately combining occlusion (no pulse due to blood flow cessation) and pulse-based (during the natural blood flow through the medium) modes of measurements. According to the invention, measurements are applied to the region of interest in a blood-perfused fleshy medium under occlusion and

before and/or after the occlusion – to the same region at the steady state (non-occluded) thereof.

The measurements may include the so-called "pure optical" measurements, namely, illumination of a measurement location and detection of a light response thereof (transmission and/or reflection/scattering), and/or photo-acoustic spectroscopy (illumination of a measurement location and detection of acoustic response thereof), and/or impedance based measurements (total electrical resistance or a component of the impedance) according to which two electrodes are brought into direct contact with the subject (e.g. human body) and real and imaginary components of reflected and/or transmitted electromagnetic signals are spectrally examined as a function of frequency. The measurements are taken with at least two different values of a certain controllable parameter. The latter may include the parameter of the applied electromagnetic field; and/or in case of optical measurements of the concentration of an optically active (scattering) substance (such as glucose) - polarization states of detected light.

There is thus provided according to one broad aspect of the invention, a method for use in non-invasive measurements in a subject, the method comprising:

(a) performing measurements on a measurement location on the subject, by applying an external electromagnetic field to the measurement location and detecting at least two responses of the measurement location characterized by at least two different values of a certain controllable parameter, and generating data indicative of the detected responses, wherein the measurements are performed while at a normal blood flow in the measurement location thereby enabling generation of first measured data indicative of a first time variation of the response for each of said at least two values of the controllable parameter, and are performed while at a condition of artificial kinetics in the measurement location enabling generation of second measured data indicative of a second time variation of

the response for each of said at least two values of the controllable parameter; and

(b) processing the first and second measured data to determine a first relation between the first time variations for the different parameter values and a second relation between the second time variations for said different parameter values; and

(c) utilizing the first and second relations to determine the at least one blood and/or tissue related parameter.

The condition of artificial kinetics may be created by applying over-systolic pressure to the vicinity of the measurement location, or to a location on the body upstream of the measurement location with respect to a normal blood flow direction in the body.

Preferably, the invention utilizes optical measurements: The measurements may include illuminating the measurement location with at least two different wavelengths of light (constituting at least two different values of the controllable parameter being that of the applied electromagnetic field) and detecting the light response of the illuminated portion of the subject (e.g., light transmitted through the portion under measurement). Alternatively, the measurements may include illuminating the measurement location with at least one wavelength of light and detecting the light response of the body portion while at different polarization states of the detected light (constituting at least two different values of the controllable parameter).

The first and second relations are preferably determined as a parametric slope of the respective time functions of the responses; or may be determined as AC_1/AC_2 and DC_1/DC_2.

A pair of the first and second parametric slopes PS_1 and PS_2 obtained for the same pair of wavelengths λ_1-λ_2 (constituting pair of the applied field parameter values) are determined as:

$$PS_1 = \frac{\partial Ln(I^1\lambda 1)/\partial(t)}{\partial Ln(I^1\lambda 2)/\partial(t)} \quad \text{and} \quad PS_2 = \frac{\partial Ln(I^2\lambda 1)/\partial(t)}{\partial Ln(I^2\lambda 2)/\partial(t)}$$

wherein I^1 and I^2 are the first and second light responses and t is time.

The desired blood parameter, BP, can be determined as

$$BP = \sum_{i=1}^{N} A_i \cdot (PS_1)_i + \sum_{i=1}^{M} B_i \cdot (PS_2)_i ,$$

wherein A_i and B_i are calibration coefficients; $(PS_1)_i$ and $(PS_2)_i$ are first and second parametric slopes obtained for the same pair of wavelengths; and i is a number of wavelength.

The measurements performed under the normal blood flow condition may be carried out before or after the measurements under the artificial kinetics condition.

The blood and/or tissue related parameter that can be determined by the technique of the invention includes concentration of substance (e.g., hemoglobin, hematocrit, glucose, HbCO, MetHb) and/or oxygen saturation.

According to another broad aspect of the invention, there is provided a method for use in non-invasive measurements in a subject, the method comprising:

(a) performing optical measurements on a measurement location on the subject, by illuminating the measurement location and detecting light responses of the measurement location characterized by at least two different values of a certain controllable parameter, and generating data indicative of the detected light response, the measurements including measurements performed while at a normal blood flow condition in the measurement location enabling generation of first measured data indicative of a first time variation of the light response for each of said at least two values of the controllable parameter, and measurements performed while at a condition of artificial kinetics in the measurement location enabling generation of second measured data indicative of a second time variation of the light response for each of said at least two parameter values; and

(b) processing the first and second measured data to determine a first relation between the first time variations for the different parameter values and a second relation between the second time variations for said different parameter values; and

(c) utilizing the first and second relations to determine at least one blood and/or tissue related parameter.

According to yet another aspect of the invention, there is provided a method for use in non-invasive measurements in a subject, the method comprising:

(a) providing first and second measured data, the first measured data being indicative of at least two first time variations of responses of a measurement location in the body to an applied electromagnetic field characterized by at least two different values of a certain controllable parameter, respectively and corresponding to a normal blood flow condition in the measurement location, and the second data being indicative of at least two second time variations of the responses of the measurement location to said field characterized by said at least two values of the controllable parameter, respectively, and corresponding to a condition of artificial kinetics in the measurement location; and

(b) processing the first and second measured data to determine a first relation between the first time variations for the different parameter values and a second relation the second time variations for said different parameter values; and

(c) utilizing the first and second relations to determine the at least one blood and/or tissue related parameter.

According to yet another broad aspect of the invention, there is provided a device for use in non-invasive measurements in a subject, the device comprising:

(a) a measurement unit comprising an electromagnetic field source assembly configured and operable for applying an external electromagnetic field to a measurement location on the subject, and a detector arrangement

configured and operable for detecting a response of the measurement location to the applied field and generating data indicative thereof;

(b) a pressure applying assembly configured and operable for applying over-systolic pressure to the body portion so as to create a condition of artificial kinetics in the measurement location characterized by a blood flow cessation;

(c) a control unit connectable to the measurement unit and to the pressure applying assembly for operating them so as to enable the measurements on the measurement location with the at least two different values of a certain controllable parameter and under a first condition of normal blood flow at the measurement location with substantially no application of pressure and under the second condition of artificial kinetics in the measurement location; the control unit being configured for receiving and processing said data indicative of the response of the measurement location to the applied field to determine first measured data indicative of a first time variation of the response for each of said at least two parameter values while at the normal blood flow condition and second measured data indicative of a second time variation of the response for each of said at least two parameter values while at the artificial kinetics condition, thereby enabling determination of a first relation between the first time variations for the different parameter values and a second relation between the second time variations for said different parameter values, and utilizing said first and second relations to determine at least one blood and/or tissue related parameter.

According to yet another broad aspect of the invention, there is provided a device for use in non-invasive measurements in a patient's body, the device comprising:

(a) an optical measurement unit, which comprises a light source assembly, and a light detector arrangement, and which is operable to cause light responses of the illuminated location characterized by at least two

different values of a certain controllable parameter; and generating data indicative thereof;

(b) a pressure applying assembly configured and operable for applying over-systolic pressure to the body portion so as to create a condition of artificial kinetics in the measurement location characterized by a blood flow cessation;

(c) a control unit connectable to the measurement unit and to the pressure applying assembly for operating them so as to enable measurements on the measurement location carried out with the at least two different values of the controllable parameter and under a first condition of normal blood flow in the measurement location with substantially no application of pressure and a second condition of artificial kinetics in the measurement location; the control unit being configured for receiving and processing said data indicative of the light response to determine first measured data indicative of a first time variation of the light response for each of said at least two parameter values while at the normal blood flow condition and second measured data indicative of a second time variation of the light response for each of said at least two parameter values while at the artificial kinetics condition, thereby enabling determination of a first relation between the first time variations for the different parameter values and a second relation between the second time variations for said different parameter values, and utilizing said first and second relations to determine at least one blood and/or tissue related parameter.

