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(54) **METHOD FOR SPECTROPHOTOMETRIC BLOOD OXYGENATION MONITORING**

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(57) **ABSTRACT**

A method and apparatus for non-invasively determining the blood oxygenation within a subject's tissue is provided that utilizes a near infrared spectrophotometric (NIRS) sensor capable of transmitting a light signal into the tissue of a subject and sensing the light signal once it has passed through the tissue via transmittance or reflectance.
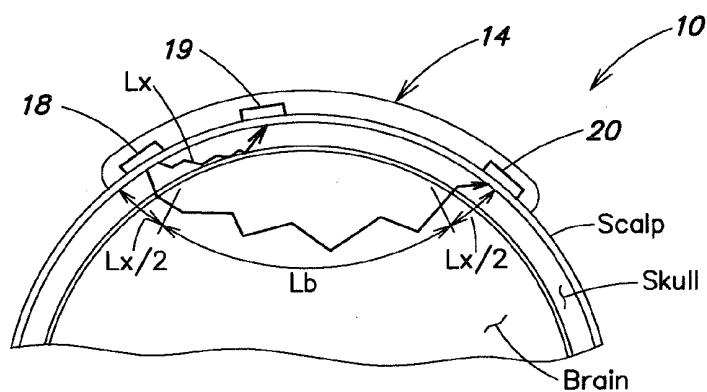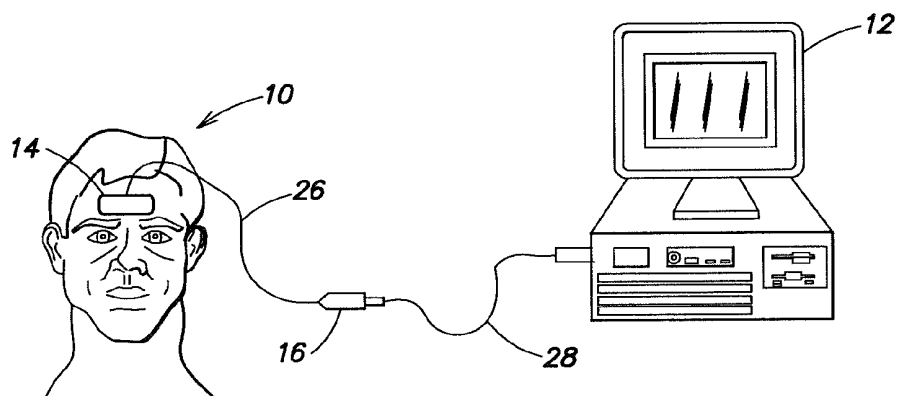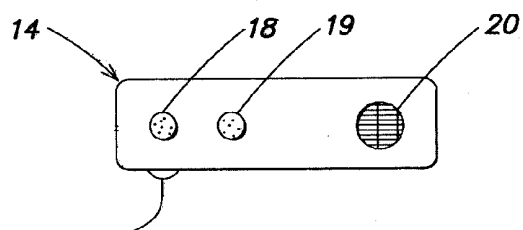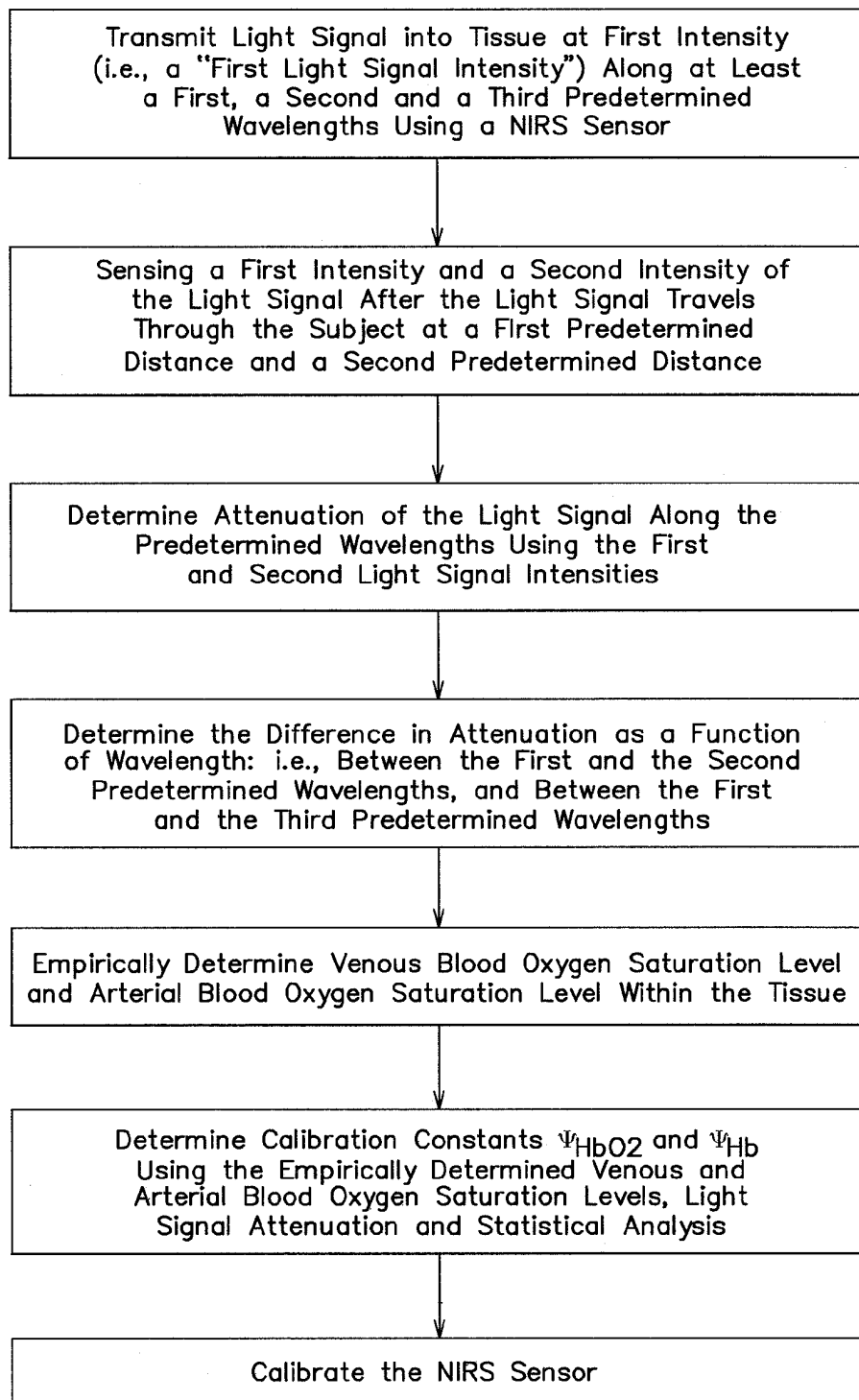
FIG. 1

