Three-wavelength technique for the measurement of oxygen saturation in arterial blood and in venous blood

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1 Arterial and Venous Oxygen Saturation

The transfer of oxygen from the lungs to tissue cells is done mainly via the hemoglobin molecules in the red blood cells. Oxygen saturation in the blood, $SO_2$, is the ratio of oxygenated hemoglobin concentration, $[HbO_2]$ to total hemoglobin concentration in the blood, $[HbO_2]+[Hb]$:

$$SO_2 = \frac{[HbO_2]}{[HbO_2]+[Hb]}.$$  (1)

The values of $SO_2$ in arterial blood, $SaO_2$, and in venous blood, $SvO_2$, are both of clinical and physiological significance. $SaO_2$ depends on the adequacy of the ventilation and respiratory function, and its normal values are 94 to 98%. Assessment of $SaO_2$ is routinely done by pulse oximetry—a noninvasive optical technique that will be described in the following.

Even after transferring the required oxygen to the tissue in the capillaries, most of the hemoglobin is still oxygenated: normal values of the oxygen saturation in the venous blood, $SvO_2$, are 70 to 80%. $SvO_2$ also has physiological and clinical diagnostic significance, mainly because the arterial–venous difference in oxygen saturation is related to the oxygen consumption in the tissue. In contrast to pulse oximetry for $SaO_2$ measurement, the available methods for the measurement of $SvO_2$ (described later) have not been accepted for clinical use.3

2 Difference Oximetry

The techniques that have been suggested for the assessment of oxygen saturation in arterial or in venous blood are mainly based on the different light absorption spectra for oxygenated (HbO$_2$) and deoxygenated (Hb) hemoglobin. Hemoglobin is the main source for light absorption in the tissue in the red and near-infrared regions, but other chromophores such as melanin, myoglobin, and cytochrome oxidase can also absorb light in these regions. The contribution of hemoglobin to the absorption in the tissue can be isolated by measuring the changes in light absorption due to changes in the arterial or venous blood volume (difference oximetry) as described here.

The absorption constant of a blood sample depends on the hemoglobin concentration in the blood sample. The extinction coefficient $e$ of the hemoglobin is defined as the absorption constant of the blood sample divided by the concentration of the hemoglobin in the sample. The total extinction coefficient, $e$, of the hemoglobin in the blood sample is related to the oxygen saturation, $SO_2$ (which is either $SaO_2$ or $SvO_2$), since...
the hemoglobin in blood is a mixture of \( \text{HbO}_2 \) of extinction coefficient \( \epsilon_D \) and \( \text{Hb} \) of extinction coefficient \( \epsilon_H \):

\[
\epsilon = \epsilon_D \text{SO}_2 + \epsilon_D (1 - \text{SO}_2) = \epsilon_D + \text{SO}_2 (\epsilon_D - \epsilon_D).
\]  

(2)

The quantitative assessment of \( \text{SO}_2 \) from measurements of light transmission through a given tissue is not straightforward because of light scattering in the tissue, which results in the escape of light from the tissue in various directions and also increases the path length of the light and the probability of absorption in the blood. Light scattering is mainly caused by the difference in refractive index between the cellular organelles and the cellular fluid and between the intracellular and the extracellular fluids.\(^3\,^4\)

The transmitted light intensity, \( I_t \), through a tissue sample of width \( d \) that includes vessels with whole blood is given by\(^5\,^6\):

\[
I_t = I_0 \exp(-G - \epsilon Cl), \quad \ln(I_0/I_t) = G + \epsilon Cl,
\]

(3)

where \( I_0 \) is the incident light intensity, \( G \) is the attenuation due to absorption and scattering in the tissue, and \( l \) is the effective optical path length (which is greater than \( d \) because of the effect of scattering). \( C \) is the concentration of the hemoglobin in the tissue, which is equal to the product of the concentration of the hemoglobin in the blood and the concentration of the blood in the tissue.

In order to calculate the extinction coefficient \( \epsilon \) of the blood from light transmission measurements [and to derive from \( \epsilon \) the related parameter \( \text{SO}_2 \), see Eq. (2)], the effect of the attenuation \( G \) due to the tissue has to be eliminated. Since blood volume in the tissue can change, either spontaneously—in the heart rate, due to heart activity—or intentionally—due to deep breathing or through venous occlusion—the absorption of the light in the blood can be separated by measuring light transmission before and after the blood volume change. Figure 1 shows changes in finger blood volume, obtained by light transmission measurements, in correlation with deep breathing (recorded by bent optical fiber sensor). Figure 2 shows changes in finger blood volume due to venous occlusion.\(^7\) In both figures, blood volume changes due to heart activity (photoplethysmography, or PPG) are also presented.

