Comparison of three methods to measure absolute cerebral hemoglobin concentration in neonates by near-infrared spectrophotometry

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Abstract. Three methods by which to determine absolute total cerebral hemoglobin concentration (tHb in μmol/L) by near-infrared spectroscopy (NIRS) have evolved: (1) tHbo, requiring oxygenation changes and arterial oxygen saturation measurements as a reference using a relative NIRS algorithm, (2) tHbg, using a geometrical multidistance principle and (3) tHbgo, a combination of both. The aim of this study was to compare the three methods quantitatively. Sixteen clinically stable preterm infants with a mean gestational age of 29.6 (range of 25.1–36.4) weeks, birthweight of 1386 (680–2820) g and a postnatal age of 2.5 (0.5–6) days, who needed supplemental oxygen, were enrolled. The mean±standard deviation tHbg was 150.2 ±41.8 μmol/L (range of 61.6–228.9 μmol/L), the tHbo was 62.1 ±27.2 μmol/L (26.0–110.8 μmol/L) and the tHbgo was 89.3 ±45.6 μmol/L (26.5–195.9 μmol/L). The correlation coefficient among the three methods were tHbg and tHbgo r = 0.736; tHbo and tHbgo r = 0.938; tHbg and tHbo r = 0.598. A multiple regression with variable selection by Mellow’s C(p) showed, that tHbg was correlated to the birthweight, the postnatal age, the heart rate and the pCO2 (r² = 0.588), tHbo and tHbgo were associated with the hemoglobin concentration in the blood, the mean arterial blood pressure and the pCO2 (r² = 0.493 and 0.406, respectively). The three methods (tHbg, tHbo, and tHbgo) give systematically different tHb readings and large intersubject variability. © 2002 Society of Photo-Optical Instrumentation Engineers.

Keywords: absolute cerebral hemoglobin concentration; oxygenation change; near infrared spectroscopy; test retest variability; neonate.

1 Introduction

Despite decreasing mortality, the incidence of brain lesions in preterm neonates is still high. There are two types of lesions: hemorrhagic (bleeding) and ischaemic (infarction). Their exact etiology is still unknown. Better knowledge of the neonatal hemodynamics may help either by creating a better understanding of the etiology or as an early indicator of lesions. Near-infrared spectroscopy (NIRS) has been applied to measure the cerebral hemodynamics. In particular, the total cerebral hemoglobin (tHb) concentration (in μmol/L) may be an early indicator of brain lesions.1–3 With respect to this application it is important to compare different methods using NIRS to determine the tHb.

Two methods by which to determine the absolute tHb by continuous wave NIRS were previously developed.

The first method (the tHbo method) requires a slow change in oxygenation and arterial oxygen saturation (SaO₂ in %) measurements as a reference.1–3 This method is used for continuous wave NIRS instruments, which only quantify relative changes in concentration of oxy- and deoxyhemoglobin (O₂Hb and HHb in μmol/L) compared to an arbitrary baseline. It has not been validated in neonates yet and has even failed to provide internal consistency during one study.2 We have included this method because it has previously been used in several studies.

The second method (the tHbg method) is based on a geometrical principle and multidistance continuous wave NIRS instrument, which quantifies the tHb continuously.4 A study to validate this in a neonatal head phantom showed that the tHbg values were falsely too high due to offsets of unknown origin.5 However, changes in O₂Hb and HHb were correctly quantified.

Therefore this method (the tHbgo method) used these O₂Hb and HHb changes during a slow oxygenation change to calculate absolute tHb values with regard to SaO₂. This tHbgo method is a combination of the first two methods and should not be subject to offsets like the tHbg method.3

The aim of this study was to compare these three methods quantitatively.

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Furthermore, the tHb calculated by the three methods was compared to important physiological variables, which were expected to influence the tHb. In particular, the partial carbon dioxide pressure \( p_{CO_2} \) in kPa and the hemoglobin concentration in the blood \( c_{Hb} \) in g/100mL were positively correlated to the tHb in previous studies. Thus this comparison shows whether the tHbg, tHbgo, and tHbo are reasonable.