FIG. 2

FIG. 3

Transmit Light Signal into Tissue at First Intensity
(i.e., a "First Light Signal Intensity") Along at Least
a First, a Second and a Third Predetermined
Wavelengths Using a NIRS Sensor

Sensing a First Intensity and a Second Intensity of
the Light Signal After the Light Signal Travels
Through the Subject at a First Predetermined
Distance and a Second Predetermined Distance

Determine Attenuation of the Light Signal Along the
Predetermined Wavelengths Using the First
and Second Light Signal Intensities

Determine the Difference in Attenuation as a Function
of Wavelength: i.e., Between the First and the Second
Predetermined Wavelengths, and Between the First
and the Third Predetermined Wavelengths

Empirically Determine Venous Blood Oxygen Saturation Level
and Arterial Blood Oxygen Saturation Level Within the Tissue

Determine Calibration Constants Ψ_{HbO2} and Ψ_{Hb}
Using the Empirically Determined Venous and
Arterial Blood Oxygen Saturation Levels, Light
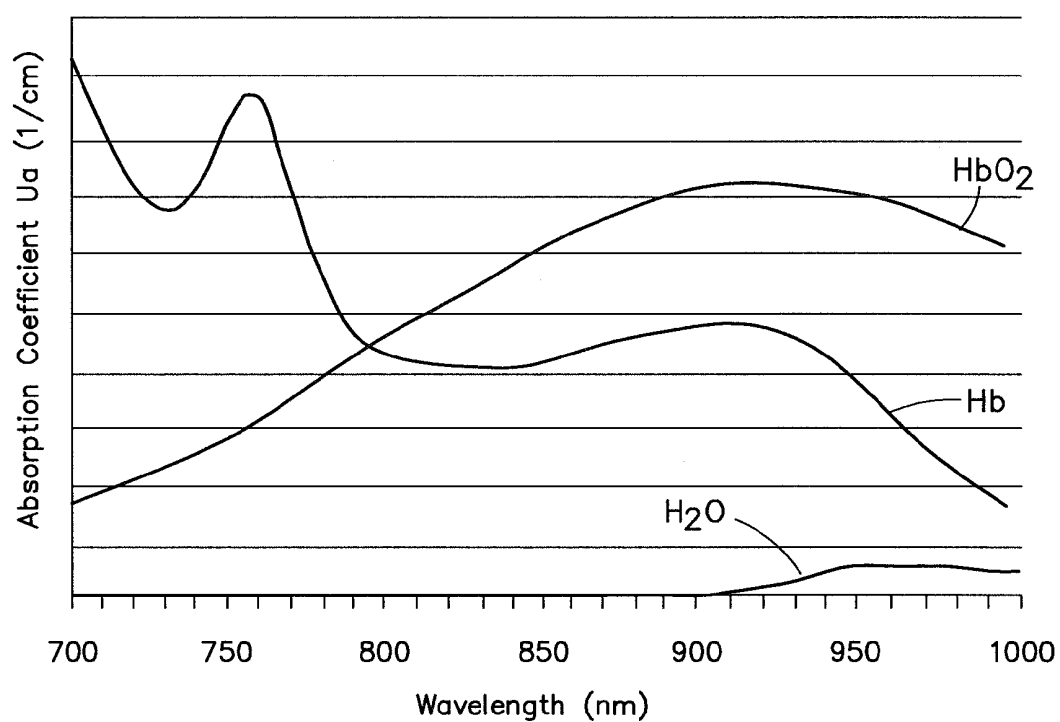Signal Attenuation and Statistical Analysis

Calibrate the NIRS Sensor

FIG. 4

FIG. 5

METHOD FOR SPECTROPHOTOMETRIC BLOOD OXYGENATION MONITORING

[0001] This application is a continuation of U.S. patent application Ser. No. 11/376,894 filed Mar. 16, 2006, which is a continuation of U.S. Pat. No. 7,072,701 filed Jul. 24, 2003, which claims the benefit of the filing date of U.S. Provisional Applications 60/398,937, filed 26 Jul. 2002, and 60/407,277 filed 30 Aug. 2002.

BACKGROUND OF THE INVENTION

[0003] 1. Technical Field

[0004] This invention relates to methods for non-invasively determining biological tissue oxygenation in general, and to non-invasive methods utilizing near-infrared spectroscopy (NIRS) techniques in particular.

[0005] 2. Background Information

[0006] The molecule that carries the oxygen in the blood is hemoglobin. Oxygenated hemoglobin is called oxyhemoglobin (HbO_2) and deoxygenated hemoglobin is deoxyhemoglobin (Hb). Total hemoglobin is the summation of the two states of hemoglobin (Total Hb=HbO_2+Hb), and is proportional to relative blood volume changes, provided that the hematocrit or hemoglobin concentration of the blood is unchanged. The mammalian cardiovascular system consists of a blood pumping mechanism (the heart), a blood transportation system (blood vessels), and a blood oxygenation system (the lungs). Blood oxygenated by the lungs passes through the heart and is pumped into the arterial vascular system. Under normal conditions, oxygenated arterial blood consists predominately of HbO_2. Large arterial blood vessels branch off into smaller branches called arterioles, which profuse throughout biological tissue. The arterioles branch off into capillaries, the smallest blood vessels. In the capillaries, oxygen carried by hemoglobin is transported to the cells in the tissue, resulting in the release of oxygen molecules ($HbO_2 \Rightarrow Hb$). Under normal conditions, only a fraction of the HbO_2 molecules give up oxygen to the tissue, depending on the cellular metabolic need. The capillaries then combine together into venuoles, the beginning of the venous circulatory system. Venuoles then combine into larger blood vessels called veins. The veins further combine and return to the heart, and then venous blood is pumped to the lungs. In the lungs, deoxygenated hemoglobin Hb collects oxygen becoming HbO_2 again and the circulatory process is repeated.