BRIEF DESCRIPTION OF THE DRAWINGS

In order to understand the invention and to see how it may be carried out in practice, preferred embodiments will now be described, by way of non-limiting example only, with reference to the accompanying drawings, in which:

Fig. 1 is a block diagram of a device of the present invention, exemplified as being applied to a patient's finger;

Figs. 2A and 2B show two examples, respectively, of a method of the invention;

Fig. 3A-B and 4A-4C show experimental results for the technique of the invention, wherein **Fig. 3A** shows the time variations of the pulse mode light responses for different wavelengths and **Fig. 3B** shows the time variations of the occlusion mode light responses for the same wavelengths, respectively; and **Figs. 4A-4C** show relations between the time variations of the light responses for the pulse and artificial kinetics modes (in terms of parametric slopes), for three different pairs of wavelengths, respectively.

DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS

Referring to **Fig. 1**, there is illustrated by way of a block diagram a device, generally designated **10**, constructed and operated according to the invention. In the present example, the device is applied to a patient's finger (constituting a subject or subject's medium), and is configured as a clip-like device or a ring-like device. Also in the present example, the device is configured for carrying out optical measurements. However, it should be understood that the invention is not limited to these specific examples.

Device **10** includes a measurement unit **12**, a pressure applying assembly **14**, and a control unit **16**. These constructional parts of the device or at least some of them may be made integral with each other (i.e., carried by a common housing, e.g., capable of being applied to the finger, e.g., a ring-like housing) or may be separate units (e.g., measurement unit and pressure applying assembly may be separate ring-like assemblies, or one being a ring and the other being a clip, as the case may be). The measurement unit and the pressure applying assembly may be connectable to the control unit (integrated or stand-alone) via wires or wireless signal transmission.

Measurement unit **12** includes a source **12A** of an external electromagnetic field to be applied to a measurement location in the body; and a detector **12B** configured for detecting a response of the measurement location to

the applied field. In the present example, field source **12A** is operable (e.g., by control unit **16**) to vary at least one of its operational parameters, e.g., a frequency of the applied field (constituting a controllable parameter). Such a field may be light or an electric signal. The response may be in the form of an optical, acoustic or electric signal.

In the present example, measurement unit **12** is an optical device configured to irradiate a region of interest (finger in the present example) with incident radiation of at least two different wavelengths in Visible, NIR or IR spectra, and detect a radiation response of the illuminated region. To this end, measurement unit **12** includes light source arrangement **12A** (and possibly also a suitable light directing assembly, e.g., optical fiber(s) and/or a lens arrangement and/or polarizer arrangement); and light detector arrangement **12B** (possibly equipped with suitable optics, and/or spectral filters, and/or polarizer arrangement). Light source arrangement **12A** includes either a single broadband illuminator, or a plurality (at least two light source elements) emitting light of different wavelength ranges.

It should be understood that light source arrangement **12A** may or may not be carried by the housing applied to the finger. For example, such a light source assembly may be a stand alone unit and an optical fiber arrangement is used for connecting the light source to the housing on the finger. Similarly, detector arrangement **12B** may be mounted on the housing or may be connected thereto via an optical fiber arrangement. The housing (clip or ring) carrying the measuring unit is appropriately provided with optical windows allowing illuminating light to pass to the region of interest and allowing collection of the light response of the region of interest. In this connection, it should be understood that the device may be configured to operate with a reflection mode and/or transmission mode. Namely, the device may include one or more light detectors (i.e., optical window(s) associated therewith) collecting light transmitted through the finger, and/or one or more light detectors collecting light reflected (scattered) from the region of interest in the finger.

Pressure applying assembly **14** includes a cuff **14A** configured for attaching to the patient's finger, and a drive unit **14B** operated by control unit **16** for operating the squeezing of cuff **14A**.

Control unit **16** is connectable to measurement unit **12** and pressure applying assembly **14** (via wires or wireless), and is configured to appropriately operate these units and to receive and process data indicative of the detected response of the measurement location. Control unit **16** is configured as a computer system including *inter alia* a memory utility **16A**, a data processing utility **16B**, and a data output utility (e.g., display) **16C**. Also, control unit **16** includes a field source controller utility **16D** (an illumination controller in the present example) and a pressure controller utility **16E** associated with the drive unit **14B**.

Reference is made to **Figs. 2A and 2B** showing the operational steps in accordance with two examples, respectively, of a method of operating device **10** of the present invention. In the present example, pure optical measurements are considered, but it should be understood that the present invention is not limited to this specific example.

In the example of **Fig. 2A**, measurements are first taken at the steady state (pulse mode), and then under the artificial kinetics condition (occlusion mode). Accordingly, during a certain time period t_p (e.g., about 20 seconds) pressure applying assembly **14** is kept inoperative, while measurement unit **12** is operated to perform measurements with at least two different wavelengths, and/or with at least two different states of polarization of the detected light (as described in the above-indicated patent US 6,804,002 assigned to the assignee of the present application). Light source assembly **12A** and detector arrangement **12B** are operated to apply illumination (e.g., with at least two different wavelengths) to a measurement location (region of interest) and detect a light response, I_p, of the illuminated region (for at least two different values of the controllable parameter – that of wavelength of illumination in the present example). Data indicative of the light response, I_p, is received at the control unit.

After this time period t_p, a condition of artificial kinetics is created at the measurement location and maintained for a certain time period t_{ak} such as not to cause irreversible changes in the fleshy medium (e.g., from a few seconds to about one minute), and optical measurements are performed on the measurement location during at least a part of this time period t_{ak}. This is implemented by operating pressure applying assembly **14** to apply over-systolic pressure in the vicinity of the measurement location or upstream of the measurement location (with respect to a normal blood flow direction) so as to create blood flow cessation at the measurement location and maintain it during the cessation time t_{ak}, and operating the light source and detector assemblies to detect a light response, I_{ak}, of the measurement location to at least two different wavelengths while at the condition of artificial kinetics (under occlusion). Data indicative of the light response, I_{ak}, is received at the control unit. It should be noted that a certain short time (about 0.5sec) exists from the moment when the pressure is initially applied and until the actual start of occlusion. Measurements taken during this short time period may be disregarded, due to the unavoidable influence of motional and/or other artifacts causing non-monotonic fluctuations of the light response signal.

In the example of **Fig. 2B**, measurements are first taken at the occlusion mode (condition of artificial kinetics), and then during the steady state (pulse mode). Accordingly, pressure applying assembly **14** is operated to apply over-systolic pressure to the vicinity of the measurement location or upstream thereof and maintain this pressure during cessation time t_{ak}. Measurement unit **12** is operated to apply optical measurements with at least two different wavelengths of light during at least a part of the cessation time. Similarly, measurements taken during a short time period from the moment when the pressure is initially applied and until the actual start of occlusion, should be disregarded. Thereafter (after time t_{ak}), the pressure is released, and a transitional state of blood flow takes place, during about 2-3 seconds. Measurements taken during this time period

may also be disregarded. After this transitional blood flow state, the normal blood flow is established, and light response, I_p, is measured.