## 2 Material and Methods

### 2.1 Instrumentation

For our study we used a Critikon 2020 Cerebral RedOx monitor (Johnson & Johnson, UK), which is based on a two channel sensor and a coupling compensation system. It uses four laser diodes with wavelengths at 776.5, 819.0, 871.4, and 908.7 nm. Silicon photodiode detectors are placed at 10 and 37 mm from the emitter’s window. Placed in the middle between those two is a light emitting diode (LED). The light intensity of the LED should be the same at both detectors. Hence a difference in coupling can be compensated for.

### 2.2 Theory

#### 2.2.1 tHbg Method

The aim of the tHbg method and specially designed sensor is to determine the cerebral hemoglobin concentrations without any influence from the extracerebral layers: skin, skull, and cerebro spinal fluid. The signal from detector 1 (Figure 1) is mainly affected by these layers, while the signal of detector 2 has a predominant component that refers to the brain. A ratio of the signals of detector 2 and detector 1 is calculated, which reduces the influence of the extracerebral layers. In the case of pure scattering without any absorption, the light intensity will decrease with the squared distance to the source. Thus the effect of scattering can be taken into account. The remaining effect is due to absorption. The absolute concentrations of deoxyhemoglobin (HHb in \( \mu \)mol/L) and of oxyhemoglobin (O\(_2\)Hb in \( \mu \)mol/L) can be calculated using a modified Beer–Lambert law. The complete algorithm is given by

\[
\begin{align*}
\begin{bmatrix}
\text{HHb} \\
\text{O}_2\text{Hb}
\end{bmatrix}
&= 
\begin{bmatrix}
k_1 & k_1 & k_1 & k_1 \\
\end{bmatrix}
\times
\begin{bmatrix}
-1000 \\
B_{\lambda_1}(r_2-r_1) \times \log_{10} \left( \frac{r_2}{r_1} \right) \\
B_{\lambda_2}(r_2-r_1) \times \log_{10} \left( \frac{r_2}{r_1} \right) \\
B_{\lambda_3}(r_2-r_1) \times \log_{10} \left( \frac{r_2}{r_1} \right) \\
B_{\lambda_4}(r_2-r_1) \times \log_{10} \left( \frac{r_2}{r_1} \right)
\end{bmatrix}
\times
\begin{bmatrix}
\frac{r_2}{r_1} \times \frac{I_{2\lambda_1}}{I_{1\lambda_1}} \times \text{LED}_1 \\
\frac{r_2}{r_1} \times \frac{I_{2\lambda_2}}{I_{1\lambda_2}} \times \text{LED}_2 \\
\frac{r_2}{r_1} \times \frac{I_{2\lambda_3}}{I_{1\lambda_3}} \times \text{LED}_2 \\
\frac{r_2}{r_1} \times \frac{I_{2\lambda_4}}{I_{1\lambda_4}} \times \text{LED}_2
\end{bmatrix}
- \begin{bmatrix}
\text{O}_1 \\
\text{O}_2
\end{bmatrix}
\end{align*}
\]

Fig. 2 Example showing consecutive slow changes in oxygenation analyzed by the tHbg algorithm. The arterial oxygen saturation (SaO\(_2\)) and oxyhemoglobin (O\(_2\)Hb) decrease and the deoxyhemoglobin (HHb) increases simultaneously during alteration of FiO\(_2\). The sum of O\(_2\)Hb and HHb corresponds to tHbg.
where $k$ is the coefficient matrix, which depends on the absorption coefficients of HHb and O$_2$Hb, $B$ is the differential pathlength factor for each wavelength, $r_x$ is the distance between the emitter and detector $x$, $I_x$ is the light intensity of the laser diode’s emitter at detector $x$ for each wavelength, $LED_x$ is the light intensity of the LED at detector $x$, and $O_3$ is the offset due to water absorption: $O_1 = 7.5 \mu$mol/L and $O_2 = 28.8 \mu$mol/L.