[0007] Oxygen saturation is defined as:

$$O_2 \text{ saturation } \% = \frac{HbO_2}{(HbO_2 + Hb)} * 100\% \qquad \text{(Eqn. 1)}$$

In the arterial circulatory system under normal conditions, there is a high proportion of HbO_2 to Hb, resulting in an arterial oxygen saturation (defined as $SaO_2\%$) of 95-100%. After delivery of oxygen to tissue via the capillaries, the proportion of HbO_2 to Hb decreases. Therefore, the measured oxygen saturation of venous blood (defined as $SvO_2\%$) is lower and may be about 70%.

[0008] One spectrophotometric method, called pulse oximetry, determines arterial oxygen saturation (SaO_2) of peripheral tissue (i.e., finger, ear, nose) by monitoring pulsatile optical attenuation changes of detected light induced by pulsatile arterial blood volume changes in the arteriolar vascular system. The method of pulse oximetry requires pulsatile blood volume changes in order to make a measurement. Since venous blood is not pulsatile, pulse oximetry cannot provide any information about venous blood.

[0009] Near-infrared spectroscopy (NIRS) is an optical spectrophotometric method of continually monitoring tissue oxygenation that does not require pulsatile blood volume to calculate parameters of clinical value. The NIRS method is based on the principle that light in the near-infrared range (700 to 1,000 nm) can pass easily through skin, bone and other tissues where it encounters hemoglobin located mainly within micro-circulation passages (e.g., capillaries, arterioles, and venuoles). Hemoglobin exposed to light in the near infra-red range has specific absorption spectra that varies depending on its oxidation state (i.e., oxyhemoglobin (HbO_2) and deoxyhemoglobin (Hb) each act as a distinct chromophore). By using light sources that transmit near-infrared light at specific different wavelengths, and measuring changes in transmitted or reflected light attenuation, concentration changes of the oxyhemoglobin (HbO_2) and deoxyhemoglobin (Hb) can be monitored. The ability to continually monitor cerebral oxygenation levels is particularly valuable for those patients subject to a condition in which oxygenation levels in the brain may be compromised, leading to brain damage or death.

[0010] The apparatus used in NIRS analysis typically includes a plurality of light sources, one or more light detectors for detecting reflected or transmitted light, and a processor for processing signals that represent the light emanating from the light source and the light detected by the light detector. Light sources such as light emitting diodes (LEDs) or laser diodes that produce light emissions in the wavelength range of 700-1000 nm at an intensity below that which would damage the biological tissue being examined are typically used. A photodiode or other light source detector is used to detect light reflected from or passed through the tissue being examined. The processor takes the signals from the light sources and the light detector and analyzes those signals in terms of their intensity and wave properties.

[0011] It is known that relative changes of the concentrations of HbO_2 and Hb can be evaluated using apparatus similar to that described above, including a processor programmed to utilize a variant of the Beer-Lambert Law, which accounts for optical attenuation in a highly scattering medium like biological tissue. The modified Beer-Lambert Law can be expressed as:

$$A_\lambda = -\log(I/I_0)_\lambda = \alpha_\lambda * C * d * B_\lambda + G \qquad \text{(Eqn. 2)}$$

wherein "A_λ" represents the optical attenuation in tissue at a particular wavelength λ (units: optical density or OD); "I_o" represents the incident light intensity (units: W/cm^2); "I" represents the detected light intensity; "α_λ" represents the wavelength dependent absorption coefficient of the chromophore (units: $OD*cm^{-}*\mu M^{-1}$); "C" represents the concentration of chromophore (units: μM); "d" represents the light source to detector (optode) separation distance (units: cm); "B_λ" represents the wavelength dependent light scattering differential pathlength factor (unitless); and "G" represents light attenuation due to scattering within tissue (units: OD).

The product of "$d*B_\lambda$" represents the effective pathlength of photon traveling through the tissue.

[0012] Absolute measurement of chromophore concentration (C) is very difficult because G is unknown or difficult to ascertain. However, over a reasonable measuring period of several hours to days, G can be considered to remain constant, thereby allowing for the measurement of relative changes of chromophore from a zero reference baseline. Thus, if time t_1 marks the start of an optical measurement (i.e., a base line) and time t_2 is an arbitrary point in time after t_1, a change in attenuation (ΔA) between t_1 and t_2 can be calculated, and variables G and 1_o will cancel out providing that they remain constant.

[0013] The change in chromophore concentration ($\Delta C = C(t_2) - C(t_1)$) can be determined from the change in attenuation ΔA, for example using the following equation derived from the modified Beer-Lambert Law:

$$\Delta A_\lambda = -\log(I_{t2}/I_{t1})_\lambda = \alpha_\lambda * \Delta C * d * B_\lambda \qquad \text{(Eqn. 3)}$$

Presently known MRS algorithms that are designed to calculate the relative change in concentration of more than one chromophore use a multivariate form of Equation 2 or 3. To distinguish between, and to compute relative concentration changes in, oxyhemoglobin (ΔHbO_2) and deoxyhemoglobin (ΔHb), a minimum of two different wavelengths are typically used. The concentration of the HbO_2 and Hb within the examined tissue is determined in μmoles per liter of tissue (μM).

[0014] The above-described MRS approach to determine oxygenation levels is useful, but it is limited in that it only provides information regarding a change in the level of oxygenation within the tissue. It does not provide a means for determining the absolute value of oxygen saturation within the biological tissue.

