Cerebral Arterial and Venous Contributions to Tissue Oxygenation Index Measured Using Spatially Resolved Spectroscopy in Newborn Lambs

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ABSTRACT

Background: Bedside assessments of cerebral oxygenation are sought to monitor cerebral injury in patients undergoing intensive care. Spatially resolved spectroscopy measures tissue oxygenation index (TOI, %) which reflects mixed cerebral arterial and venous oxygenations. We aimed to evaluate arterial and venous components of TOI (cerebral arterial to venous volume ratio [A:V ratio]) in the newborn lamb brain using cerebral arterial and venous blood samples, and to investigate the impact of acute hypoxemia on the A:V ratio and TOI.

Method: Nine lambs were ventilated with varied inspired oxygen to generate arterial oxygen saturations between 25% and 100%. Cerebral arterial and venous oxygen saturations analyzed using cooximeter of arterial and superior sagittal sinus blood were used to estimate TOI (TOIcox), assuming cerebral arterial oxygen saturation

restimated using TOIsrs = cerebral arterial volume fraction*cerebral arterial oxygen saturation + cerebral venous volume fraction*cerebral venous oxygen saturation.

Results: Median (range) TOIsrs was 48.5% (32.0 – 64.1%), and TOIcox was 48.4% (13.7–74.4%), and the two were significantly correlated (R² = 0.77). The mean difference between TOIsrs and TOIcox was 2.4% (limits of agreement ± 18.1%). The TOIsrs – TOIcox difference varied with oxygen saturations, with TOIsrs higher than TOIcox at low saturations, and lower at high saturations. Cerebral arterial volume fraction was 22.9–27.5% in normoxia and markedly increased in hypoxemia.

Conclusion: TOI corresponds with cerebral oxygenation. The variable agreement of TOIsrs with TOIcox may reflect changes in cerebral A:V ratio due to arterial oxygenation-related vasoreactivity.

What We Already Know about This Topic

- Spatially resolved spectroscopy, a potentially useful bedside assessment of cerebral oxygenation, has as a drawback uncertain admixture of mixed arterial and venous oxygenations.

What This Article Tells Us That Is New

- Cooximeter assay of arterial and superior sagittal sinus blood were well correlated, with a small mean difference, but with a variable agreement that most probably reflects changes in cerebral arterial to venous volume ratio due to arterial oxygenation-related vasoreactivity.

A BNORMAL cerebral hemodynamics and oxygen delivery are major etiologic factors for cerebral injury of sick infants and children undergoing intensive care,1–3 prompting the search for bedside monitoring cerebral circulation and oxygenation to aid their clinical management and improve outcomes. Near infrared spectroscopy (NIRS) provided a noninvasive method to measure changes in cerebral tissue oxygenation in several investigations.4,5 An enhancement of NIRS technology, spatially resolved spectroscopy (SRS), allows continuous recording of the tissue oxygenation index (TOI, %) as an absolute quantitative measurement.6

Footnotes:

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Cerebral TOI measurement has been successfully applied in studies of infants susceptible to hypoxic brain injury, such as preterm infants\textsuperscript{17} and infants with congenital cardiac disease,\textsuperscript{18} suggesting its potential utility as a bedside monitor to identify cerebral hypoxic-ischemia in routine neonatal and pediatric intensive care.

Cerebral TOI, the ratio of oxyhemoglobin to total hemoglobin in all cerebral vascular compartments, represents a mixed cerebral oxygen saturation in a multicompartamental system of arteries, arterioles, capillaries, venules, and veins; each of these compartments has different saturations and volumes. As an index of "mixed" cerebral oxygenation, TOI is therefore dependent on the ratio of the arterial and venous compartment volumes and their relative oxygenations. Previous studies using different methodologies have reported cerebral arterial to venous ratios (A:V ratio) to average around 25:75,\textsuperscript{9–15} suggesting that TOI is mostly influenced by cerebral venous oxygen saturation. Notably, there are differences between the reported cerebral A:V ratio, possibly due to the different imaging techniques used,\textsuperscript{9–13} as NIRS interrogates mainly the smaller vessels and microcirculation, whereas magnetic resonance imaging views the larger vessels.\textsuperscript{16} In addition, changes occur in cerebral hemodynamics during common clinical events, such as vasodilatation of the arterial, venous, and microcirculation arising from acute hypoxemia,\textsuperscript{17–21} suggesting that TOI is mostly influenced by cerebral venous oxygen saturation. Notably, there are differences between the reported cerebral A:V ratio, possibly due to the different imaging techniques used,\textsuperscript{9–13} as NIRS interrogates mainly the smaller vessels and microcirculation, whereas magnetic resonance imaging views the larger vessels.\textsuperscript{16} In addition, changes occur in cerebral hemodynamics during common clinical events, such as vasodilatation of the arterial, venous, and microcirculation arising from acute hypoxemia,\textsuperscript{17–21} there might be significant changes in cerebral blood volumes and the A:V ratio which would impact upon the TOI measurement and its interpretation.