Common for both examples, data indicative of the light responses I_p and I_{ak} are processed to determine measured data indicative of time variations of these light responses for each of the at least two wavelengths λ_1 and λ_2: $I^{\lambda 1}{}_p(t)$, $I^{\lambda 2}{}_p(t)$ and $I^{\lambda 1}{}_{ak}(t)$, $I^{\lambda 2}{}_{ak}(t)$. These measured data are further processed to determine a relation between the time variations of the light responses, namely a relation R_1 between functions $I^{\lambda 1}{}_p(t)$, $I^{\lambda 2}{}_p(t)$, and a relation R_2 between functions $I^{\lambda 1}{}_{ak}(t)$, $I^{\lambda 2}{}_{ak}(t)$. This allows for calculating the desired blood parameter. In this connection, it should be understood that the wavelengths of illumination are appropriately selected for measuring a specific blood parameter.

The so-determined relations R_1 and R_2 between the time variations of the pulse- and occlusion-mode light responses enable to reduce time element both for the pulsatile and the occlusion related components of the optical response. The use of more than two wavelengths in each measurement session, allows for determining the relation between the light responses' variations for different pairs of wavelengths, which provide different sensitivities to different blood parameters.

The following are experimental results of the invention. **Fig. 3A** shows the time variations of the pulse mode light responses, $I^1{}_p(t)$, $I^2{}_p(t)$, $I^3{}_p(t)$, $I^4{}_p(t)$, for, respectively, 610nm, 670nm, 812 and 880nm wavelength; and **Fig. 3B** shows the time variations of the occlusion mode light responses, $I^1{}_{ak}(t)$, $I^2{}_{ak}(t)$, $I^3{}_{ak}(t)$, $I^4{}_{ak}(t)$, for the same wavelengths, respectively.

Figs. 4A-4C show relations R_1-R_2, R_1'-R_2' and R_1''-R_2'' for, respectively, the following pairs of wavelengths λ_1-λ_2: 670nm-880nm, 610nm-880nm, 810nm-880nm, where the wavelengths are selected for the concurrent determination of hemoglobin concentration and oxygen saturation, wavelength 880nm being the so-called *"reference wavelength"*. In the present example, the relation R is determined as a parametric slope (PS) namely a ratio between variation of the

light response for one wavelength λ_1 and the variation of the light response for the reference wavelength λ_1, for example calculated as: $\frac{\partial \ln(I_{\lambda 1})/\partial t}{\partial \ln(I_{\lambda 2})/\partial t}$.

As indicated above, different pairs of wavelengths provide different sensitivities to different blood parameters. For example, the value of PS for 670nm and 880nm in the pulse mode (pulsatile signal) is most sensitive for HbO2/(Hb +HbO2) ratio (oxygen saturation), but reveals a small sensitivity to the hemoglobin concentration as well. The value of PS for 610nm and 880nm in the occlusion mode is very sensitive to hemoglobin/hematocrit, and is also sensitive at a certain degree to the blood Hb oxygen saturation. It should be noted that there are additional parameters, like blood flow and/or tissue hematocrit that can affect the PS value. Therefore, the use of additional pairs of wavelength is preferred in order to account or compensate for the variable parameters of management.

For the determination of Hb(SPO2) or glucose concentration, the following expression can be used:

$$Hb = \sum_{i=1}^{N} A_i \cdot (PS)_i \qquad (1)$$

where A_i are determined by using previous calibration; $(PS)_i$ are different pairs of parametric slopes; and i is a number of wavelength.

The calibration stage consists of the following: Measurements are taken *in vivo* for the population of patients, ranging from very low Hb values up to very high Hb values. Then, the reference Hb from the patients' blood is taken, using any standard Lab method. Thereafter, PS is calculated for the pulse and occlusion modes, and coefficients of the regression formula are determined using a standard mean least square calculation technique.

Examples of **Figs. 4A-4C** demonstrate the differences between PS as function of Hb for pulsatile and post occlusion signals.

Mathematically it means that pulsatile PS is determined as:

$$PS(pulse) = \frac{\partial Ln(I_{\lambda 1})/\partial(x)}{\partial Ln(I_{\lambda ref})/\partial(x)} \qquad (2)$$

wherein x is the blood pulsatile changes, and PS for post occlusion signal is determined as:

$$PS(occlusion) = \frac{\partial Ln(I_{\lambda 1})/\partial(\mu_{\lambda transport1}(\lambda))}{\partial Ln(I_{\lambda ref})/\partial(\mu_{\lambda transport1}(\lambda ref))} \cdot \frac{\partial(\mu_{\lambda transport1}(\lambda))/\partial(t)}{\partial(\mu_{\lambda transport1}(\lambda ref))/\partial(t)} \qquad (3)$$

wherein I is the optical response signal

The time dependent behavior of $\mu_{\lambda transport1}$ during the occlusion is the optical parameter driven by artificial kinetics.

Expressions (2) and (3) are supplemental to each other. The combination of these expressions provides additional information. The simplest combination is:

$$Hb = \sum_{i=1}^{N} A_i \cdot (PS(pulse))_i + \sum_{i=1}^{M} B_i \cdot (PS(occlusion))_i \qquad (4)$$

For example, using only pulsatile component (expression 1) for Hb determination results in correlation of r=65%, using only post occlusion signal on some dataset results in correlation r=63%. However, the combination of both signals (expression 4) provides a 85% correlation between the calculated and real value (invasively measured Hb value).

Naturally, if the explicit expressions (2) and (3) are provided in any form, then equations (2) and (3) can be solved symbolically or numerically as a set of equations.

It should be noted that this methodology can be used not only with the parametric slope being a primer parameter, but for any form or derivative of such a parametric slope or a differential thereof or Ln(I), or for any combination of them. The assessment of various parameters can be facilitated by using a combination of signals of pulse, pre-occlusion blood state manipulation and post-occlusion, for example: SPO2, Hb, Glucose, HbCO, MetHb.

Those skilled in the art will readily appreciate that many modifications and changes may be applied to the invention as hereinbefore exemplified without departing from its scope defined in and by the appended claims. In the method claims which follow, characters which are used to designate claim steps, are provided for convenience only and do not apply any particular order of performing the steps.

CLAIMS:

1. A method for use in non-invasive measurements in a subject, the method comprising:

(a)performing measurements on a measurement location on the subject, by applying an external electromagnetic field to the measurement location and detecting at least two responses of the measurement location characterized by at least two different values of a certain controllable parameter, and generating data indicative of the detected responses, wherein the measurements are performed while at a normal blood flow in the measurement location thereby enabling generation of first measured data indicative of a first time variation of the response for each of said at least two values of the controllable parameter, and performed while at a condition of artificial kinetics in the measurement location enabling generation of second measured data indicative of a second time variation of the response for each of said at least two values of the controllable parameter; and

(b)processing the first and second measured data to determine a first relation between the first time variations for the different parameter values and a second relation between the second time variations for said different parameter values; and

(c)utilizing the first and second relations to determine the at least one blood and/or tissue related parameter.

2. The method of Claim 1, wherein the condition of artificial kinetics is created by applying over-systolic pressure to the vicinity of the measurement location, or to a location on the subject upstream of the measurement location with respect to a normal blood flow direction in the body.