[0015] At present, information regarding the relative contributions of venous and arterial blood within tissue examined by NIRS is either arbitrarily chosen or is determined by invasive sampling of the blood as a process independent from the NIRS examination. For example, it has been estimated that NIRS examined brain tissue comprising about 60 to 80% venous blood and about 20 to 40% arterial blood. Blood samples from catheters placed in venous drainage sites such as the internal jugular vein, jugular bulb, or sagittal sinus have been used to evaluate NIRS measurements. Results from animal studies have shown that NIRS interrogated tissue consists of a mixed vascular bed with a venous-to-arterial ratio of about 2:1 as determined from multiple linear regression analysis of sagittal sinus oxygen saturation ($SssO_2$) and arterial oxygen saturation (SaO_2). An expression representing the mixed venous/arterial oxygen saturation ($SmvO_2$) in MRS examined tissue is shown by the equation:

$$SmvO_2 = Kv * SvO_2 + Ka * SaO_2 \qquad \text{(Eqn. 4)}$$

where "SvO_2" represents venous oxygen saturation; "SaO_2" represents arterial oxygen saturation; and Kv and Ka are the weighted venous and arterial contributions respectively, with Kv+Ka=1. The parameters Kv and Ka may have constant values, or they may be a function of SvO_2 and SaO_2. Determined oxygen saturation from the internal jugular vein ($SijvO_2$), jugular bulb ($SjbO_2$), or sagittal sinus ($SssO_2$) can be used to represent SvO_2. Therefore, the value of each term in Equation 4 is empirically determined, typically by discretely sampling or continuously monitoring and subsequently evaluating patient arterial and venous blood from tissue that the NIRS sensor is examining, and using regression analysis to determine the relative contributions of venous and arterial blood independent of the NIRS examination.

[0016] To non-invasively determine oxygen saturation within tissue at certain depth, it is necessary to limit the influence from the superficial tissues. For example, to determine brain oxygen saturation of adult human with NIRS technology, the contamination from extracranial tissue (scalp and skull) must be eliminated or limited.

[0017] What is needed, therefore, is a method for non-invasively determining the level of oxygen saturation within biological tissue that can determine the absolute oxygen saturation value rather than a change in level; a method that provides calibration means to account for energy losses (i.e., light attenuation) due to light scattering within tissue, other background absorption losses from biological compounds, and other unknown losses including measuring apparatus variability; and a method that can non-invasively determine oxygen saturation within tissue at certain depth by limiting the influence from the superficial tissues.

DISCLOSURE OF THE INVENTION

[0018] It is, therefore, an object of the present invention to provide a method for non-invasively determining the absolute oxygen saturation value within biological tissue.

[0019] It is a further object of the present invention to provide a method that provides calibration means to account for energy losses due to scattering as well as other background absorption from biological compounds.

[0020] It is a still further object of the present invention to provide a method that can non-invasively determine oxygen saturation within tissue at certain depth that limits the influence from the superficial tissues.

[0021] According to the present invention, a method and apparatus for non-invasively determining the blood oxygen saturation level within a subject's tissue is provided that utilizes a near infrared spectrophotometric (NIRS) sensor capable of transmitting a light signal into the tissue of a subject and sensing the light signal once it has passed through the tissue via transmittance or reflectance. The method includes the steps of: (1) transmitting a light signal into the subject's tissue, wherein the transmitted light signal includes a first wavelength, a second wavelength, and a third wavelength; (2) sensing a first intensity and a second intensity of the light signal, along the first, second, and third wavelengths after the light signal travels through the subject at a first and second predetermined distance; (3) determining an attenuation of the light signal for each of the first, second, and third wavelengths using the sensed first intensity and sensed second intensity of the first, second, and third wavelengths; (4) determining a difference in attenuation of the light signal between the first wavelength and the second wavelength, and between the first wavelength and the third wavelength; and (5) determining the blood oxygen saturation level within the subject's tissue using the difference in attenuation between the first wavelength and the second wavelength, and the difference in attenuation between the first wavelength and the third wavelength.

[0022] The present method makes it possible to account for energy losses (i.e., light attenuation) due to light scattering within tissue, other background absorption losses from biological compounds, and other unknown losses including measuring apparatus variability. By determining differential attenuation as a function of wavelength, the energy losses due to scattering as well as other background absorption from

biological compounds are cancelled out or minimized relative to the attenuation attributable to deoxyhemoglobin, and attenuation attributable to oxyhemoglobin.

[0023] In order to account for the resulting minimized differential attenuation attributable to tissue light scattering characteristics, fixed light absorbing components, and measuring apparatus characteristics, each of the parameters must be measured or calibrated out. Since direct measurement is difficult, calibration to empirically determined data combined with data developed using the NIRS sensor is performed by using regression techniques. The empirically determined data is collected at or about the same time the data is developed with the NIRS sensor. Once the calibration parameters associated with attenuation attributable to tissue light scattering characteristics, fixed light absorbing components, and measuring apparatus characteristics have been determined, the NIRS sensor can be calibrated.

[0024] The calibrated sensor can then be used to accurately and non-invasively determine the total oxygen saturation level in the original subject tissue or other subject tissue. In addition, if the effective pathlength of photon traveling through the tissue is known, for example, the separation distance ("d") between the light source to the light detector is known or is determinable, and the value of "B_λ", which represents the wavelength dependent light scattering differential pathlength factor is known or is determinable, then the total amount of concentrations of deoxyhemoglobin (Hb) and oxyhemoglobin (HbO$_2$) within the examined tissue can be determined using the present method and apparatus.

[0025] The calibrated sensor can be used subsequently to calibrate similar sensors without having to invasively produce a blood sample. Hence, the present method and apparatus enables a non-invasive determination of the blood oxygen saturation level within tissue. For example, an operator can create reference values by sensing a light signal or other reference medium using the calibrated sensor. The operator can then calibrate an uncalibrated sensor by sensing the same light signal or reference medium, and subsequently adjusting the uncalibrated sensor into agreement with the calibrated sensor. Hence, once a reference sensor is created, other similar sensors can be calibrated without the need for invasive procedure.

[0026] There are, therefore, several advantages provided by the present method and apparatus. Those advantages include: 1) a practical non-invasive method and apparatus for determining oxygen saturation within tissue that can be used to determine the total blood oxygen saturation within tissue as opposed to a change in blood oxygen saturation; 2) a calibration method that accounts for energy losses (e.g., light attenuation) due to light scattering within tissue, other background absorption losses from biological compounds, and other unknown losses including measuring apparatus variability; 3) a practical non-invasive method and apparatus for determining oxygen saturation within tissue that can distinguish between the contribution of oxygen saturation attributable to venous blood and that saturation attributable to arterial blood; and 4) a practical non-invasive method and apparatus for determining oxygen saturation within tissue at certain depth that limits the influence from the superficial tissues.