As yet, no study has estimated changes in cerebral arterial and venous blood volumes in acute hypoxemia, or evaluated the impact of such changes on TOI measurements. Should the ratio change in clinical conditions of acute hypoxemia, the interpretation of cerebral TOI could be critically affected. Using the newborn lamb model, we aimed to estimate cerebral arterial volume fractions during a range of hypoxic conditions, using TOI measured by SRS (TOIsrs), and oxygen saturations measured by cooximeter in cerebral arterial (CSaO2) and superior sagittal sinus blood (CSvO2). We also tested the accuracy of a fixed cerebral A:V ratio of 25:75 for estimating TOIsrs in hypoxemia, by comparing TOIsrs with mixed cerebral oxygenation estimates (TOIcox) derived using CSaO2 and CSvO2.

Materials and Methods

\textbf{Animal Preparation}

Nine newborn lambs of Merino-Border Leicester cross were studied at 3–6 days after birth. All procedures were performed in accordance with guidelines established by the National Health and Medical Research Council of Australia and were approved by the Ethics in Animal Experimentation Committee of Monash University (Melbourne, Victoria, Australia). A nonocclusive intravenous catheter (Intracath 19 GA; Becton Dickinson, Sandy, UT) was inserted into the left jugular vein of the newborn lamb for administration of maintenance fluid and anesthetic medication. The lamb was intubated and ventilated under general anesthesia (100 mg \cdot kg\textsuperscript{-1} \alpha-chloralose and 5 mg \cdot kg\textsuperscript{-1} ketamine hydrochloride for induction, followed by 25–50 mg \cdot kg\textsuperscript{-1} \alpha-chloralose for maintenance). An intravenous catheter (Insyte-N 24 G; Becton Dickinson) filled with a saline-heparin solution (50 IU \cdot ml\textsuperscript{-1}) was inserted into the right axillary artery to enable continuous monitoring of arterial pressure and extraction of arterial blood samples for analysis of oxyhemoglobin saturation. For cerebral venous blood sampling, a similar catheter (Insyte-N 24 G; Becton Dickinson) was inserted into the superior sagittal sinus through a small hole (2-mm diameter) drilled in the skull along the sagittal suture just anterior to the lamboid suture.

\textbf{Tissue Oxygenation Index (TOI)}

Spatially resolved spectroscopy (NIRO 200 Spectrophotometer; Hamamatsu Photonics K.K., Hamamatsu City, Japan) was employed for continuous TOI recording. Two aligned photodetectors are separated from each other by 4 mm and housed inside the detection probe, which is placed at 4 cm from the emission probe. The probes were placed over the fronto-parietal region and covered with light-proof dressing. NIRS measurements of changes in concentrations (\textmu mol \cdot cm\textsuperscript{-1}) of oxy-, deoxy-, and total hemoglobin were recorded continuously. The SRS algorithm measures TOI by using slopes of near infrared light attenuation \textit{versus} the different distances of the two photodetectors from the emission probe. By fitting these data to a modified diffusion equation of light transport in tissue, the ratio of concentrations of oxyhemoglobin to total hemoglobin, and hence the absolute average tissue oxygen saturation, \textit{i.e.}, TOI, is computed continuously\textsuperscript{6,22} and logged at 6 Hz.

