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Notes on the apparent discordance of pulse oximetry and multi-wavelength haemoglobin photometry

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Multi-wavelength photometers, blood gas analysers and pulse oximeters are widely used to measure various oxygen-related quantities. The definitions of these quantities are not always correct. This paper gives insight in the various definitions for oxygen quantities. Furthermore, the possible influences of dyshaemoglobins and fetal haemoglobin on the accuracy of pulse oximetry are discussed.

As pulse oximeters are constructed for the determination of arterial oxygen saturation, they should be validated with sample oxygen saturation values and not with the oxyhaemoglobin fraction. The influence of carboxyhaemoglobin is insubstantial over an oxygen saturation range of 0% to 100%. Through the presence of methaemoglobin, pulse oximetry will give an underestimation above 70% and an overestimation below 70% oxygen saturation. The influence of fetal haemoglobin is insignificant in the neonatal use of pulse oximetry, in the range of 75% to 100% arterial oxygen saturation. However, a pulse oximeter underestimates the arterial oxygen saturation at the 25% level with 5%, if the pulse oximeter has been calibrated in human adults. Such a low level of arterial oxygen saturation can be present in the fetus during labor.

Key words: Dyshemoglobins; fetal hemoglobin; multi-wavelength analysis; oxygen saturation; pulse oximetry.

Pulse oximetry is different from conventional two-wavelength in vitro oximetry in the way in which the photometric signals are produced. However, the relationship between these signals and the quantity to be measured is essentially the same as has been used from the very beginning of photometric oxygen saturation (\(\frac{vO_2}{v}\)) measurement. Therefore, it was quite unexpected that the general use of this type of oximeter gave rise to widespread uncertainty concerning what pulse oximetry actually measured (1-4). This uncertainty did not arise from pulse oximetry per se, but resulted from experiments in which pulse oximetry data were compared with simultaneously obtained results of multi-wavelength photometers (CO-Oximeters) (5-8).

In this article we reflect on various definitions used for oxygen-related quantities in which this uncertainty has its roots. A related problem is whether dyshaemoglobins and human fetal haemoglobin affect the accuracy of pulse oximetry (9, 10). We therefore discuss the effect of dyshaemoglobins and fetal haemoglobin on blood sample analysis by CO-Oximeters, as well as on pulse oximetry.

Oxygen saturation estimated by multi-wavelength photometers

The first oximeters for use in vitro were two-wavelength photometers which measured the ratio of the concentrations of oxyhaemoglobin (\(cO_2Hb\)) and deoxyhaemoglobin (\(cHHb\)) in haemolysed whole blood. For such a two-wavelength system \(sO_2\) is written as follows:

\[
sO_2 = \frac{cO_2Hb}{cO_2Hb + cHHb} \quad (\text{Eq. 1})
\]

More recent types of multi-wavelength analysers use more wavelengths (four to six) which make it possible to measure, besides concentrations of oxyhaemoglobin and deoxyhaemoglobin, also concentrations of dyshaemoglobins. Dyshaemoglobins are haemoglobin derivatives that are permanently or temporarily unable to bind oxygen in the physiological oxygen range. The common dyshaemoglobins are carboxyhaemoglobin (COHb), methaemoglobin (MetHb) and sulphaemoglobin (SHb). Generally, SHb is negligible in human blood (11). From the concentration of the measured quantities, fractions of the
The fraction of oxyhaemoglobin (FOHb) and the total haemoglobin concentration (ctHb) are calculated as follows (Eq. 2 and 3):

\[ FOHb = \frac{c_O_2Hb}{ctHb} \quad \text{(Eq. 2)} \]
\[ ctHb = c_O_2Hb + c_COHb + c_MetHb \quad \text{(Eq. 3)} \]

From equations 1 and 3 follows the equation for the \( sO_2 \):

\[ sO_2 = \frac{c_O_2Hb}{(ctHb - c_COHb - c_MetHb)} \quad \text{(Eq. 4)} \]

At this point confusion started. In the absence of dysaemoglobins \( sO_2 \) is equal to \( FOHb \). However, often small amounts of dysaemoglobins are present in blood, and in that case \( FOHb \) (equation 2) was thought to be a better way of defining the oxygen saturation than \( sO_2 \) according to equation 4 (5-8). To distinguish these quantities, \( FOHb \) according to equation 2 was called “fractional saturation”, while \( sO_2 \) according to equation 4 was called “functional saturation”. The term “fractional saturation” is misleading while \( sO_2 \) reflects the ratio of oxyhaemoglobin to total haemoglobin and not the extent to which the haemoglobin has been saturated with oxygen; the term even does not comply with the definition of “saturation”. As “fractional saturation” is a misnomer, the term “functional” is redundant.

Confusion increased when pulse oximetry data were compared with \( FOHb \) as measured by multi-wavelength photometers, demonstrating that pulse oximeters were insensitive to considerable amounts of dysaemoglobins (5-7). This was interpreted as a short-coming of the pulse oximeter, whereas it was a sign of proper wavelength selection, making the two-wavelength system specifically sensitive to changes in \( sO_2 \). Pulse oximetry data should therefore be compared to \( sO_2 \) measured by the multi-wavelength photometer using equation 4.