3. The method of Claim 1 or 2, wherein said certain controllable parameter comprises a wavelength of the applied electromagnetic field, the measurements being performed with the at least two wavelengths of said field.

4. The method of Claim 3, wherein the measurements are performed with more than two wavelengths of said field.

5. The method of Claim 3 or 4, wherein the measurements comprise illuminating the measurement location with at least two different wavelengths of light and detecting the light response of the subject's portion under measurement.

6. The method of Claim 5, wherein the light response includes light transmitted through and/or scattered from the body portion.

7. The method of any one of preceding Claims, wherein each of the first and second relations is determined as a parametric slope of the respective time functions of the responses.

8. The method of Claims 5 and 7, wherein a pair of the first and second parametric slopes PS_1 and PS_2 obtained for the same pair of wavelengths λ_1-λ_2 are determined as:

$$PS_1 = \frac{\partial Ln(I^1\lambda 1)/\partial(t)}{\partial Ln(I^1\lambda 2)/\partial(t)}$$

and

$$PS_2 = \frac{\partial Ln(I^2\lambda 1)/\partial(t)}{\partial Ln(I^2\lambda 2)/\partial(t)}$$

wherein I^1 and I^2 are the first and second light responses.

9. The method of Claim 8, wherein the desired blood related parameter BP is determined as

$$BP = \sum_{i=1}^{N} A_i \cdot (PS_1)_i + \sum_{i=1}^{M} B_i \cdot (PS_2)_i$$

wherein A_i and B_i are calibration coefficients; $(PS_1)_i$ and $(PS_2)_i$ are first and second parametric slopes obtained for the same pair of wavelengths; and i is a number of wavelength.

10. The method of any one of preceding Claims, wherein said measurements performed while at the normal blood flow condition include measurements carried out prior to the measurements under the artificial kinetics condition, and/or thereafter.

11. The method of any one of preceding Claims, wherein said at least one blood and/or tissue related parameter includes at least one of the following: concentration of substance in blood and oxygen saturation.

12. The method of Claim 11, wherein said substance includes at least one of the following: hemoglobin, hematocrit, glucose.

13. The method of any one of preceding Claims, wherein said subject is a human body.

14. A method for use in non-invasive measurements in a subject, the method comprising:

(a)providing first and second measured data, the first measured data being indicative of at least two first time variations of responses of a measurement location in the body to an applied electromagnetic field characterized by at least two different values of a certain controllable parameter, respectively and corresponding to a normal blood flow condition in the measurement location, and the second data being indicative of at least two second time variations of the responses of the measurement location to said field characterized by said at least two values of the controllable parameter, respectively, and corresponding to a condition of artificial kinetics in the measurement location; and

(b)processing the first and second measured data to determine a first relation between the first time variations for the different parameter values and a second relation the second time variations for said different parameter values; and

(c)utilizing the first and second relations to determine the at least one blood and/or tissue related parameter.

15. A device for use in non-invasive measurements in a subject, the device comprising:

(a)a measurement unit comprising an electromagnetic field source assembly configured and operable for applying an external electromagnetic field to a measurement location on the body, and a detector arrangement configured

and operable for detecting a response of the measurement location to the applied field and generating data indicative thereof;

(b) a pressure applying assembly configured and operable for applying over-systolic pressure to the body portion so as to create a condition of artificial kinetics in the measurement location characterized by a blood flow cessation;

(c) a control unit connectable to the measurement unit and to the pressure applying assembly for operating them so as to enable the measurements on the measurement location with the at least two different values of a certain controllable parameter and under a first condition of normal blood flow at the measurement location with substantially no application of pressure and under the second condition of artificial kinetics in the measurement location; the control unit being configured for receiving and processing said data indicative of the response of the measurement location to the applied field to determine first measured data indicative of a first time variation of the response for each of said at least two parameter values while at the normal blood flow condition and second measured data indicative of a second time variation of the response for each of said at least two parameter values while at the artificial kinetics condition, thereby enabling determination of a first relation between the first time variations for the different parameter values and a second relation between the second time variations for said different parameter values, and utilizing said first and second relations to determine at least one blood and/or tissue related parameter.

16. The device of Claim 15, wherein said field source includes at least one light source and said detector unit includes at lest one light detector.

17. The device of Claim 15 or 16, wherein the control unit operates the measurement unit and the pressure applying assembly such that said measurements carried out at the normal blood flow condition include measurements performed prior to the measurements under the artificial kinetics condition, and/or thereafter.

18. The device of any one of Claims 15 to 17, wherein the control unit is preprogrammed to determine each of the first and second relations as a parametric slope of the respective time functions of the responses.

19. The device of Claims 16 and 18, wherein the control unit is preprogrammed to determine a pair of the first and second parametric slopes PS_1 and PS_2 for the same pair of wavelengths λ_1-λ_2 as:

$$PS_1 = \frac{\partial Ln(I^1\lambda 1)/\partial(t)}{\partial Ln(I^1\lambda 2)/\partial(t)}$$

and

$$PS_2 = \frac{\partial Ln(I^2\lambda 1)/\partial(t)}{\partial Ln(I^2\lambda 2)/\partial(t)}$$

wherein I^1 and I^2 are the first and second light responses.

20. The device of Claim 18, wherein the control unit is preprogrammed to utilize the first and second parametric slopes to determine the desired blood parameter BP as

$$BP = \sum_{i=1}^{N} A_i \cdot (PS_1)_i + \sum_{i=1}^{M} B_i \cdot (PS_2)_i$$

wherein A_i and B_i are calibration coefficients; $(PS_1)_i$ and $(PS_2)_i$ are first and second parametric slopes obtained for the same pair of wavelengths; and i is a number of wavelength.