\textbf{Physiologic Measurements}

Beat-to-beat arterial oxygen saturation (\textit{SpO}_2) was measured with a pulse oximeter placed on the lamb’s tongue (Nellcor 200; Nellcor Incorporated, Pleasanton, CA). Arterial blood pressure was measured with a calibrated strain-gauge pressure transducer (Cobe CDX III; Cobe Laboratories, Lakewood, CO), referenced to the mid-thoracic level, and connected to a bridge amplifier (Quad Bridge Amp; AD- Instruments, Sydney, Australia). The signals were sampled at 400 Hz and displayed throughout the study (PowerLab/16R SP; ADInstruments).

Physiologic data and optical data from the NIRO-200 were collected simultaneously (Chart v.5.5; ADInstruments) for subsequent analysis.

\textbf{Cooximeter}

Blood samples of 500 ml were collected from the superior sagittal sinus and the axillary artery in heparinized plastic syringes and analyzed immediately for oxyhemoglobin saturation (CSvO2 and CSaO2, respectively, OSM2 Hemoxime-
ter; Radiometer, Copenhagen, Denmark), and arterial partial pressure for oxygen (\(P_aO_2\)).

**Induced Hypoxemia**

Measurements were performed while \(S_aO_2\) was ≡95%, then over a range of arterial hypoxemia (\(S_aO_2\) of 25–94%) induced by ventilating the lamb using 10–40% fractional inspired oxygen (\(F_iO_2\)), balance nitrogen. \(S_aO_2\) was monitored with pulse oximetry (\(S_pO_2\)) and confirmed with arterial blood gas analysis. After \(S_pO_2\) was held stable for at least 5 min at each reduced \(F_iO_2\), blood was sampled from the superior sagittal sinus and the axillary artery for measurement of \(C_SvO_2\) and \(C_SaO_2\), and calculation of \(TOI_{cox}\).

Anesthesia, ventilation, carbon dioxide levels, and body temperature of the lamb were carefully controlled and maintained stable throughout the study. After each experiment, the lamb was killed under general anesthesia with an intravenous injection of pentobarbitone (325 mg · kg\(^{-1}\)).

**Changes in Cerebral Blood Volume (\(\Delta CBV\))**

A differential pathlength factor of 4.99 was used to convert NIRS measurements of the change in total hemoglobin (\(\Delta HBT\), \(\mu\)molar · cm) into \(\mu\)molar.\(^{23,24}\) \(\Delta CBV\) (ml · 100 g\(^{-1}\)) was calculated from \(\Delta HBT\) during hypoxia from the baseline total hemoglobin (HBT) recorded at \(S_aO_2\) of ≥95%, using the following formula\(^{25}\):

\[
\Delta CBV = (\Delta HBT \times MW_{hemoglobin} \times 10^{-6})/\]
\[
(tHb \times 10^{-2} \times CLVHR \times DT \times 10)
\]

where \(MW_{hemoglobin} = \) molecular weight of hemoglobin = 64,500, \(tHb = \) concentration of hemoglobin in large vessels in g · 100 ml\(^{-1}\), \(CLVHR = \) cerebral to large vessel hemotocrit ratio = 0.69,\(^{26}\) and \(DT = \) brain tissue density in g · ml\(^{-1}\) = 1.05.

**Data Analysis**

Data were analyzed using a two-tailed testing procedure. TOI measured by SRS (TOIsrs) was determined as the average of SRS measurements during the 30 s before arterial and venous blood sampling. Estimated TOI (TOIcox) was calculated from cooximeter measurements using a fixed cerebral A:V ratio of 25:75:

\[
TOI_{cox} = 0.25 \times C_SaO_2 + 0.75 \times C_SvO_2
\]

TOIsrs were compared with the corresponding TOIcox using Pearson linear regression analysis (SigmaStat; SPSS Inc., Chicago, IL). An analysis of agreement of TOIsrs and TOIcox, taking into account replicated measurements within subjects, was conducted using the method described by Bland and Altman.\(^{27,28}\)

The cerebral arterial and venous volume fractions (A and V, respectively, %) for each paired measurements of TOIsrs (by SRS) and TOIcox (by cooximeter) were determined by solving the following equations for A and V,

\[
y = 0.51x + 0.25
\]

\[
R^2 = 0.77, P < 0.0001
\]