Since HHb and O$_2$Hb are quantified absolutely, tHbg can be determined as the sum of both (Figure 2). The algorithm is described in detail by in Ref. 4.

### 2.2.2 tHbo Method

If only the signal from detector 2 (Figure 1) is analyzed, the Critikon instrument is technically equivalent to other systems such as the Hamamatsu NIRO 500 (Japan), the NIRO 300 (with respect to the O$_2$Hb, HHb, and tHb concentrations), or the Critikon 2001 (UK). Even the wavelengths employed by the Hamamatsu NIRO 500 (775, 810, 870, and 904 nm), the NIRO 300 (775, 810, 850, and 913 nm), and the Critikon 2001 (same as the Critikon 2020) are quite similar to ours. These instruments only quantify changes in the hemoglobin concentration.

At the beginning of each measurement the light attenuation is set to zero and only subsequent changes in light attenuation are taken into consideration. It is assumed that these changes can be attributed to changes in the hemoglobin concentration in the tissue under investigation. To convert the changes in attenuation to concentration changes, the Beer–Lambert law was modified [Eq. (2)]. This modification is in agreement with the diffusion approximation, which is valid if scattering is much higher than absorption.

Our second algorithm corresponds to the UCL4 algorithm described in Ref. 6 for the Hamamatsu NIRO 500.

To determine the absolute tHb, the tHbo method requires a slow change in oxygenation, which is achieved by altering the oxygen fraction inspired. SaO$_2$ is measured by pulse oximetry (a Hellige SMK132 with a 3 s averaging time or a Nellcor N-200 with a 2 s averaging time) and is kept within a normal range (85%–99%). The relative O$_2$Hb signal, which is measured just like in conventional NIRS, varies parallel to the SaO$_2$ (Figure 3). The tHb can be quantified by comparing the change in O$_2$Hb to the change in SaO$_2$ [Eq. (3)]. The change in O$_2$Hb is equal but opposite to the change in HHb as long as the tHb remains constant. Under this circumstance it is possible to improve the signal to noise ratio by taking $(\Delta O_2 Hb - \Delta HHb)/2$ instead of $\Delta O_2 Hb$ [Eq. (3)].

$$tHbo = 100*\Delta O_2 Hb/\Delta SaO_2$$

$$= 100*(\Delta O_2 - \Delta HHb)/(2*\Delta SaO_2) \ (\mu\text{mol/L}).$$

This method is described in detail in Ref. 3.

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**Fig. 3** Same slow changes in oxygenation as in Fig. 2 evaluated by the tHbo algorithm. The arterial oxygen saturation (SaO$_2$) and the cerebral oxyhemoglobin concentration (O$_2$Hb) increase and decrease simultaneously as the inspired oxygen fraction is altered.
2.2.3 tHbgo Method
For this method the same procedure to determine tHbo from oxygenation changes was applied to the O₂Hb and HHb concentrations determined by the tHbg algorithm (Figure 2).

2.3 Data Analysis
All data used in this study had adequate technical quality, i.e., the instrument did not indicate poor signal quality.

The data with a sample time of 1 s were converted into 10 s values by averaging. Changes in oxygenation were analyzed using a computer program according to the procedure in Ref. 3. The beginning and the end of a decrease or increase in oxygenation was identified by looking at the SaO₂ trace only. A change in oxygenation was defined to be any change in SaO₂ of more than 4% over a period of more than 1.2 min. In each infant at least six changes in oxygenation were carried out consecutively and for each one tHbo and tHbgo were calculated by a computer program. For the tHbo method 36% of the measurements passed the quality criteria established in Ref. 3: the change in SaO₂ was >4% over >1.2 min, the line of regression had an \( r^2 > 0.85 \), and the \( \Delta \text{Hb} \) was smaller than 25% of the \((\Delta \text{O}_2 \text{Hb} – \Delta \text{HHb})/2\). Only 24% of the tHbgo method measurements fulfilled the quality criteria so all measurements of four infants were rejected.