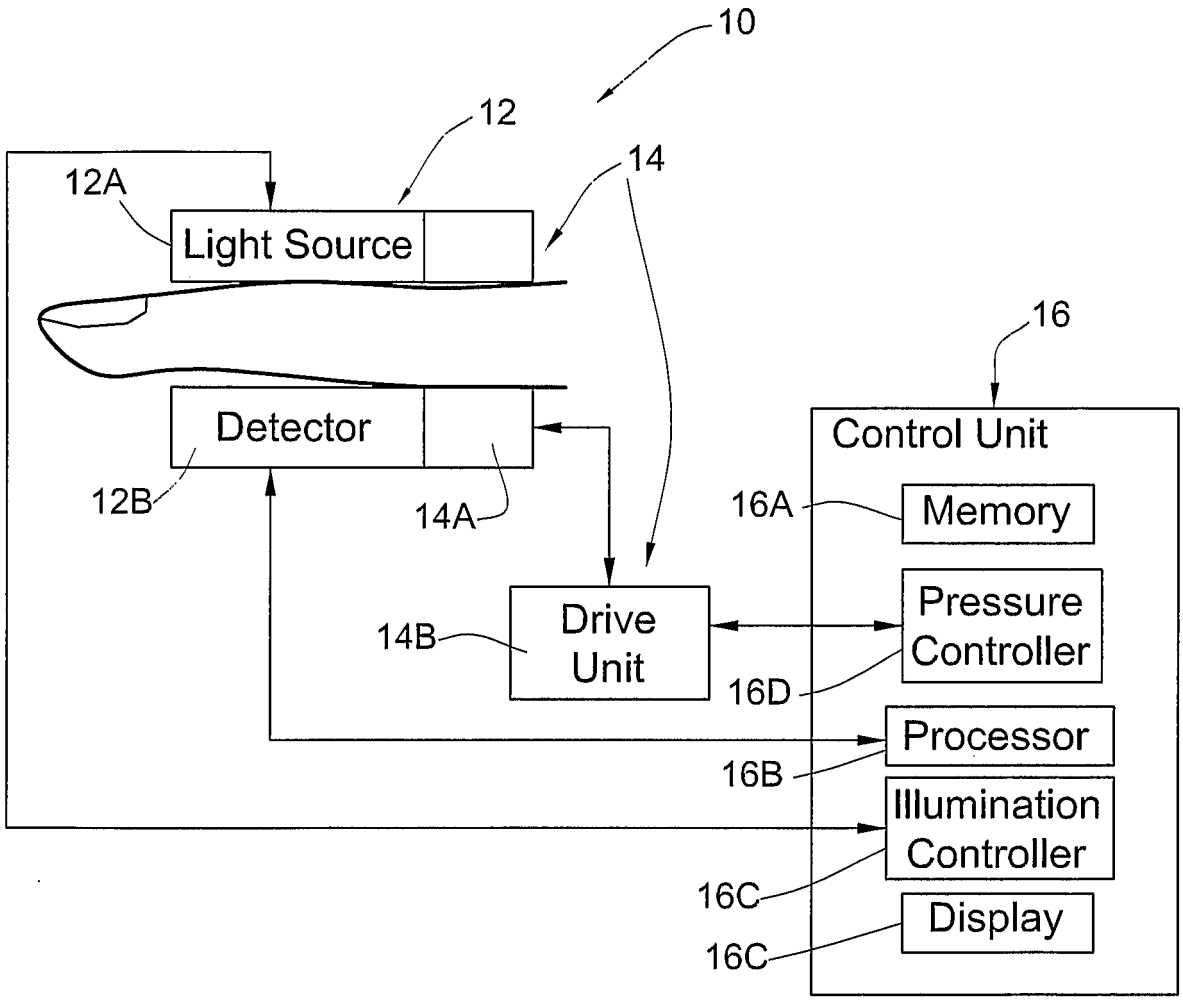
10
12
14
12A
Light Source
16
Detector
Control Unit
12B
14A
16A
Memory
Pressure Controller
14B
Drive Unit
16D
Processor
16B
Illumination Controller
16C
Display
16C

FIG. 1

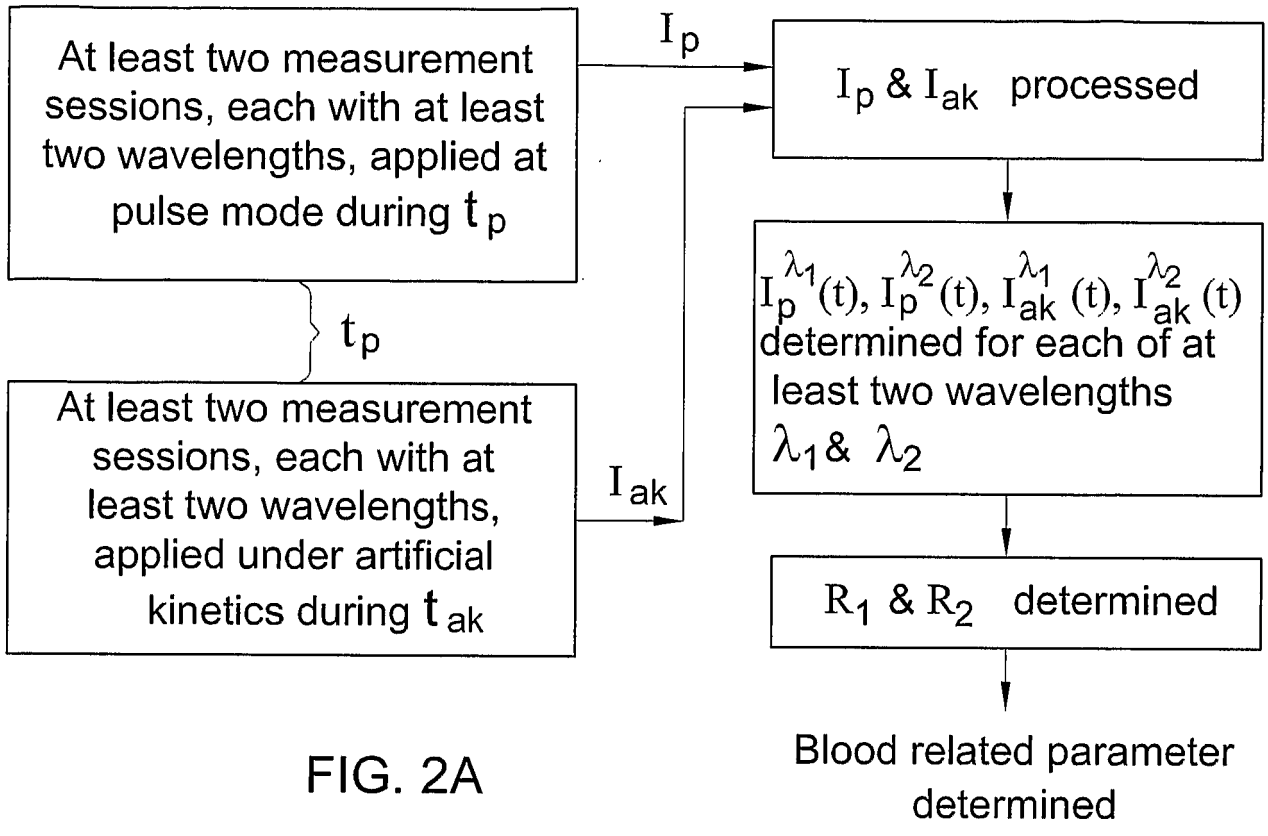
At least two measurement sessions, each with at least two wavelengths, applied at pulse mode during t_p
t_p
At least two measurement sessions, each with at least two wavelengths, applied under artificial kinetics during t_{ak}
I_p
I_{ak}
I_p & I_{ak} processed
$I_p^{\lambda_1}(t)$, $I_p^{\lambda_2}(t)$, $I_{ak}^{\lambda_1}(t)$, $I_{ak}^{\lambda_2}(t)$ determined for each of at least two wavelengths λ_1 & λ_2
R_1 & R_2 determined
Blood related parameter determined