If \( I_L \) is the lower light transmission through the tissue during the higher tissue blood volume and \( I_H \) is the higher transmitted light at lower tissue blood volume, then

\[
I_L = I_H \exp(-\epsilon \Delta Cl), \quad \ln(I_H/I_L) = \epsilon \Delta Cl,
\]

(4)

where \( \epsilon \) is the extinction coefficient for the blood volume increase, and \( \Delta C \) is the increase of hemoglobin concentration (in the tissue) due to the increase of blood volume. For small blood volume changes \( I_H - I_L \ll I_L \), and \( \ln(I_H/I_L) \) can be approximated by \( (I_H - I_L)/I_L \), so that:

\[
(I_H - I_L)/I_L = \epsilon \Delta Cl.
\]

(5)

Equation (5) is the basis for difference oximetry. We now describe the pulse oximetry technique for \( \text{SaO}_2 \) measurement. Then we describe the techniques for \( \text{SwO}_2 \) measurement.

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**Fig. 1** The curves of light transmission through the finger tissue (top) as a function of time during deep breathing. The lower curve presents the respiratory signal (obtained by measuring chest circumference changes). The high-frequency changes in light transmission are photoplethysmographic pulses—blood volume changes due to heart activity. The lower frequency changes in blood volume are due to respiration.

**Fig. 2** The curves of light transmission through the fingertip as a function of time for two wavelengths in the infrared region, during venous occlusion. (The period of the venous occlusion is indicated by two arrows.) The decrease in light transmission during the period of the venous occlusion is due to the higher venous blood volume, which increased by occluding the veins in the arm. The high-frequency changes in light transmission are photoplethysmographic pulses. (From Nitzan et al.\(^7\))
The photoplethysmographic signal. Light transmission through the finger decreases during systole. \( I_0 \) and \( I_s \) indicate the maximum and minimum values of light transmission during the heart period, respectively.

From the left ventricle into the peripheral vascular system. The maximal and minimal values of the PPG signal \((I_D^0 \text{ and } I_S^0)\) in Fig. 3, respectively) are proportional to the light irradiance transmitted through the tissue at end-diastole and at systole, when tissue blood volume is minimal or maximal, respectively.

In pulse oximetry, light transmission is measured at two wavelengths, \( \lambda_1 \) and \( \lambda_2 \), and \( I_D \) and \( I_S \) are substituted for \( I_H \) and \( I_L \), respectively in Eq. (5). The ratio of ratios \( R \), defined by

\[
R = \frac{[I_H^0 - I_L^0]/[I_H^0 - I_L^0]}{[I_D^0 - I_S^0]/[I_D^0 - I_S^0]},
\]

satisfies the equation

\[
R = \frac{e_1}{e_2},
\]

if the difference in the blood concentration change \( \Delta C \) between the two wavelengths can be neglected (\( \Delta C_1 = \Delta C_2 \)) and if we further assume that \( I_1 \) is not too different from \( I_2 \). The assumption that the illuminated tissue is the same for the two wavelengths seems to be valid for transmission PPG in the finger or earlobe but may be less accurate in reflection PPG, where the penetration depth for the two wavelengths may be different.

Under these assumptions, the relationship between the measured parameter \( R \) and the physiological parameter \( \text{SaO}_2 \) in the arterial blood can be derived through Eqs. (2) and (7), after simple manipulation:

\[
\text{SaO}_2 = \frac{e_{D1} - e_{D2}}{R(e_{O2} - e_{D2}) + (e_{D1} - e_{O1})}.
\]

Equation (8) could provide the required relationship between \( \text{SaO}_2 \) and \( R \), but since the values of \( e_O \) and \( e_D \) the extinction coefficients for HbO\(2^-\) and Hb, are known for all wavelengths. However, the assumption that \( I_1 \) is not too different from \( I_2 \), so that \( R \) can be approximated by \( e_1/e_2 \), can introduce significant error in the calculation of \( \text{SO}_2 \). In particular, the commercial pulse oximeters generally choose one of the wavelengths in the infrared region, above the isosbestic wavelength (805 nm), and the other in the red region, where the difference between \( e_O \) and \( e_D \) is maximal. The scattering constant for red light differs significantly from that of the infrared light, resulting in nonnegligible difference between the optical path lengths for the two wavelengths.