Several changes in oxygenation yielded a valid tHbo value, while the tHbgo value was rejected due to poor quality or vice versa. In that case the valid value was removed too, because we wanted to compare both methods for exactly the same data. For each remaining tHbgo measurement the mean of the continuously available tHbg was calculated. The test retest variability (TRV) (in %) was determined for each method by analysis of the variance. For each infant the mean of tHbg, tHbo, and tHbgo was determined. The data were checked for normality.

To compare the three methods we proceeded in the following way. Two methods were compared at a time and their correlation coefficient (\( r \)) was calculated. Furthermore we calculated the limits of agreement as described in the literature.7

Using a regression procedure with variable selection by Mellow’s C(p),8 we determined other parameters which influence the tHbg, tHbo, and tHbgo. The following parameters were available: gestational age (GA) (in weeks), birthweight (BW) (in g), postnatal age (PA) (in days), \( c \text{Hb} \), \( p \text{CO}_2 \), heart rate (HR) (in bpm), and mean arterial blood pressure (MAP) (in mmHg) measured continuously through an umbilical arterial catheter.

3 Results
Twenty clinically stable, mechanically ventilated preterm infants who needed supplemental oxygen were included in this study. These two requirements were due to the fact that only under these circumstances could a controlled change in oxygenation to obtain the tHbo and tHbgo be carried out. Four infants were excluded, because all their tHbo or tHbgo measurements were not of good enough quality.5 The remaining 16 neonates had a mean gestational age of 29.6 (range of 25.1–36.4) weeks, birthweight of 1386 (680–2820) g, and postnatal age of 2.5 (0.5–6) days. As for brain lesions, we found ischaemic lesions in none, subependymal hemorrhage in three, and intraventricular hemorrhage in three of the infants. A total of 202 measurements was analyzed. There were 3.1 (1–6) measurements per infant. The success rate per attempt was 36% for tHbo and 24% for tHbgo. At least one measurement was successful in 90% of the infants for tHbo and in 80% of the infants for tHbgo.

This study was approved by the ethical committee of our institution and informed consent was obtained.

The mean±standard deviation (SD) tHbg was 150.2±41.8 \( \mu \text{mol/L} \) (range of 61.6–228.9 \( \mu \text{mol/L} \)), the tHbo was 62.1±27.2 \( \mu \text{mol/L} \) (26.0–110.8 \( \mu \text{mol/L} \)), and the tHbgo was 89.3±45.6 \( \mu \text{mol/L} \) (26.5–195.9 \( \mu \text{mol/L} \)). These values were highly significantly different among methods (Wilcoxon signed rank test \( p < 0.001 \)). All three variables are plotted against each other in Figures 4–6 as \( x–y \)-plots.

### Figure 4
Absolute cerebral hemoglobin concentration measured by the tHbg method plotted vs the cerebral hemoglobin concentration measured by the tHbgo method, which is based on analysis of change in oxygenation. The error bars indicate the standard deviation and are displayed only for infants that had more than two measurements. The equation of the regression line is also displayed.

### Figure 5
Absolute cerebral hemoglobin concentration measured by the two methods, tHbo vs tHbgo, which require a change in oxygenation.
The mean difference between two methods and its 95% confidence limits are shown in Table 1.

In the results of the regression analysis the best model for tHbg with a $C(p) = 3.76$ and an adjusted $r^2 = 0.588$ included the four variables, BW, PA, MAP, and $pCO_2$. For tHbo and tHbgo the model had $C(p) = 1.7$ or 3.2, respectively, and adjusted $r^2 = 0.493$ or 0.406, respectively, with the three variables, cHb, MAP, and $pCO_2$.

The only significant bivariate correlation (Pearson) among the three methods, tHbg, tHbgo, and tHbo, and other variables was the one between cHb and tHbgo ($r^2 = 0.404$, $p = 0.008$).