[0027] In an alternative embodiment, aspects of the above-described methodology are combined with pulse oximetry techniques to provide a non-invasive method of distinguishing between blood oxygen saturation within tissue that is attributable to venous blood and that which is attributable to arterial blood. Pulse oximetry is used to determine arterial oxygen saturation, and the arterial oxygen saturation is, in turn, used to determine the venous oxygen saturation.

[0028] These and other objects, features, and advantages of the present invention method and apparatus will become apparent in light of the detailed description of the invention provided below and the accompanying drawings. The methodology and apparatus described below constitute a preferred embodiment of the underlying invention and do not, therefore, constitute all aspects of the invention that will or may become apparent by one of skill in the art after consideration of the invention disclosed overall herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0029] FIG. 1 is a diagrammatic representation of a NIRS sensor.

[0030] FIG. 2 is a diagrammatic representation of a NIRS sensor placed on a subject's head.

[0031] FIG. 3 is a diagrammatic view of a NIRS sensor.

[0032] FIG. 4 is a block diagram of the present methodology for calibrating a MRS sensor.

[0033] FIG. 5 is a graph showing an exemplary plot of absorption coefficient vs. wavelength.

DETAILED DESCRIPTION THE INVENTION

[0034] The present method of and apparatus for non-invasively determining the blood oxygen saturation level within a subject's tissue is provided that utilizes a near infrared spectrophotometric (NIRS) sensor that includes a transducer capable of transmitting a light signal into the tissue of a subject and sensing the light signal once it has passed through the tissue via transmittance or reflectance. The present method and apparatus can be used with a variety of NIRS sensors. The present method is not limited to use with this preferred NIRS sensor, however.

[0035] Referring to FIGS. 1-5, the preferred NIRS sensor includes a transducer portion 10 and processor portion 12. The transducer portion 10 includes an assembly housing 14 and a connector housing 16. The assembly housing 14, which is a flexible structure that can be attached directly to a subject's body, includes one or more light sources 18 and light detectors 19, 20. A disposable adhesive envelope or pad is used for mounting the assembly housing 14 easily and securely to the subject's skin. Light signals of known but different wavelengths from the light sources 18 emit through a prism assembly. The light sources 18 are preferably laser diodes that emit light at a narrow spectral bandwidth at predetermined wavelengths. In one embodiment, the laser diodes are mounted within the connector housing 16. The laser diodes are optically interfaced with a fiber optic light guide to the prism assembly that is disposed within the assembly housing 14. In a second embodiment, the light sources 18 are mounted within the assembly housing 14. A first connector cable 26 connects the assembly housing 14 to the connector housing 16 and a second connector cable 28 connects the connector housing 16 to the processor portion 12. The light detector 20 includes one or more photodiodes. The photodiodes are also operably connected to the processor portion 12 via the first and second connector cables 26, 28. The processor portion 12 includes a processor for processing light intensity signals from the light sources 18 and the light detectors 19, 20.

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[0036] The processor utilizes an algorithm that characterizes a change in attenuation as a function of the difference in attenuation between different wavelengths. The present method advantageously accounts for but minimizes the effects of pathlength and parameter "E", which represents energy losses (i.e., light attenuation) due to light scattering within tissue (G), other background absorption losses from biological compounds (F), and other unknown losses including measuring apparatus variability (N).

$$E = G + F + N.$$

[0037] Referring to FIG. 1, the absorption $A_{b\lambda}$ detected from the deep light detector 20 comprises attenuation and energy loss from both the deep and shallow tissue, while the absorption $A_{x\lambda}$ detected from the shallow light detector 19 comprises attenuation and energy loss from shallow tissue only. Absorptions $A_{b\lambda}$ and $A_{x\lambda}$ can be expressed in the form of Equation 5 and Equation 6 below which is a modified version of Equation 2 that accounts for energy losses due to "E":

$$A_{b\lambda} = -\log(I_b/I_o)_\lambda = \alpha_\lambda * C_b * L_b + \alpha_\lambda * C_x * L_x + E_\lambda \quad \text{(Eqn. 5)}$$

$$A_{x\lambda} = -\log(I_x/I_o)_\lambda = \alpha_\lambda * C_x * L_x + E_{x\lambda} \quad \text{(Eqn. 6)}$$

Substituting Equation 6, into Equation 5 yields which represents attenuation and energy loss from deep tissue only:

$$A'_\lambda = A_{b\lambda} - A_{x\lambda} = \alpha_\lambda * C_b * L_b + (E_\lambda - E_{x\lambda}) = -\log\left(\frac{I_b}{I_x}\right)_\lambda \quad \text{(Eqn. 7)}$$

Where L is the effective pathlength of the photon traveling through the deep tissue and A'_1 and A'_2 are the absorptions of two different wavelengths. Let $E'_\lambda = E_\lambda - E_{x\lambda}$, therefore:

$$A'_1 - A'_2 = \Delta A'_{12} \quad \text{(Eqn. 8)}$$

Substituting Equation 7 into Equation 8 for A'_1 and A'_2, $\alpha A'_{12}$ can be expressed as:

$$\Delta A'_{12} = \alpha_{\lambda 12} * C_b * L_b + \Delta E'_{12} \quad \text{(Eqn. 9)}$$

and rewritten Equation 9 in expanded form:

$$\Delta A'_{12} = ((\alpha_{r1} - \alpha_{r2})[Hb]_b + (\alpha_{o1} - \alpha_{o2})[HbO_2]_b)L_b + (E'_1 - E'_2) \quad \text{(Eqn. 10)}$$

$$= (\Delta\alpha_{r12} * [Hb]_b * L_b) + (\Delta\alpha_{o12} * [HbO_2]_b * L_b) + \Delta E'_{12}$$

where:

[0038] $(\Delta\alpha_{r12} * [Hb]_b * L_b)$ represents the attenuation attributable to Hb;

[0039] $(\Delta\alpha_{o12} * [HbO_2]_b * L_b)$ represents the attenuation attributable to HbO_2; and

$\Delta E'_{12}$ represents energy losses (i.e. light attenuation) due to light scattering within tissue, other background absorption losses from biological compounds, and other unknown losses including measuring apparatus variability.