FIG. 2A

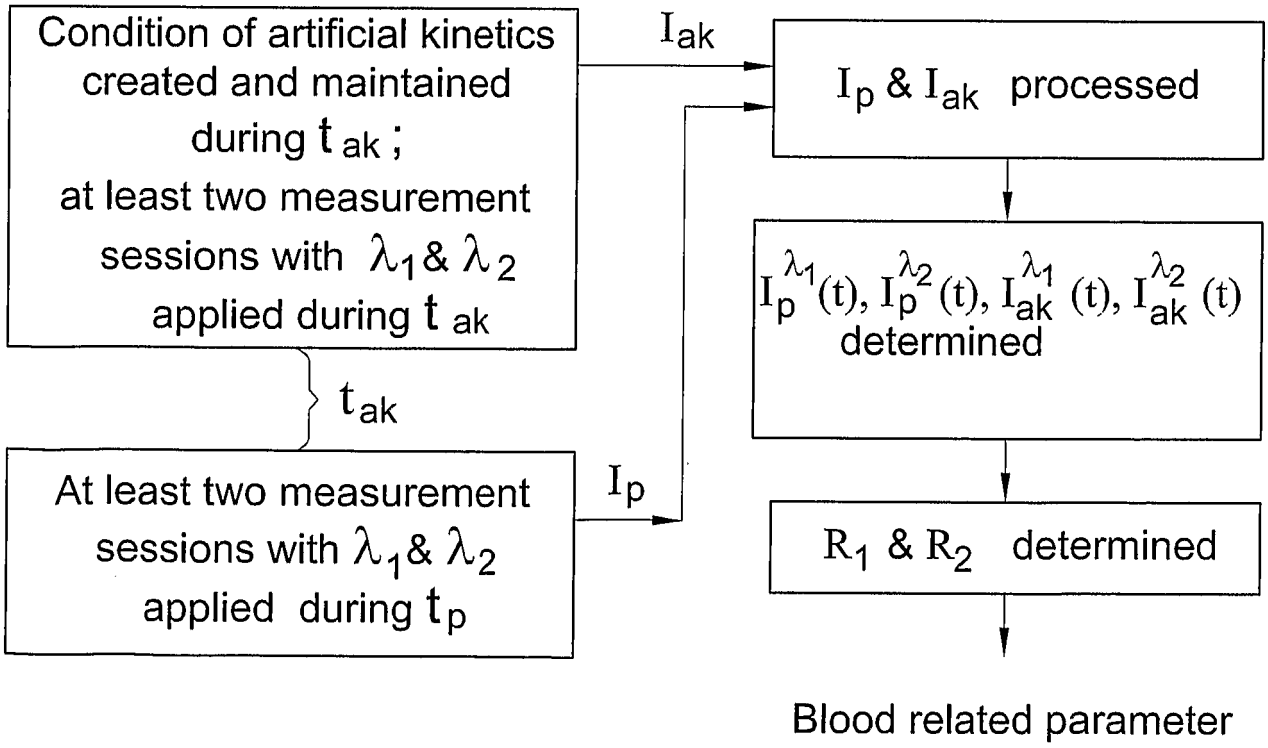
Condition of artificial kinetics created and maintained during t_{ak} ; at least two measurement sessions with λ_1 & λ_2 applied during t_{ak}
t_{ak}
At least two measurement sessions with λ_1 & λ_2 applied during t_p
I_{ak}
I_p
I_p & I_{ak} processed
$I_p^{\lambda_1}(t)$, $I_p^{\lambda_2}(t)$, $I_{ak}^{\lambda_1}(t)$, $I_{ak}^{\lambda_2}(t)$ determined
R_1 & R_2 determined
Blood related parameter

FIG. 2B

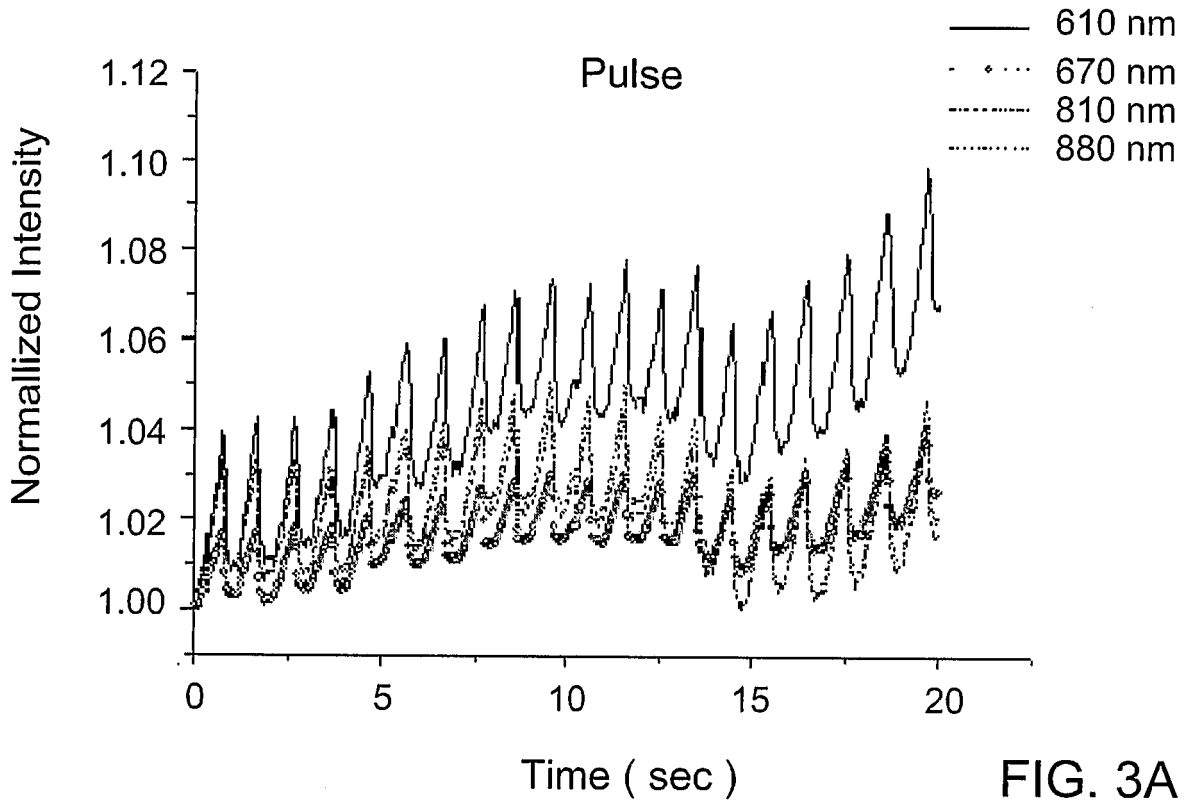
Pulse
610 nm
670 nm
810 nm
880 nm
Normallized Intensity
1.12
1.10
1.08
1.06
1.04
1.02
1.00
0
5
10
15
20
Time (sec)