**Oxygen saturation estimated through the oxygen haemoglobin dissociation curve**

Another way to determine \( sO_2 \) is by the use of pH/blood gas analysers. These analysers are able to measure the partial pressure of oxygen (\( pO_2 \)), the partial pressure of carbon dioxide (\( pCO_2 \)) and the pH, which are used to calculate \( sO_2 \). \( sO_2 \) is related to \( pO_2 \) as visualized by the oxyhaemoglobin dissociation curve (ODC) (12, 13). The position of the ODC is represented by the \( p50 \), i.e., the \( pO_2 \) corresponding to an \( sO_2 \) of 50%. The standard ODC yields a \( p50 \) of 3.55 kPa (26.6 mmHg) for human adult blood at a plasma pH of 7.4, a \( pCO_2 \) of 5.33 kPa (40 mmHg), and a temperature of 37 °C (14, 15). When oxygen affinity decreases, the ODC shifts to the right and the \( p50 \) increases. Such a shift can be caused by a decrease in pH, an increase of \( pCO_2 \), a rise in temperature and an increase in the 2,3-diphosphoglycerate (2,3-DPG) concentration in the erythrocytes. For changes in pH, \( pCO_2 \) and temperature, pH/blood gas analysers use an algorithm to correct the estimation of \( sO_2 \) (12, 13, 15). For human adult blood with normal haemoglobin and normal 2,3-DPG, the estimated \( sO_2 \) values are fairly accurate. However, the calculated \( sO_2 \) will be inaccurate if the 2,3-DPG concentration is outside the normal range, or if haemoglobin of other species, fetal haemoglobin, dysaemoglobins or abnormal haemoglobins are present (16). As the pH/blood gas analysers are mostly combined with multi-wavelength photometers, the total oxygen concentration (\( ctO_2 \)) can also be calculated:

\[ ctO_2 = (ctHb - c_COHb - c_MetHb) \cdot \alpha + pO_2 \cdot \alpha_0 \quad \text{(Eq. 5)} \]

\( cdysHb \) is the dysaemoglobin concentration, and \( \alpha \) and \( \alpha_0 \) are the concentrational solubility coefficient of oxygen in blood. At 37 °C, \( \alpha_0 \) is 0.01 mmol/L·kPa.

The effect of fetal haemoglobin and dysaemoglobins on sample \( sO_2 \) values and pulse oximetry saturation readings

Recently, pulse oximetry has been used for monitoring the fetus during labor. Human fetal haemoglobin (HbF) and human adult haemoglobin (HbA) differ slightly in their spectra in the visible range (Table 1) (10). These small differences, however, may lead to a slight overestimation in \( sO_2 \) of blood samples, if the human adult matrix is used in the multi-wavelength photometer. For fully saturated neonatal cord blood samples with a HbF fraction between 62% and 86%, the OSM HbA (Radiometer Medical A/S, Denmark) measured 103.6% to 105.6% \( sO_2 \) using the adult matrix (17). Nowadays, most multi-wavelength photometers are equipped with a correction algorithm (fetal matrix) to obtain the proper \( sO_2 \) value of a fetal or neonatal blood sample.

The small differences in spectra between HbF and HbA may also affect the accuracy of pulse oximetry. Most
DEFINITIONS AND ERRORS IN PULSE OXIMETRY

Pulse oximeters are programmed with a calibration curve derived from studies in healthy adults. These calibration curves may not be applicable to the neonate with high concentrations of HbF. Zijlstra et al. (10), using the wavelengths commonly encountered in pulse oximetry (660 nm and 940 nm), have shown that these small differences in the spectra are of minor importance for the accuracy of neonatal pulse oximetry. Since the fetus has much lower arterial $\text{O}_2$ values, we recalculated the influence of HbF over an extended $\text{O}_2$ range, in the same way as described earlier (10), using equation 6.

$$\text{S}_\text{O}_2 = \frac{\text{E}_{660} - \text{E}_{940}}{\text{E}_{660} - \text{E}_{660} - (\text{E}_{660} - \text{E}_{940}) \cdot (\text{A}_{660}/\text{A}_{940})}$$  (Eq. 6)

in which $\text{A}_{660}/\text{A}_{940}$, the ratio of the absorbance at 660 nm and 940 nm is considered to correspond with the spectrophotometric ratio measured by the pulse oximeter. As shown in Table 2, the effect of 100% HbF is of minor importance for the accuracy of pulse oximetry at 75% to 100% $\text{S}_\text{O}_2$, but at 25% $\text{S}_\text{O}_2$, an underestimation of about 5% $\text{S}_\text{O}_2$ is present. Equation 6, based on Lambert-Beer’s law, is often used as a simple theoretical model for pulse oximetry. This model does not take into account the influence of multiple scattering of light. Schmitt (18) described a more complex model with absorption and scattering coefficients, for transmission as well as reflection pulse oximetry. Under the assumption that HbF only changes the absorption coefficients and not the scattering coefficients, we found comparable results as described in Table 2 when using the model of Schmitt (18) and incorporating the absorption coefficients as given in Table 1 (Fig. 1).