The TRV was 7.6% for the tHbg method, 20.1% for the tHbo method, and 21.3% for the tHbgo method.

4 Discussion

The aim of this study was to quantitatively compare three methods: tHbg, tHbo, and tHbgo. If the three methods were in perfect agreement, we would find bias = 0 in Table 1, slope = 1, intercept = 0, and $r^2 = 1$ for the equations in Figures 4–6. The actual values differ considerably from the ones expected.

The results (Table 1) of the analysis according to Bland and Altman show that the values measured by the three methods are clearly not equivalent. The precision is in the same range as the actual value of the measurement. This type of analysis is the standard method and is very powerful in showing agreement among methods. However, when the disagreement is systematic, as in our case, i.e., in the case of high $r$, regression analysis is more helpful in interpreting the relation. We try to give an explanation for the disagreement among methods in the following.

To do so it would have been desirable to compare the values obtained by NIRS to a gold standard method. Although magnetic resonance imaging (MRI) or PET would be useful as a reference, they require the injection of a contrast agent, which would yield the risk of an allergic reaction. Furthermore, the infant needs to be transported to the scanner, which in itself is a risk for mechanically ventilated and critically ill patients. The infant has to be immobilized during the scan. We considered such a procedure to be unethical and refrained from it.

Animal experiments are not comparable due to the large geometrical differences in anatomical structure, especially that of the head. NIRS has already been shown to give erroneous values for cerebral blood flow in dogs, but two studies proved that NIRS is a valid method by which to determine the cerebral blood flow of neonates.

Thus the only acceptable ways to test the three methods are either in the infants directly or in a phantom model, with similar geometry as the infants head, which has already been done.

For tHbo it is possible to compare the values to previous studies in infants using the same method. To do this the values were converted into cerebral blood volume (CBVO) (in mL/100 g) using

$$CBVO = 0.890 \times tHbo/cHb \text{ (mL/100 g)}$$

where 0.890 is a constant, which accounts for unit conversion of tetrameric tHbo into grams, volume brain to its weight, and the cerebral to large vessel ratio of 0.69 for the cHb.

Thus we receive the following mean value ± standard deviation: CBVO = 3.3 ± 1.0 mL/100 g. For healthy infants CBVO values were previously measured by Ref. 1: 2.2 ± 0.4, Ref. 2: 3.7 ± 1.1, and Ref. 3: 2.5 ± 0.9 mL/100 g. Consequently our CBVO values are comparable to previous ones.

4.1 Comparison of tHbg and tHbgo

For the tHbg and tHbgo algorithm, validation studies of neonatal head phantoms have been carried out. In Ref. 13 a clear layer that mimicked cerebro spinal fluid was inserted into the phantom. According to Ref. 14 this kind of uniformly

Table 1 Mean difference (bias) between two methods and its 95% confidence limits. The limits are wide, i.e., the agreement between methods is low. (SD = standard deviation, precision = $2 \times$ SD, RSD = relative SD = 100 × SD/mean.)

<table>
<thead>
<tr>
<th>Difference</th>
<th>Mean (µmol/l)</th>
<th>SD (µmol/l)</th>
<th>Precision (µmol/l)</th>
<th>Upper 95% limit (µmol/l)</th>
<th>Lower 95% limit (µmol/l)</th>
<th>RSD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>tHbg–tHbgo</td>
<td>60.0</td>
<td>33.8</td>
<td>67.6</td>
<td>126.3</td>
<td>-6.2</td>
<td>28.2</td>
</tr>
<tr>
<td>tHbg–tHbo</td>
<td>87.8</td>
<td>33.5</td>
<td>67.0</td>
<td>153.4</td>
<td>22.2</td>
<td>31.6</td>
</tr>
<tr>
<td>tHbo–tHbgo</td>
<td>-27.6</td>
<td>22.6</td>
<td>45.2</td>
<td>16.5</td>
<td>-72.0</td>
<td>29.8</td>
</tr>
</tbody>
</table>
thick clear layer does not represent the effect of cerebro spinal fluid in vivo. Therefore we consider the model in Ref. 5 to best reflect the situation in the infant. In that study, it was shown, on the one hand, that changes in \( \text{O}_2 \text{Hb} \) and \( \text{HHb} \) were quantified correctly, independent of the light scattering and, on the other hand, that the absolute \( \text{O}_2 \text{Hb} \) and \( \text{HHb} \) values had substantial offsets, i.e., the values overestimated the actual concentration by a constant amount. These offsets depended on light scattering. Their origin was unclear. From these findings we would expect the \( \text{tHbg} \) to be correct, because it only takes changes of \( \text{O}_2 \text{Hb} \) and \( \text{HHb} \) into account whereas the \( \text{tHb} \) is subject to the offsets.