[0040] The multivariate form of Equation 10 is used to determine $[HbO_2]_b$ and $[Hb]_b$ with three different wavelengths:

$$\begin{bmatrix} \Delta A'_{12} - \Delta E'_{12} \\ \Delta A'_{13} - \Delta E'_{13} \end{bmatrix} (L_b)^{-1} = \begin{bmatrix} \Delta\alpha_{r12} & \Delta\alpha_{o12} \\ \Delta\alpha_{r13} & \Delta\alpha_{o13} \end{bmatrix} \begin{bmatrix} [Hb]_b \\ [HbO_2]_b \end{bmatrix} \quad \text{(Eqn. 11)}$$

Rearranging and solving for $[HbO_2]_b$ and $[Hb]_b$, simplifying the $\Delta\alpha$ matrix into $[\Delta\alpha']$:

$$\begin{bmatrix} \Delta A'_{12} \\ \Delta A'_{13} \end{bmatrix} [\Delta\alpha']^{-1} (L_b)^{-1} - \begin{bmatrix} \Delta E'_{12} \\ \Delta E'_{13} \end{bmatrix} [\Delta\alpha']^{-1} (L_b)^{-1} = \begin{bmatrix} [Hb]_b \\ [HbO_2]_b \end{bmatrix} \quad \text{(Eqn. 12)}$$

Then combined matrices $[\Delta A'] [\Delta\alpha']^{-1} = [A_C]$ and $[\Delta E] [\Delta\alpha']^{-1} = [\psi_c]$:

$$\begin{bmatrix} A_{Hb} \\ A_{HbO_2} \end{bmatrix} (L_b)^{-1} - \begin{bmatrix} \psi_{Hb} \\ \psi_{HbO_2} \end{bmatrix} (L_b)^{-1} = \begin{bmatrix} [Hb]_b \\ [HbO_2]_b \end{bmatrix} \quad \text{(Eqn. 13)}$$

The parameters A_{HB} and A_{HbO2} represent the product of the matrices $[\Delta A_\lambda]$ and $[\Delta a']^{-1}$ and the parameters ψ_{Hb} and ψ_{HbO2} represent the product of the matrices $[\Delta E'_\lambda]$ and $[\Delta\alpha']^{-1}$. To determine the level of cerebral blood oxygen saturation (SnO_2), Equation 13 is rearranged using the form of Equation 1 and is expressed as follows:

$$SnO_2 \% = \frac{(A_{HbO_2} - \psi_{HbO_2})}{(A_{HbO_2} - \psi_{HbO_2} + A_{Hb} - \psi_{Hb})} * 100\% \quad \text{(Eqn. 14)}$$

Note that the effective pathlength L_b cancels out in the manipulation from Equation 13 to Equation 14.

[0041] The value for SnO_2 is initially determined from $SmvO_2$ using Equation 4 and the empirically determined values for SvO_2 and SaO_2. The empirically determined values for SvO_2 and SaO_2 are based on data developed by discrete sampling or continuous monitoring of the subject's blood performed at or about the same time as the sensing of the tissue with the sensor. The temporal and physical proximity of the NIRS sensing and the development of the empirical data helps assure accuracy. The initial values for Kv and Ka within Equation 4 are clinically reasonable values for the circumstances at hand. The values for A_{HbO2} and A_{Hb} are determined mathematically using the values for $I_{b\lambda}$ and $I_{x\lambda}$ for each wavelength sensed with the MRS sensor (e.g., using Equation 5 and 6). The calibration parameters ψ_{Hb} and ψ_{HbO2}, which account for energy losses due to scattering as well as other background absorption from biological compounds, are then determined using Equation 14 and non-linear regression techniques by correlation to different weighted values of SvO_2 and SaO_2 (i.e., different values of Ka and Kv). Statistically acceptable values of Kv and Ka and ψ_{Hb} and ψ_{HbO2} are converged upon using the non-linear regression techniques. Experimental findings show that after proper selection of Ka and Kv, the calibration parameters ψ_{Hb} and ψ_{HbO2} are constant within a statistically acceptable margin of error for an individual NIRS sensor used to monitor brain oxygenation on different human subjects. In other words, once the sensor is calibrated it can be used on various human subjects and produce accurate information for each human subject. The same is true for animal subjects.

[0042] In an alternative method of determining the absolute oxygen saturation value Equation 7 is rewritten:

$$A'_\lambda - E'_\lambda = -\log\left(\frac{I_b}{I_x}\right)_\lambda - E'_\lambda \quad \text{(Eqn. 15)}$$

$$= \alpha_\lambda * C * L_b$$

$$= (\alpha_{r\lambda}[Hb]_b + \alpha_{o\lambda}[HbO_2]_b)L_b$$

For a two wavelength system, let "R" be a calibration index parameter:

$$R = \frac{A_1' - E_1'}{A_2' - E_2'} \qquad \text{(Eqn. 16)}$$

$$= \frac{(\alpha_{r1}[Hb]_b + \alpha_{o1}[HbO_2]_b)L_b}{(\alpha_{r2}[Hb]_b + \alpha_{o2}[HbO_2]_b)L_b}$$

$$= \frac{\alpha_{r1} + \alpha_{o1}\dfrac{[HbO_2]_b}{[Hb]_b}}{\alpha_{r2} + \alpha_{o2}\dfrac{[HbO_2]_b}{[Hb]_b}}$$

$$= \frac{\alpha_{r1} + \alpha_{o1}\dfrac{SnO_2}{1 - SnO_2}}{\alpha_{r2} + \alpha_{o2}\dfrac{SnO_2}{1 - SnO_2}}$$

Canceling out L_b and substituting:

$$\frac{[HbO_2]_b}{[Hb]_b} = \frac{SnO_2}{1 - SnO_2} \quad \text{from } SnO_2 = \frac{[HbO_2]_b}{[HbO_2]_b + [Hb]_b}$$

the following expression for SnO_2 is obtained:

$$SnO_2 = \frac{\alpha_{r1} - \alpha_{r2}R}{(\alpha_{r1} - \alpha_{o1}) + (\alpha_{o2} - \alpha_{r2})R} \qquad \text{(Eqn. 17)}$$

[0043] The value of A_1' and A_2' are determined by measuring I_b and I_x for each wavelength. The parameters E_1' and E_2' can be considered as empirically determined calibration coefficients derived from the "best-fit" combinations of the weighted ratios of venous and arterial blood-oxygen saturation of the brain. By using non-linear regression techniques, the values of E_1' and E_2' are determined by correlating to different combinations of venous and arterial oxygen saturation weighted values to find the "best-fit" relationship of "R" as a function of A_1', A_2', E_1' and E_2' (Equation 17) to a specific ratio of venous and arterial saturation weighted values.