FIG. 3A

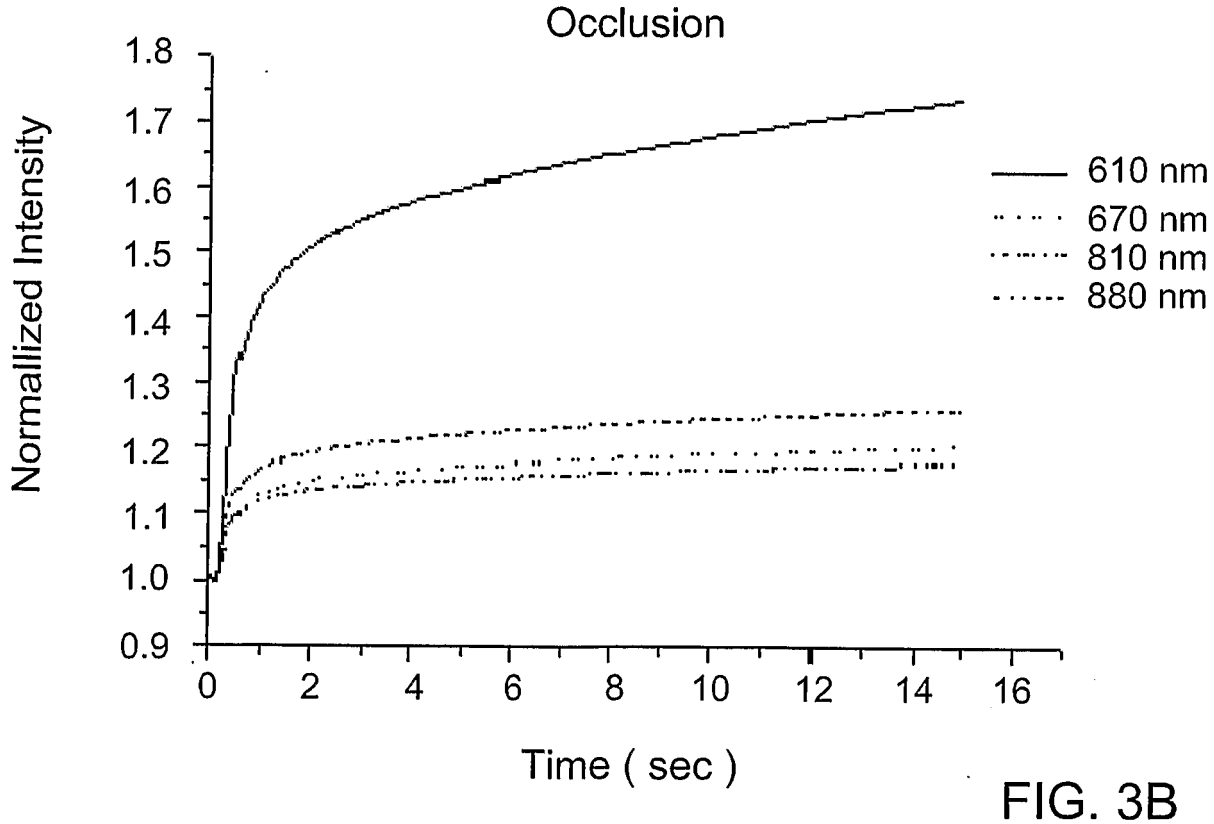
Occlusion
610 nm
670 nm
810 nm
880 nm
Normallized Intensity
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
2
4
6
8
10
12
14
16
Time (sec)

FIG. 3B

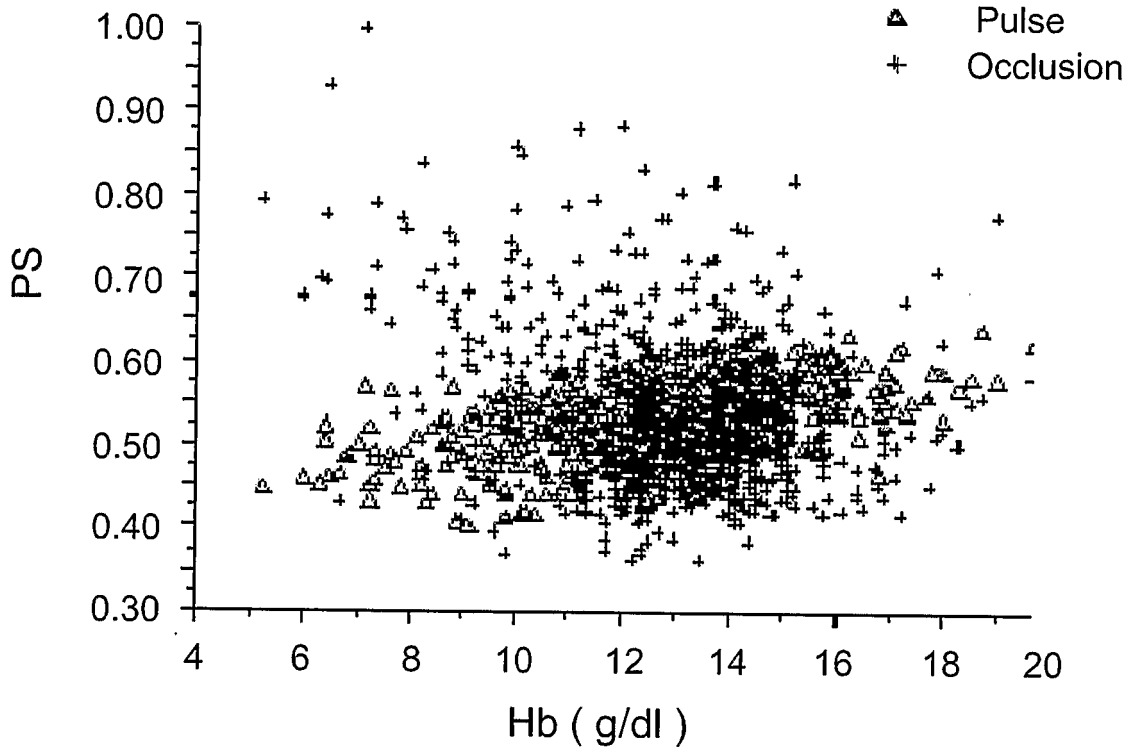
Pulse
Occlusion
PS
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
4
6
8
10
12
14
16
18
20
Hb (g/dl)

FIG. 4A

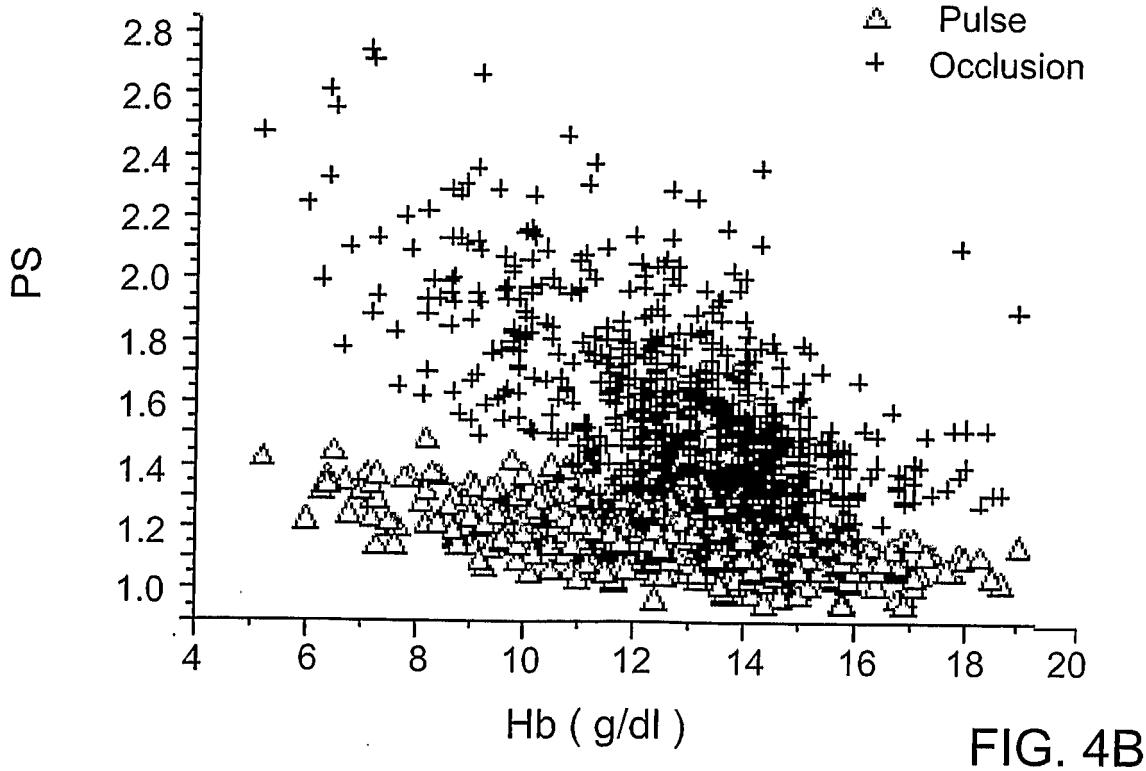
Pulse
Occlusion
PS
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
4
6
8
10
12
14
16
18
20
Hb (g/dl)