**Results**

Forty-nine pairs of TOIsrs and TOIcox were obtained for comparison, of which 18 were performed when the lambs were normoxemic with \(S_aO_2\) ≥95%, and 31 were performed during induced hypoxemia when \(S_aO_2\) was 25–94%. Two animals had 8 pairs of measurements, two had 6 pairs, and the remaining five animals had 7, 5, 4, 3, and 2 pairs of measurements each, respectively. Overall, the median (range) of TOIsrs was 48.5% (32.0–64.1%). Median (range) of TOIcox was 48.4% (13.7–74.4%). Figure 1 illustrates the significant correlation between TOIsrs and TOIcox (\(R^2 = 0.77, P < 0.0001\)). The mean difference between TOIsrs and TOIcox (fig. 2) was 2.4% and limits of agreement (±2 SD) were ±18.1%.\(^{27,28}\) The TOIsrs − TOIcox difference varied with the level of TOIcox, with TOIsrs higher than TOIcox at low values of cerebral oxygenation, and lower at high values of cerebral oxygenation. The TOIsrs − TOIcox difference (±2 SD) was 10.3(11.9)% for TOIcox at <40%, 0.07(10.9)% for TOIcox at 40–60%, and −9.0(11.6)% for TOIcox at ≥60%.

\[
\text{TOIsrs} = A^*C_SaO_2 + V^*C_SvO_2
\]

\[
A + V = 100\%
\]
During hypoxia, total cerebral blood volume increased exponentially at low PaO₂ levels ($R^2 = 0.57$, $P < 0.0001$) (fig. 3). Six values of cerebral arterial volume fraction of less than 0% (CSvO₂ < TOIsrs) and two of more than 100% (CSaO₂ < TOIsrs) were excluded from analysis of relationship between cerebral arterial volume fraction and PaO₂. The mixed-effect model and its equation for the cerebral arterial volume fraction-PaO₂ relationship are illustrated in figure 4; this was characterized by a relatively small increase of cerebral arterial volume fraction from 14% to 22.9% when PaO₂ decreased from 140 mmHg to 100 mmHg, from 22.9% to 33.8% when PaO₂ decreased from 100 mmHg to 60 mmHg, and an accelerated increase from 33.8% to 49.4% when PaO₂ decreased from 60 mmHg to 20 mmHg. In the normoxic range of PaO₂ of 80–100 mmHg, cerebral arterial volume fraction was 22.9–27.5%. Mean arterial blood pressure and partial pressure of carbon dioxide (PaCO₂) were maintained steady throughout the experiments, and showed no correlation with changes in the calculated cerebral arterial volume fractions (table 1).

**Discussion**

This is the first study to evaluate TOI measurements and changes in cerebral A:V ratio in a range of oxygen saturations, using oxygen saturation in cerebral arterial and venous blood. Our results showed that using a fixed cerebral A:V ratio of 25:75 for TOI estimation results in varied agreement of TOIsrs (obtained using SRS) with TOIcox (estimated from cooximeter) according to level of oxygenation, with TOIsrs higher than TOIcox at low values of oxygen saturation, and lower at high values of oxygen saturation. Divergence of TOIsrs and TOIcox may be related to changes in cerebral arterial volume fraction and the cerebral A:V ratio due to cerebral vasoreactivity to altered arterial oxygenation. Our results suggest that significant arterial vasodilatation occurs at lower arterial oxygenation, making the assumed A:V ratio of 25:75 and the corresponding estimate of TOIcox erroneously low.