From Eqs. (5) and (6), using the assumption that \( \Delta C_1 \approx \Delta C_2 \):

\[
R(l_2/l_1) = e_1/e_2.
\]

By replacing \( R \) with \( R(l_2/l_1) \), Eq. (8) becomes

\[
\text{SaO}_2 = \frac{e_{D1} - R(e_{O2} - e_{D2})}{e_{D1} - e_{O1}}.
\]

The factor \( l_2/l_1 \) cannot generally be neglected, and if it is not known, \( \text{SaO}_2 \) cannot be derived from the measured value of \( R \) and Eq. (10). In practice, one determines the relationship between \( R \) and \( \text{SaO}_2 \) by calibrating each kind of pulse oximeter sensor. By replacing \( R \) with \( R(l_2/l_1) \), Eq. (8) becomes

\[
\text{SaO}_2 = (a + bR)/(c + dR)
\]

where the constants \( a-d \) or \( e-f \) are determined from the corresponding measured values of \( R \) and \( \text{SaO}_2 \). Equation (11) provides the required calibration for the derivation of \( \text{SaO}_2 \) from the measured parameter \( R \). The calibration is based on the assumption that \( l_2/l_1 \) does not change between different persons and different physiological and clinical situations. The validity of this assumption is limited, and deviations from it are probably the main origin for the inaccuracy in the assessment of \( \text{SaO}_2 \) by pulse oximetry.

The manufacturers of pulse oximeters generally claim an accuracy of 2%, which is the standard deviation (SD) of the differences between oxygen saturation values measured by the pulse oximeter and in vitro measurement by co-oximeter, the gold standard. An SD of 2% means that for 5% of the examinations, an error of 4% (2SD) is expected. Since the whole range of \( \text{SaO}_2 \) in normal subjects is 94 to 98%, and even for sick patients the interesting range for \( \text{SaO}_2 \) is 85 to 98%, an error of 4% is significant. Pulse oximetry is valuable for monitoring patients during surgical operations or in intensive-care units, where sudden decrease of \( \text{SaO}_2 \) by 4% indicates deterioration of the respiratory function of the patient. It cannot provide accurate assessment of the respiratory function of patients suffering from pulmonary diseases and of the effectiveness of their treatment.

If the two wavelengths used in the pulse oximeter are close to one another, then it is reasonable to assume that \( l_2/l_1 \) is approximately 1. In this case, \( \text{SaO}_2 \) can be derived from Eq. (8) without calibration. This was shown in our study, where we measured \( \text{SaO}_2 \) without calibration, using two infrared wavelengths (767 and 811 nm) and Eq. (8). The \( \text{SaO}_2 \) values were somewhat lower than those obtained by a commercial pulse oximeter, but the accuracy of the technique was
increased by substituting value of 0.97 for $l_2/l_1$ (obtained from published data) in Eq. (10). However, since $l_2/l_1$ is not known for the specific examination, the accuracy is still limited.

4 Three-Wavelength Difference Oximetry for the Measurement of $\text{SaO}_2$ and $\text{SvO}_2$

In the current paper, we suggest a method for the determination of $\text{SaO}_2$ from PPG measurement in three wavelengths, $\lambda_1$, $\lambda_2$, and $\lambda_3$, which avoids the need for calibration. From the minimal ($I_S$) and maximal ($I_D$) values of the PPG curves, the parameters $R_{12}$ and $R_{13}$ will be defined as:

$$R_{12} = \frac{[(I_D - I_3)/I_3]_{1}}{[(I_D - I_3)/I_3]_{2}},$$

$$R_{13} = \frac{[(I_D - I_3)/I_3]_{1}}{[(I_D - I_3)/I_3]_{3}},$$

(12)

similar to Eq. (6) for two wavelengths. Then, Eq. (10) will be used for the two pairs $\lambda_1$, $\lambda_2$, and $\lambda_1$, $\lambda_3$:

$$\text{SaO}_2 = \frac{e_{D1} - R_{12}(l_2/l_1)e_{D2}}{R_{12}[(l_2/l_1)(e_{O2} - e_{D2}) + (e_{D1} - e_{O1})]},$$

$$\text{SaO}_2 = \frac{e_{D1} - R_{13}(l_3/l_1)e_{D3}}{R_{13}[(l_3/l_1)(e_{O2} - e_{D3}) + (e_{D1} - e_{O1})]},$$

(13)

where $l_1$, $l_2$, and $l_3$ are the path lengths of the three wavelengths, $\lambda_1$, $\lambda_2$, and $\lambda_3$, respectively.