FIG. 4B

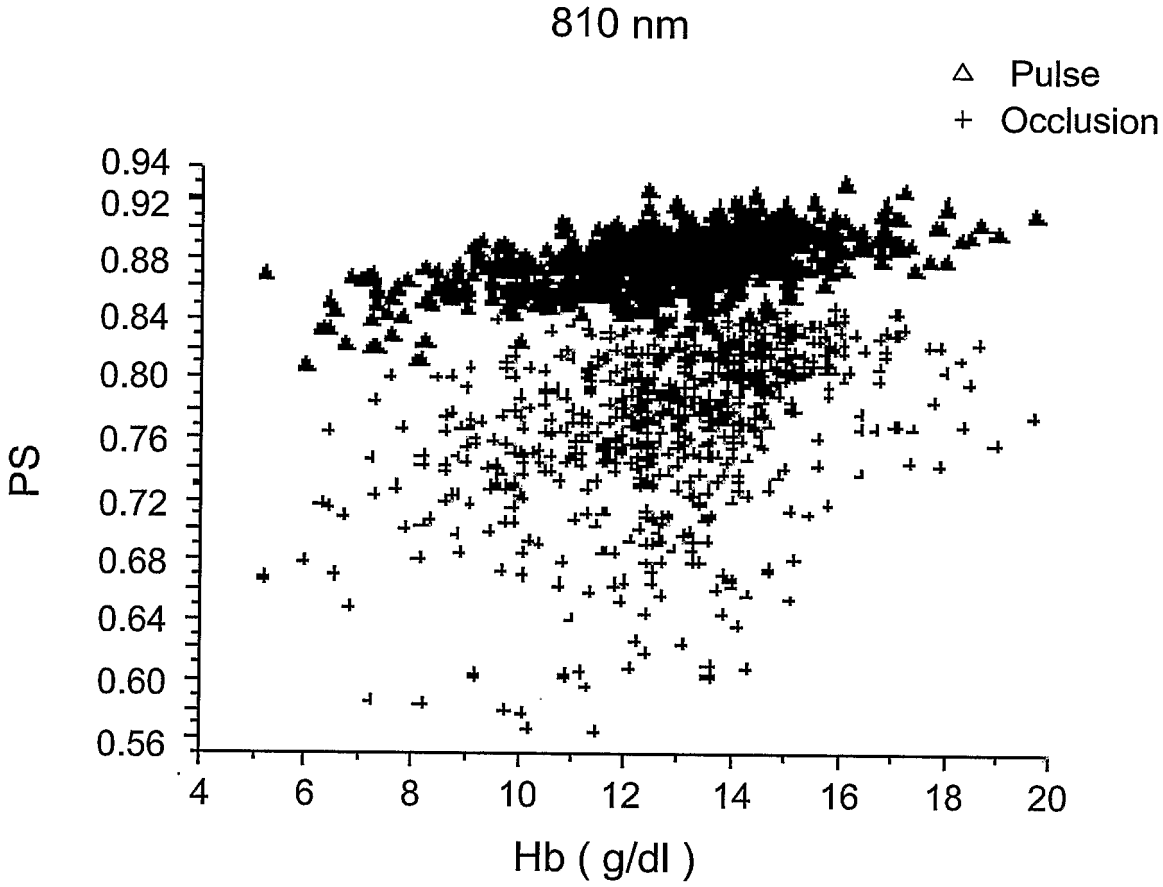
810 nm
Pulse
Occlusion
PS
0.94
0.92
0.88
0.84
0.80
0.76
0.72
0.68
0.64
0.60
0.56
4
6
8
10
12
14
16
18
20
Hb (g/dl)

FIG. 4C

INTERNATIONAL SEARCH REPORT

International application No
PCT/IL2006/000962

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B5/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61B

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US 6 400 972 B1 (FINE ILYA [IL]) 4 June 2002 (2002-06-04) cited in the application column 7, line 1 - column 11, line 41; claims 1-13	1-7, 10-18,20 8,9,19
Y A	US 6 711 424 B1 (FINE ILYA [IL] ET AL) 23 March 2004 (2004-03-23) cited in the application column 16, line 54 - column 17, line 10	8,9,19 1-7, 10-18,20
X A	WO 2004/105596 A1 (ORSENSE LTD [IL]; FINE ILYA [IL]; FINAROV ALEXANDER [IL]) 9 December 2004 (2004-12-09) page 7, line 7 - page 8, line 5 page 17, line 14 - page 23, line 29	15-19 1-14

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 November 2006	17/11/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Manschot, Jan

INTERNATIONAL SEARCH REPORT

International application No
PCT/IL2006/000962

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6 587 704 B1 (FINE ILYA [IL] ET AL) 1 July 2003 (2003-07-01) cited in the application column 13, lines 14-46	1-20

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IL2006/000962

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6400972 B1	04-06-2002	AU 764876 B2	04-09-2003
		AU 4643599 A	05-01-2000
		CA 2332921 A1	23-12-1999
		CN 1315844 A	03-10-2001
		EP 1087693 A1	04-04-2001
		WO 9965384 A1	23-12-1999
		IL 124965 A	14-08-2002
		JP 3689335 B2	31-08-2005
		JP 2002518075 T	25-06-2002
US 6711424 B1	23-03-2004	AU 1678800 A	03-07-2001
		EP 1251772 A1	30-10-2002
		WO 0145553 A1	28-06-2001
WO 2004105596 A1	09-12-2004	EP 1628564 A1	01-03-2006
US 6587704 B1	01-07-2003	NONE	

专利名称(译)	用于受试者中的非侵入性测量的方法和装置		
公开(公告)号	EP1942790A1	公开(公告)日	2008-07-16
申请号	EP2006780416	申请日	2006-08-17
申请(专利权)人(译)	ORSENSE LTD.		
当前申请(专利权)人(译)	ORSENSE LTD.		
[标]发明人	FINE ILYA		
发明人	FINE, ILYA		
IPC分类号	A61B5/00 A61B5/145 A61B5/1455		
CPC分类号	A61B5/6826 A61B5/0048 A61B5/0095 A61B5/14532 A61B5/14546 A61B5/1455 A61B5/6838		
优先权	11/205321 2005-08-17 US		
其他公开文献	EP1942790B1		
外部链接	Espacenet		

摘要(译)

提出了一种用于受试者（例如患者体内）的非侵入性测量的方法和系统。根据该技术，通过将外部电磁场施加到测量位置并检测测量位置的至少两个响应并且生成指示检测到的响应的数据，在对象中的测量位置上执行测量。这些至少两个响应的特征在于某个可控参数的至少两个不同值。测量包括在测量位置中的正常血流条件下执行的测量，使得能够生成指示针对至少两个参数值中的每一个的响应的第一时间变化的第一测量数据，并且包括在条件下执行的测量会话。在测量位置中的人工动力学，能够产生指示所述至少两个参数值中的每一个的响应的第二时间变化的第二测量数据。处理第一和第二测量数据以确定不同参数值的第一时间变化与所述不同参数值的第二时间变化之间的第二关系之间的第一关系。第一和第二关系用于确定至少一个血液和/或组织相关参数。