The influence of 10% COHb and 10% MetHb are also given in Table 2. The calculations were performed on the basis of the absorbivities for COHb and MetHb according to Zijlstra et al. (10). The error caused by 10% COHb is insubstantial over the whole $\text{S}_\text{O}_2$ range, but MetHb gives an underestimation at >70% $\text{S}_\text{O}_2$ and an overestimation at <70% $\text{S}_\text{O}_2$.

**Table 2.** Influence of Hbf, COHb, and MetHb on $\text{S}_\text{O}_2$ by spectro-photometric method using 660 nm and 940 nm wavelengths.

<table>
<thead>
<tr>
<th>Derivative oxygen saturation (%)</th>
<th>100% HbA</th>
<th>75.0</th>
<th>50.0</th>
<th>25.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>50% HbF</td>
<td>100.2</td>
<td>74.4</td>
<td>48.6</td>
<td>22.7</td>
</tr>
<tr>
<td>100% HbF</td>
<td>100.4</td>
<td>73.8</td>
<td>47.1</td>
<td>20.3</td>
</tr>
<tr>
<td>HbA:10% COHb</td>
<td>99.1</td>
<td>74.2</td>
<td>49.3</td>
<td>24.4</td>
</tr>
<tr>
<td>HbA:10% MetHb</td>
<td>93.0</td>
<td>73.7</td>
<td>54.4</td>
<td>35.1</td>
</tr>
<tr>
<td>50% HbF:10% COHb</td>
<td>99.3</td>
<td>73.6</td>
<td>47.9</td>
<td>22.1</td>
</tr>
<tr>
<td>50% HbF:10% MetHb</td>
<td>92.9</td>
<td>73.3</td>
<td>53.6</td>
<td>33.9</td>
</tr>
<tr>
<td>100% HbF:10% COHb</td>
<td>99.5</td>
<td>73.0</td>
<td>46.4</td>
<td>19.8</td>
</tr>
<tr>
<td>100% HbF:10% MetHb</td>
<td>92.8</td>
<td>72.8</td>
<td>52.8</td>
<td>32.7</td>
</tr>
</tbody>
</table>

* 100% HbA, 100% adult haemoglobin used as reference.
* HbA:10% COHb, 100% adult haemoglobin, of which 10% is liganded with CO.
* 50% HbF:10% COHb, 50% fetal haemoglobin and 50% adult haemoglobin, of which 10% is liganded with CO.

The slight differences between the data in this table and those of Table 4 in reference 10 are due to the fact that the present data are calculated on the basis of all measured absorbivities, whereas in reference 10 only statistically significant differences between the absorbivities of HbA and Hbf have been taken into account.

**DISCUSSION**

The widespread use of multi-wavelength photometers, blood gas analysers and pulse oximeters makes it possible to measure various oxygen-related quantities. It depends on the clinical problem which oxygen quantity or combination of quantities is most suitable. In most cases several quantities are necessary for a proper description of the oxygen status of the blood.
It has been reported that in the presence of high levels of COHb, pulse oximetry provides erroneous readings (5, 7). However, this is based on a misunderstanding of pulse oximetry as described earlier (10). Pulse oximeters are developed to determine the arterial oxygen saturation and should therefore be validated with \( \text{s}_0 \) values in blood samples determined according to equation 4 and not by the oxyhaemoglobin fraction. Validation studies which use the oxyhaemoglobin fraction as the standard are comparing apples with oranges.

The common dyshaemoglobins are COHb and MetHb. COHb levels are low in healthy non-smoking adults, but may rise to 10% as a consequence of smoking and urban pollution (11). In non-smoking pregnant women and their newborns, COHb concentrations are reported to be < 0.5%. COHb concentrations in blood of newborns of cigarette smoking mothers were higher (COHb=1.9%, SD=1.2%) (19). However, as shown in Table 2, the influence of CoHb on the accuracy of pulse oximetry is of minor importance in the neonatal arterial \( \text{s}_0 \) range, the \( \text{s}_0 \) at low \( \text{s}_0 \) levels and overestimate the \( \text{s}_0 \) at high \( \text{s}_0 \) levels. This is in agreement with earlier reports (7, 10).

Fetal haemoglobin may lead to a small overestimation of \( \text{s}_0 \) in blood samples (17) if the adult matrix is used in the multi-wavelength photometer, because the absorption spectra of fetal and adult haemoglobin differ slightly (10). To obtain the proper \( \text{s}_0 \) for fetal or neonatal blood, most multi-wavelength photometers offer correction possibilities. The influence of Hbf on the accuracy of pulse oximetry will be of minor importance in the neonatal arterial \( \text{s}_0 \) range. However, for the fetus, which has a much lower normal arterial \( \text{s}_0 \) range, the underestimation may be as large as 5% \( \text{s}_0 \) at the level of 25% arterial \( \text{s}_0 \) if oximeters are used with a calibration line determined in adults. Using a more complex model we also found an underestimation of 5% \( \text{s}_0 \) under the assumption that Hbf only changes the absorption coefficients and not the scattering coefficients (18).

REFERENCES

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