[0044] In the determination of the SnO_2 percentage, the effective photon pathlength L_b cancels out. If, however, the photon pathlength is known or estimated, then the determination of the total value of Hb and/or HbO_2 is possible. For example, if a value for pathlength L_b is input into Equation 13 along with the calibration values ψ_{Hb} and ψ_{HbO2}, then the total value of Hb and/or HbO_2 can be calculated. According to Equation 2, pathlength L can be estimated from the product of "B*d". The light source to detector separation (optode) distance parameter "d" in the pathlength calculation is a measurable value and can be made constant by setting a fixed distance between light source to detector in the NIRS sensor design. Alternatively, the parameter "d" can be measured once the optodes are placed on the subject by use of calipers, ruler, or other distance measurement means. The pathlength differential factor "B" is more difficult to measure and requires more sophisticated equipment. From a large data set of measured neonatal and adult head differential pathlength factor values, an estimation of the value of "B" can be determined within a statistically acceptable margin of error. Sub-

stitution of these predetermined values of "B" into Equation 13 results in the determination of the total values of Hb and HbO_2.

[0045] An alternative method of determining total values of Hb and HbO_2 combines Equation 3 and Equation 13 together. The multivariate form of Equation 3 is shown below:

$$\begin{bmatrix} -\log(I_{t2}/I_{t1})_{\lambda 1}/L_{\lambda 1} \\ -\log(I_{t2}/I_{t1})_{\lambda 2}/L_{\lambda 2} \\ -\log(I_{t2}/I_{t1})_{\lambda 3}/L_{\lambda 3} \end{bmatrix} = \begin{bmatrix} \alpha_{Hb\lambda 1} & \alpha_{HbO_2 \lambda 1} \\ \alpha_{Hb\lambda 2} & \alpha_{HbO_2 \lambda 2} \\ \alpha_{Hb\lambda 3} & \alpha_{HbO_2 \lambda 3} \end{bmatrix} * \begin{bmatrix} \Delta Hb \\ \Delta HbO_2 \end{bmatrix} \qquad \text{(Eqn. 18)}$$

At time $t = t_1$, the values of ΔHb and ΔHbO_2 are zero. Applying Equation 13, and knowing the calibration values of ψ_{Hb} and ψ_{HbO2} at a predetermined differential pathlength factor "B" and optode separation "d", the total absolute values of Hb and HbO_2 are determined at time $t = t_1$, which are represented by $[Hb]_{t1}$ and $[HbO_2]_{t1}$ respectively. At time $t = t_2$, the values of ΔHb and ΔHbO_2 are then determined using Equation 18. The total values of Hb and HbO_2 are then determined at time $t = t_2$ using the following equations:

$$[Hb]_{t2} \Delta Hb(t_2) + [Hb]_{t1} \qquad \text{(Eqn. 19)}$$

$$[HbO_2]_{t2} = \Delta HbO_2(t_2)[HbO_2]_{t1} \qquad \text{(Eqn. 20)}$$

Equations 19 and 20 are valid only if all the shared parameters in Equations 13 and 18 are exact. Reduced to practice, the advantage of combining Equations 13 and 18 results in improved signal to noise ratio (SNR) in the calculation of the total values for Hb and HbO_2. Conversely, improved SNR in the calculation of SnO_2 is also obtained from the following expression:

$$SnO_2 \% = \frac{HbO_2}{(HbO_2 + Hb)} * 100\% \qquad \text{(Eqn. 21)}$$

[0046] After the calibration parameters ψ_{Hb} and ψ_{HbO2} are determined using the above-described methodology for an individual NIRS sensor, this particular sensor is said to be calibrated. A calibrated NIRS sensor affords accurate measurement of total tissue oxygen saturation, SnO_2, by noninvasive means. The calibrated sensor can be used thereafter on any human patient, including adults and neonates. The same is true for animal subject if the sensor was calibrated on animals. Although the present method is described above in terms of sensing blood oxygenation within cerebral tissue, the present method and apparatus are not limited to cerebral applications and can be used to determine blood oxygenation within tissue found elsewhere within the subject's body.

[0047] According to an additional aspect of the present invention, the above-described method can also be used to establish a calibrated "reference" sensor that can be used to calibrate similar sensors through the use of a phantom sample (also referred to as a "reference sample"). The phantom sample has optical characteristics that are similar to the tissue being examined by the MRS sensor. The calibrated reference MRS sensor is used to sense the phantom sample and produce reference values. Similar, but uncalibrated, NIRS sensors can thereafter be calibrated by sensing the same phantom sample and adjusting either the hardware of the uncalibrated sensor or the output of the uncalibrated sensor until the output of the uncalibrated sensor agrees with the reference values pro-

duced by the calibrated reference sensor. Therefore, the calibration parameters ψ_{Hb} and ψ_{HbO2} for the uncalibrated sensor would be determined from the phantom sample. This technique makes it unnecessary to calibrate each new sensor in the manner described above, and thereby provides a relatively quick and cost effective way to calibrate NIRS sensors.

[0048] Besides Hb and HbO$_2$, other biological constituents of interest (e.g., cytochrome aa$_3$, etc.) could be determined using the multivariate forms of equations 2, 3, 6 or 7. For each additional constituent to be determined, an additional measuring wavelength will be needed.