Hypoxemia is a potent and robust vasodilatory stimulus to cerebral vessels, which is present in fetal, neonatal, and adult animals and humans, with the vessel response being similar across maturation.39 In both the mature and the newborn brain, cerebral vasodilatation occurs as PaO₂ decreases to ∼50 mmHg, the point at which arterial oxygen saturation starts to fall significantly.30 Below this PaO₂ threshold, cerebral blood flow rises exponentially as arterial oxygenation falls,30 a mechanism that serves to maintain oxygen delivery to the brain constant until extremely low levels of oxygenation are reached.31 Thus, the pattern of cerebral vasodilatation in hypoxemia, which is characterized by an accelerating response at PaO₂ < 60 mmHg, is a potential explanation for our findings of increased total cerebral blood volume and cerebral arterial volume fraction at lower arterial oxygenation. Although the cerebral vasodilatation may occur in all vascular compartments including the arterial, venous, and capillary circulations,17–21 our results suggest that, in acute hypoxemia, the arterial volume expansion dominates the to-

| Table 1. Regression of Cerebral Arterial Volume Fraction with Physiological Variables |
|---------------------------------|-----------------|--------|
| *Partial arterial pressure of carbon dioxide (mmHg)* | 0.006 | NS |
| *Mean arterial blood pressure (mmHg)* | 0.02 | NS |
tal increase in cerebral blood volume; the arterial fraction increased to 43% at a PaO2 of 35 mmHg (fig. 4). On the other hand, in chronic hypoxia the cerebral A:V ratio may return to baseline values, as a study in children in chronic hypoxia with averaged PaO2 of ∼35 mmHg reported cerebral A:V ratios to be similar to normoxic children.

The change in cerebral arterial and venous volume fractions during hypoxemia may not be uniform throughout the brain. In newborn animals, the oxygen-cerebral blood flow reactivity shows regional differences in the brain, with the white matter showing the least vasoreactivity in response to changes in oxygenation. Accordingly, the changes in TOIsrs and cerebral arterial volume fraction found in our study are likely to be dominated by vascular changes in the cerebral cortex. Importantly, we compared TOIsrs with CSvO2 obtained from the superior sagittal sinus which principally drains the cerebral cortex region which was also illuminated by the SRS, strengthening the validity of our results.

Our study provides new insight into the measurement of mixed cerebral oxygenation using NIRS technology under clinical conditions of acute hypoxemia. The utility of monitoring mixed cerebral oxygenation in pediatric and neonatal intensive care has been described in many critical clinical situations, such as cardiac conditions with wide fluctuations in hemodynamics and arterial oxygenation that can lead to cerebral hypoxemia and injury. Importantly, several case reports have illustrated the value of intraoperative monitoring of mixed cerebral oxygenation in congenital heart surgery by identifying critical events which led to timely interventions. Previous studies in animals and humans using NIRS have found a mixed cerebral oxygenation of 40–50% to be the limits below which significant cerebral hypoxia with poor neurologic outcome occurs. Based on a fixed A:V ratio of 25:75, the lower limit for mixed cerebral oxygenation of 40% during arterial hypoxemia with an SpO2 equaling 80% represents a cerebral venous oxygenation (CSvO2) of 27%. However, much lower values for CSvO2 are more likely to exist than those predicted from the fixed A:V ratio. Allowing for the increase in arterial volume in hypoxemia (fig. 4), a mixed cerebral oxygenation of 40% with SpO2 of 80% would represent a CSvO2 value of 13% with A:V ratio of 40:60, much lower than the CSvO2 predicted using the fixed A:V ratio of 25:75. These estimates of CSvO2 aid in understanding the risk for hypoxic neuronal injury at a TOI of 40%, as the low cerebral venous oxygenation would result in critically low levels of cerebral tissue oxygenation, due to the small and insignificant oxygen tension gradients between the extracellular fluid compartment and the cerebral microvasculature.

While the change in cerebral A:V ratio should be taken into account in interpretation of TOI measurements, the highly significant correlation between TOIsrs and TOIcox (fig. 1) supports the use of TOI measurement as a sensitive trend monitor for identification of cerebral hypoxemia, as found in other studies. Other common conditions in sick infants, such as hypercapnia, hypotension, or vasopar-

ralysis due to hypoxic-ischemic injury, could also increase baseline cerebral blood volume and change the cerebral A:V ratio. Further studies are warranted to investigate the A:V ratio in these conditions, together with the corresponding effects on measurements of mixed cerebral oxygenation by NIRS.