The slope of the line of regression (Figure 4) of 0.92, which is close to the expected value of 1 and the high offset of 68.0 \( \mu \text{mol/L} \), supports this, that is, that the disagreement between these two methods is caused by this offset. Thus the results are in agreement with the study using the phantom. \( r \) is lower than expected: \( r = 0.736 \). This means, that there is relatively large intersubject variability between the \( \text{tHbg} \) and \( \text{tHb} \). Although it is beyond the scope of this paper to identify the exact reasons for this, we want to point out the likeliest reasons.

- Some of it can be attributed to the TRV of the two methods: The TRV for \( \text{tHbg} \) was 21.3\%, which corresponds to the TRV found for cerebral blood volume measurements using a similar method in Refs. 1–3. The TRV for \( \text{tHb} \) was 7.6\%.
- The offset in the \( \text{tHbg} \) reading could vary from infant to infant. In the phantom work, we found that the offset depends on light scattering. It could very well be that there is interinfant variability in light scattering, which depends on the gestational age, which is closely related to the BW of the infant. This may explain why \( \text{tHbg} \) is associated with BW. Interinfant variability in the differential pathlength factor affects both methods in the same way [Eqs. (1) and (2)] and therefore cannot account for the large variability between the methods.
- The \( \text{tHb} \) method relies on pulse oximetry as a reference. The resolution and error of the pulse oximeter are 1\%. If there were an error in the quantification of changes in \( \text{SaO}_2 \) among infants, this would contribute to the intersubject variability as well.

### 4.2 Comparison of \( \text{tHbo} \) and \( \text{tHbg} \)

The \( \text{tHb} \) method has neither been validated in infants nor are phantom data available. It has been tested in infants for internal consistency.\(^2\) The \( \text{tHb} \) was changed by altering the \( \text{pCO}_2 \). When the relative change in \( \text{tHb} \) measured directly by this algorithm was compared to the difference in \( \text{tHb} \) before and after the change in \( \text{pCO}_2 \) a fourfold discrepancy was found. Thus the algorithm, which is used for the \( \text{tHb} \) method, failed to demonstrate any internal consistency.

In comparing \( \text{tHb} \) and \( \text{tHbg} \) (Table 1 and Figure 5) we find high and significant bias, but also a high correlation with \( r = 0.94 \), which is remarkably close to 1. This shows that the strong disagreement is highly systematic. Again we want to point out the most likely reasons for the strong disagreement, i.e., why the \( \text{tHb} \) gives significantly lower values than the \( \text{tHbg} \).

- The \( \text{tHbg} \) method uses a multidistance approach. According to Ref. 14 such an approach is not sensitive to the superficial layers of tissue (skin and skull), whereas the \( \text{tHb} \) method takes into account all the tissue. If the skin and skull had a lower \( \text{tHb} \) than the brain, this would explain why \( \text{tHb} \) gives significantly lower values than \( \text{tHbg} \). Using Monte Carlo simulations for the neonatal head and a source detector distance of 37 mm, the contribution by extracerebral tissues to changes in absorption was estimated to be between 15\% and 32\%, depending on the model.\(^16\)
- The \( \text{tHb} \) algorithm was not internally consistent for a reason that is not known.\(^5\) The errors in the algorithm, which caused internal inconsistency, could affect both the slope and the intercept.
- The \( \text{tHbg} \) method relies on a coupling compensation system and a second detector channel. Thus the setup is technically quite different from the \( \text{tHb} \) setup. The algorithms are consequently also different. It is impossible to predict how this affects the \( \text{tHb} \) readings.