[0049] In an alternative embodiment, the above-described methodology can be combined with pulse oximetry techniques to provide an alternative non-invasive method of distinguishing between oxygen saturation attributable to venous blood and that attributable to arterial blood. As demonstrated by Equation 4, SmvO$_2$ is determined by the ratio of venous oxygen saturation SvO$_2$ and arterial oxygen saturation SaO$_2$. A calibrated NIRS sensor affords accurate measurement of total tissue oxygen saturation, SnO$_2$, by using regression techniques by correlation to mixed venous oxygen saturation SmvO$_2$. Therefore, the following expression will result:

$$SnO_2 = SmvO_2 = K_v * SvO_2 + Ka * SaO_2 \qquad \text{(Eqn. 22)}$$

Non-invasive pulse oximetry techniques can be used to determine the arterial oxygen saturation (SaO$_2$) of peripheral tissue (i.e., finger, ear, nose) by monitoring pulsatile optical attenuation changes of detected light induced by pulsatile arterial blood volume changes in the arteriolar vascular system. Arterial blood oxygen saturation determined by pulse oximetry is clinically denoted as SpO$_2$. If NIRS monitoring and pulse oximetry monitoring are done simultaneously and SpO$_2$ is set equal to SaO$_2$ in Equation 23, then venous oxygen saturation can be determined from the following expression:

$$SvO_2 = \frac{SnO_2 - (Ka * SpO_2)}{Kv} \qquad \text{(Eqn. 23)}$$

For the brain, venous oxygen saturation SvO$_2$ would be determined from internal jugular vein (SijvO$_2$), jugular bulb (SjbO$_2$), or sagittal sinus (SssO$_2$) and the parameters Ka and Kv would be empirically determined during the calibration of the NIRS sensor. Under most physiological conditions, SpO$_2$ is representative of brain arterial oxygen saturation SaO$_2$. Therefore, depending on which venous saturation parameter was used to calibrate the NIRS sensor, this clinically important parameter (i.e., SijvO$_2$, SjbO$_2$, or SssO$_2$) can be determined by Equation 24 by non-invasive means.

[0050] Since many changes and variations of the disclosed embodiment of the invention may be made without departing from the inventive concept, it is not intended to limit the invention otherwise than as required by the appended claims.

What is claimed is:

1-3. (canceled)

4. A method for non-invasively determining an absolute non-pulsatile blood oxygen saturation level within a subject's tissue, said method comprising the steps of:

providing a sensor having at least one transducer in communication with a processor, the transducer having at least one light source, and at least one light detector spaced apart from the light source;

transmitting light signals from the light source into the subject's tissue, wherein the transmitted light signals include a plurality of wavelengths;

sensing the light signals using the light detector and communicating information representative of the sensed light signals to the processor;

determining an attenuation of the transmitted light signals for each of the plurality of wavelengths using the processor to process the information representative of the sensed light signals; and

determining the absolute non-pulsatile blood oxygen saturation level within the subject's tissue using the processor, which determining includes determining a difference in attenuation between the plurality of wavelengths.

5. The method of claim 4, wherein the sensor is calibrated to account for energy losses attributable to one or more of light scattering, absorption from biological compounds other than hemoglobin, and apparatus variability.

6. The method of claim 5, wherein the sensor is calibrated based on a comparison of non-invasively collected oxygen saturation data and invasively collected oxygen saturation data.

7. The method of claim 4, further comprising the step of calibrating the sensor to account for energy losses attributable to one or more of light scattering, absorption from biological compounds other than hemoglobin, and apparatus variability.

8. The method of claim 7, wherein the calibrating includes using information representative of a comparison of non-invasively collected oxygen saturation data and invasively collected oxygen saturation data.

9. The method of claim 7, further comprising the step of determining one or both of an absolute non-pulsatile oxyhemoglobin concentration value and an absolute non-pulsatile deoxyhemoglobin concentration value.

10. The method of claim 7, wherein the step of calibrating includes calibrating the sensor to be subject independent.

11. The method of claim 4, further comprising the step of determining an arterial oxygen saturation of the subject using a pulse oximeter.

12. The method of claim 11, further comprising the step of determining a venous oxygen saturation within the subject's tissue using the arterial oxygen saturation determined using the pulse oximeter.

13. The method of claim 4, wherein the at least one transducer includes a first light detector spaced apart from the light source by a first distance, and a second detector spaced apart from the light source by a second distance, wherein the first distance is less than the second distance.

14. The method of claim 13, wherein the at least one sensor includes a first transducer and a second transducer, and the step of transmitting light signals includes transmitting light signals from the light source of the first transducer into the subject's tissue and transmitting light signals from the light source of the second transducer into the subject's tissue; and

wherein the step of sensing the light signals includes sensing the light signals from the light source of the first transducer using the first and second detectors of the first transducer, and sensing the light signals from the light source of the second transducer using the first and second detectors of the second transducer.

15. An apparatus for non-invasively determining an absolute non-pulsatile blood oxygen saturation level within a subject's tissue, comprising:

a sensor having at least one transducer, the transducer having at least one light source and at least one light detector spaced apart from the light source, and a processor in communication with the transducer;

wherein the transducer is operable to transmit light signals from the light source into the subject's tissue, wherein the transmitted light signals include a plurality of wavelengths, and operable to sense the light signals using the light detector and communicate information representative of the sensed light signals to the processor;

wherein the processor is adapted to determine an attenuation of the transmitted light signals for each of the plurality of wavelengths using the information representative of the sensed light signals, and is adapted to determine the absolute non-pulsatile blood oxygen saturation level within the subject's tissue, which saturation level determination includes determining a difference in attenuation between the plurality of wavelengths.

16. The apparatus of claim 15, wherein the sensor is calibrated to account for energy losses attributable to one or more of light scattering, absorption from biological compounds other than hemoglobin, and apparatus variability.

17. The apparatus of claim 16, wherein the sensor is calibrated based on a comparison of non-invasively collected oxygen saturation data and invasively collected oxygen saturation data.

18. The apparatus of claim 16, wherein the sensor is calibrated to be subject independent.

19. The apparatus of claim 16, wherein the processor is adapted to determine one or both of an absolute non-pulsatile oxyhemoglobin concentration value and an absolute non-pulsatile deoxyhemoglobin concentration value.

20. The apparatus of claim 15, further comprising a pulse oximeter operable to determine an arterial oxygen saturation of the subject.

21. The apparatus of claim 20, wherein the processor is adapted to determine a venous oxygen saturation value within the subject's tissue using the arterial oxygen saturation determined using the pulse oximeter.

22. The apparatus of claim 15, wherein the at least one transducer includes a first light detector spaced apart from the light source by a first distance, and a second detector spaced apart from the light source.

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专利名称(译)	分光光度法血氧监测方法

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摘要(译)

提供了一种用于非侵入性地确定受试者组织内的血液氧合的方法和装置，其利用近红外分光光度（NIRS）传感器，其能够将光信号传输到受试者的组织中并且一旦其通过就感测光信号。组织通过透射率或反射率。