$R_{12}$ and $R_{13}$ of Eqs. (13) can be measured, and the extinction coefficients $e_D$ and $e_O$ for the three wavelengths can be found in the literature. However, in order to determine $\text{SaO}_2$, it is necessary to find $I_2/I_1$ and $I_3/I_1$. The path length $l$ (as well as the differential path length factor DPF, the ratio between the path length and the distance between the light source and the detector) increases with the scattering constant and decreases with the absorption constant. Since the dependence of scattering on the wavelength is smooth, the relationship between the path length $l$ and the wavelength $\lambda$ is also smooth in the spectral region where the extinction coefficients for hemoglobin are smoothly dependent on the wavelength, such as 750 to 900 nm. If $\lambda_1$, $\lambda_2$, and $\lambda_3$ are chosen as three adjacent wavelengths in an appropriate infrared region, one can assume a linear relationship between small changes in the path length $l$ and small changes in the wavelength $\lambda$:

$$l = l_0 + K(\lambda - \lambda_0),$$

(14)

yielding the following relationship between $l_1/l_2$ and $l_1/l_3$:

$$(\lambda_2 - \lambda_1)/(\lambda_3 - \lambda_1) = (l_2 - l_1)/(l_3 - l_1) = (l_2/l_1 - 1)/(l_3/l_1 - 1).$$

(15)

From the three equations, Eqs. (13) and Eq. (15), $\text{SaO}_2$ can be determined without prior information about $I_2/I_1$ and $I_3/I_1$, since we have three equations in three unknowns: $\text{SaO}_2$, $I_2/I_1$, and $I_3/I_1$.

$\text{SvO}_2$ cannot be obtained by using an algorithm similar to that of the conventional pulse oximetry for $\text{SaO}_2$ assessment, because the in vitro calibration used in pulse oximetry is not suitable for $\text{SvO}_2$ assessment. Calibration by extracting blood from the arteries for $\text{SaO}_2$ assessment is possible, because oxygen saturation is the same in the whole arterial system, since the arterial blood is distributed to all systemic organs from a single source—the left ventricle—and oxygen is not dissipated through the arterial wall. On the other hand, calibration by extracted venous blood cannot be applied for $\text{SvO}_2$ measurement, since blood extracted from big veins does not necessarily have the same value of oxygen saturation as that of the small veins of a specific tissue site, where the oximetry examination was performed.

Our three-wavelength technique, which avoids the need for calibration, also enables the determination of $\text{SvO}_2$ from the measurement of light transmission through the tissue in three wavelengths, during venous blood volume increase after applying external pressure above venous pressure to the veins proximal to the measurement site. From the minimal ($I_L$) and maximal ($I_H$) values of light transmission, the parameters $R_{12}$ and $R_{13}$ will be defined as:

$$R_{12} = \frac{[(I_H - I_L)/I_L]_{1}}{[(I_H - I_L)/I_L]_{2}},$$

$$R_{13} = \frac{[(I_H - I_L)/I_L]_{1}}{[(I_H - I_L)/I_L]_{3}},$$

(16)

Then, Eq. (13) will be used for the two pairs $\lambda_1$, $\lambda_2$, and $\lambda_1$, $\lambda_3$:

$$\text{SvO}_2 = \frac{e_{D1} - R_{12}(l_2/l_1)e_{D2}}{R_{12}[(l_2/l_1)(e_{O2} - e_{D2}) + (e_{D1} - e_{O1})]},$$

$$\text{SvO}_2 = \frac{e_{D1} - R_{13}(l_3/l_1)e_{D3}}{R_{13}[(l_3/l_1)(e_{O2} - e_{D3}) + (e_{D1} - e_{O1})]},$$

(17)

Here too, $l_1$, $l_2$, and $l_3$ are the path lengths of the three wavelengths, $\lambda_1$, $\lambda_2$, and $\lambda_3$, respectively.

Just as with the derivation of $\text{SaO}_2$, if $\lambda_1$, $\lambda_2$, and $\lambda_3$ are chosen so that Eq. (15) is fulfilled, $\text{SvO}_2$ can be determined together with the other two unknowns, $I_2/I_1$ and $I_3/I_1$ from the three equations, Eqs. (17) and Eq. (15).

5 Discussion

$\text{SaO}_2$ measurement by pulse oximetry is extensively used for assessing the adequacy of the cardiopulmonary system, mainly during surgical operations. Pulse oximetry is based on the different absorption spectra for oxygenated and deoxygenated hemoglobin and on the assumption that the PPG pulse reflects changes in arterial blood. Since the exact value of the path length increase due to light scattering is not known, in vitro calibration is required for deriving $\text{SaO}_2$ from the measured light attenuation data. The calibration is possible for the assessment of arterial blood oxygen saturation since the value of $\text{SaO}_2$ is the same in all the arteries. However, the derivation of an average factor of calibration between the light attenuation measured data and $\text{SaO}_2$ by utilizing examinations of a specific group of subjects is an inevitable source of error when this average factor is used for $\text{SaO}_2$ examination on a specific patient.