Although it is critical for fully interpreting TOI measurements, available data on cerebral arterial and venous volume fractions are very limited, especially in the newborn brain. Using various imaging techniques, the baseline cerebral arterial volume fraction has been found to be 25% in normal adults, and 25–30% in adult animals under normoxic conditions. The cerebral arterial volume fraction of 22.9–27.5% we obtained at the normoxic range of PaO2 between 80 and 100 mmHg is consistent with these previous adult estimates. A single study of children using NIRS has reported lesser values of 12–15%. Given the similarity of our normoxic newborn lamb data with normoxic adult data in both animals and humans, it seems unlikely that the lower values reported in children are age-related and may be due to the methodology used. The study by Watzman and colleagues used jugular venous oxygenation for comparison with mixed cerebral oxygenation measured using NIRS devices. As jugular venous saturations represent global measurements including extracerebral tissue, they may differ significantly from the actual cerebral venous saturation. Higher venous saturations from less metabolically active extracerebral tissues might have contributed to the relatively low values of calculated cerebral arterial volume fraction reported. Our study used cerebral venous oxygen saturation measured in superior sagittal sinus blood as the “gold standard” for calculating TOIcox, as the region draining into the sinus corresponds closely to the tissues illuminated by the SRS. The contribution of extracerebral tissues to the measured TOI by SRS is likely to be small, as TOI has high sensitivity and specificity to intracerebral changes in oxygenation and is not affected by anatomical factors including skull thickness and cerebrospinal fluid layer.

Several factors might affect the results of our calculated cerebral arterial volume fraction. There may be intrinsic biologic variability, as previous studies also found wide interindividual variability in the baseline cerebral A:V ratio. In addition, as the TOI signal samples only a small region of the cerebral circulation to a penetration depth of about 2 cm, the measurement is subject to regional variation in cerebral metabolism and venous oxygenation, and to inhomogeneous cerebral blood flow and volume distribution. The capillary oxygenation and blood volume, which are not included in our calculation, may also cause inaccuracy in the estimated cerebral arterial volume fraction. Among technical sources of variation are the assumptions relating to geometry and homogeneity of tissue upon which the SRS algorithm is based, leading to imprecision of TOIsrs values should those assumptions not hold in practice. Possibly, these variations may explain the systematic difference between TOIsrs and TOIcox, represented by the positive intercept of their regressions.
sion (fig. 1). Interestingly, a similar intercept was reported in another in vivo validation study using SRS in children \(^6\) but was absent in an in vitro phantom study. \(^5\) Variation in tissue geometry and homogeneity, including changes related to oxygenation, may also lead to some physiologically erroneous estimates of cerebral arterial fraction of more than 100% or less than 0%. Nevertheless, the averaged cerebral arterial volume fraction and its relationship with oxygenation (fig. 4) are consistent with the known cerebral circulatory response to hypoxia, in which there is a steep increase in cerebral perfusion at PaO\(_2\) below \(\sim 60\) mmHg. \(^3\) The similarity of the cerebral arterial volume fraction-PaO\(_2\) relationship we have made with the well described cerebral perfusion-PaO\(_2\) relationship lends support to the use of our results in interpreting TOI measurements in clinical hypoxemia. As the agreement of TOIsrs and TOIcox was closer in the midrange (fig. 2), a limitation in technical sensitivity of the SRS methodology could possibly exist at extreme values of oxygenation. However, this is unlikely because in phantom studies, \(^6\) TOI measurements accurately detected oxygenation values from 10% to 100%, and we found the two measurements (TOIsrs and TOIcox) to be correlated (fig. 1) over the entire range of PaO\(_2\) that we examined.

**Conclusion**

The cerebral arterial volume fraction was 22.9–27.5% in normoxia, but increased rapidly at PaO\(_2\) values less than 60 mmHg. This increase is likely to represent cerebral arterial vasodilatation during hypoxemia that aims to preserve cerebral oxygen delivery. As the cerebral arterial volume fraction becomes dominant in the TOI measurement during acute hypoxemia, the A:V ratio increases, and the fall in cerebral venous saturation may be much greater than that estimated using the commonly used fixed cerebral A:V ratio of 25:75. These changes in cerebral arterial and venous volume fractions in acute hypoxemia need to be taken into account when interpreting TOI measurements in clinical settings such as anesthesia and intensive care.

**References**