The most likely reason for the high correlation between the two methods is the operating dependence, i.e., the same NIRS and pulse oximeter data are used for the same period of time.

### 4.3 Comparison of \( \text{tHbg} \) and \( \text{tHbo} \)

The discrepancy between these two methods can be explained by combining the effects mentioned for \( \text{tHbg} \) versus \( \text{tHb} \) and for \( \text{tHbo} \) versus \( \text{tHb} \).

### 4.4 Comparison to Physiological Data

All three, \( \text{tHbg} \), \( \text{tHb} \), and \( \text{tHbo} \), showed a highly significant correlation to physiological data (\( p < 0.0001 \)).

It is known that the acute changes in \( \text{pCO}_2 \) affect the \( \text{tHb} \) (e.g., in Ref. 2) within patients. This does not necessarily mean that this is the case when making a comparison among infants. Considering the wide range of \( \text{pCO}_2 \) among infants (4.7–7.6 kPa), it is still the most likely reason why \( \text{pCO}_2 \) is the variable most strongly associated with \( \text{tHbg} \), \( \text{tHbo} \), and \( \text{tHb} \).

In healthy infants cerebral autoregulation is assumed to keep cerebral hemodynamics independent of the MAP. However, in critically ill infants autoregulation may be abolished,\(^17\) which could be the reason why the variable MAP is found in all three models.

It is reasonable that we find the variable \( c \text{Hb} \) in the models for \( \text{tHbg} \) and \( \text{tHb} \). The higher the concentration of hemoglobin in the blood the more likely it is to find a high cerebral concentration. This variable is also significantly related to \( \text{tHbg} \) in a bivariate model. The \( \text{PA} \) is significantly negatively correlated to the \( c \text{Hb} \). This could be the reason why \( \text{PA} \) is associated with \( \text{tHbg} \) instead of with \( c \text{Hb} \).

The association of BW with \( \text{tHb} \) previously discussed is probably due to the offsets of this method, which depend on scattering.\(^5\) It has been shown that scattering is dependent on the gestational age, which is closely correlated to the BW.\(^15\)

### 4.5 Advantages and Disadvantages of Each Method

\( \text{tHbg} \) is much easier to apply than the other methods, because it does not require a change in oxygenation. Hence \( \text{tHbg} \) is the
only usable method for infants who do not require additional oxygen. The parameters are continuously available. Furthermore, the geometrical method allows one to measure the tissue’s oxygen saturation.\textsuperscript{4} It also shows the highest correlation to the physiological variables. From this point of view one could conclude that the tHbg method is the most trustworthy method. However, according to the phantom study,\textsuperscript{5} tHbg is subject to offsets, which depend on scattering of the tissue. The relationship between the tHbg and the BW confirms this drawback. The tHbo method requires changes in oxygenation and thus is only applicable in infants who require additional oxygen. It was not internally consistent according to previous findings.\textsuperscript{2} The high correlation ($r = 0.94$) between tHbo and tHbgo shows that both methods are systematically highly related, although their absolute values are quite different.

The tHgo method also requires changes in oxygenation. It is probably less trustworthy than tHbo, because it has a lower correlation to physiological variables for the same model. However, tHbgo also shows a significant correlation with $cHb$ in the bivariate model. The difference between the two methods is probably small and in addition in the tHbgo method the rejection rate of measurements is much higher.

Thus it is difficult to recommend one particular method. Whatever method is used, it will be important to consider that the absolute values depend strongly on the method.

5 Conclusion

The three methods (tHbg, tHbo, and tHbgo) give systematically different tHb readings and show large intersubject variability.

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