The proposed technique calculates $\text{SaO}_2$ through PPG measurements of three wavelengths in the near infrared, utilizing the values of the extinction coefficients for oxygenated
and deoxygenated hemoglobin for the three wavelengths. SaO₂ is derived from the R-values with no need for calibration, avoiding this source of error.

Our technique is different from former three-wavelength pulse oximetry techniques that have already been suggested for measurement of SaO₂ in the presence of carboxyhemoglobin or methemoglobin.14 The latter have absorption spectra differing from that of oxygenated or deoxygenated hemoglobin. These techniques are based on the conventional pulse oximetry and require calibration, while our technique is based on Eqs. (13) and (15).

Mannheimer et al.15 also suggested a technique for SaO₂ measurement, based on three wavelengths in order to compensate for different scattering at different wavelengths. This is done by deriving two values of SaO₂ by means of two pairs of wavelengths in the regular technique, using calibration for the determination of SaO₂ from R through equation like Eqs. (11). The first pair of wavelengths provides the SaO₂ initial assessment, and the other SaO₂ value, derived from the other pair of wavelengths, is used for correcting the initial assessment. In our technique, the two pairs of PPG measurement are utilized simultaneously, together with a third equation, Eq. (15), for the determination of SaO₂, and there is no need for calibration.

The elimination of the need for calibration enables the measurement of SvO₂ by measurement of venous blood volume increment in the tissue induced by venous occlusion. The value of SvO₂ is lower if the blood flow to the tissue is reduced while the demand for oxygen from the tissue remains unchanged. Hence the measurement of SvO₂ provides information about the tissue oxygen consumption or about the tissue blood flow. It should be noted, however, that the theoretical basis for the suggested technique is suitable for transmission measurements, which can be performed on fingers, hands, earlobes, and babies’ feet. The use of three-wavelength difference oximetry for reflection measurements depends on the validity of the assumption that the illuminated tissue is the same for the three wavelengths; this is wrong if the penetration depth for the three wavelengths is significantly different [see Eqs. (5)–(7)].

Tissue near-infrared spectroscopy (NIRS) is a noninvasive optical technique for the determination of oxygenation and hemodynamics in tissue and in particular venous blood oxygen saturation, SvO₂. NIRS is aimed at the evaluation of the concentrations of chromophores (such as HbO₂ and Hb) in the tissue from the measurement of light transmission in several wavelengths and deriving from it the absorption constant in these wavelengths. Several techniques have been developed for the isolation of the absorption constant from the scattering effects: time-resolved spectroscopy, frequency-domain spectroscopy, and spatially resolved spectroscopy.3,5,6,16,17

The advantage of NIRS techniques is that they can provide absolute values of HbO₂ and Hb concentration. Pulse oximetry and the other difference oximetry techniques, either with or without calibration, can provide information only on oxygen saturation, in arterial or in venous blood. However, NIRS techniques have two drawbacks: they are expensive because they require sophisticated technology and they are generally based on the similarity of the tissue to a mathematical model with simplified boundary conditions.5,6,17 In practice, tissue blood oxygen saturation values obtained by NIRS techniques were found to be lower than expected from physiological data obtained by other techniques.16,18

As stated earlier, the problem in the determination of the absorption constant is the unknown value of the path length. In some studies, the problem was solved by using the mean values of the differential path length factor (DPF, the ratio of path length l and the light source and detector spacing), determined in healthy persons by one of the NIRS techniques.3,9,10,20 This method is based on the assumption that for a given sort of tissue, the DPF is approximately constant for all healthy persons and patients and is approximately independent of the different physiological and clinical situations. This assumption is debatable because the intensity of scattering differs between individuals and can change during changes in metabolism19 and because DPF differs between males and females19,21 and the standard deviations for males and for females are 15 to 18%.

The current paper presents a three-wavelength method for measuring oxygen saturation in arterial or venous blood, which is calibration-free and does not rely on a theoretical model that does not model real tissue very well. The method has the potential to lead to an accurate technique for oxygen saturation measurements, but experimental validation of the theory is still required to confirm this claim.

Acknowledgment

The study was partly supported by the E. W. Joseph Fund.

References