Regional differences in tissue oxygenation during cardiopulmonary bypass for correction of congenital heart disease in neonates and small infants: Relevance of near-infrared spectroscopy

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Objective: Cardiac surgery with cardiopulmonary bypass for correction of congenital heart disease in neonates and small infants is associated with considerable neurologic sequelae. We assessed the extent to which mixed venous oxygen saturation as a measure for adequacy of perfusion, reflects the oxygenation status of upper and lower body compartments. Moreover, we evaluated potential benefits of near-infrared spectroscopic monitoring of regional tissue oxygenation.

Methods: Twenty patients (body weight < 10 kg) undergoing open cardiac procedures with cardiopulmonary bypass were enrolled. Blood samples were obtained in parallel from inferior and superior caval vein cannulas and mixed venous line and assessed for venous oxygen saturation and lactate levels. Data were compared to simultaneously measured tissue oxygenation indices obtained by near-infrared spectroscopy from brain and lower limb.

Results: Venous oxygen saturation was lower and lactate concentration higher in blood from superior relative to inferior venous line. Mixed venous oxygen saturation correlated with venous oxygen saturation from inferior venous line and tissue oxygenation index of lower limb. No correlation was found between mixed venous oxygen saturation and venous oxygen saturation from superior venous line or cerebral tissue oxygenation index.

Conclusion: In neonates and small infants undergoing cardiac surgery with cardiopulmonary bypass, considerable regional differences exist in venous oxygen saturation. Mixed venous oxygen saturation primarily represents lower-torso oxygen status but poorly reflects and systematically overestimates upper-body oxygenation. Near-infrared spectroscopy yields additional information on regional oxygenation and may be valuable in early and sensitive detection of regional malperfusion in critical organs such as the brain.

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Recent improvements in cardiopulmonary bypass (CPB), surgical techniques, and intensive care have facilitated complex surgical procedures and perfusion for the correction of congenital heart disease (CHD) in even the smallest neonates, with low perioperative mortalities under 3%.¹ Incidences of neurologic complications after CPB in neonates and infants remain high, however, and neurologic sequelae have been reported in as many as 26% of patients.² Neonates and young infants with complex CHD who have undergone open procedures with CPB still exhibit neurologic abnormalities approximately 5 years after the initial surgery, with hypotonia and developmental delay reported in 28.4% at age of school entry.³ Seven years after surgical correction, children with cyanotic cardiac defects remain at increased risk for attentional dysfunction in the field of executive control, and these attentional deficits are correlated with the durations of aortic crossclamping and CPB.⁴ Incomplete cerebral ischemia and regional tissue hypoxia have been implicated as

Abbreviations and Acronyms

CHD	= congenital heart disease
CPB	= cardiopulmonary bypass
NIRS	= near-infrared spectroscopy
SvO ₂	= venous oxygen saturation
S $\bar{v}$ O ₂	= mixed venous oxygen saturation
TOI	= tissue oxygenation index

potential mechanisms underlying neurologic damage after CPB.⁵ This notion is supported by a close correlation between the perioperative arterial and cerebral blood oxygenations and the risk for postoperative brain damage in neonates.^{6,7}

To date, the only commonly used online-monitored parameter for the quality of perfusion and oxygenation during CPB in neonates and small infants is the mixed venous oxygen saturation (S $\bar{v}$ O₂), as optically measured in the common venous line of the CPB system.⁸ The S $\bar{v}$ O₂ is, however, a poor predictor of regional oxygenation levels in different organs and compartments of the body.^{9,10} Physiologically, regional inhomogeneities in tissue oxygenation can be attributed to organ-specific differences in tissue perfusion, in the regulation of vasomotor tone, in local diffusion distances, or in oxygen consumption. This situation is further complicated during surgical correction of CHD, because preexisting malformations of the vascular system—including hypoplastic vessels, shunts, or collateralization—as well as impaired arterial inflow or venous drainage through the CPB cannulas may cause additional inhomogeneities of perfusion.

Recently, near-infrared spectroscopy (NIRS), a noninvasive method for transcutaneous measurement of oxyhemoglobin and deoxyhemoglobin concentrations in tissue, has increasingly been used to monitor cerebral oxygenation during CPB.¹¹ The use of multiple sensor–detector systems allows in addition the comparison of regional tissue oxygenations, such as between the head and the flank¹² or between different cerebral areas.¹³ In a recent case report, we documented regional malperfusion in a patient with complex aortic anatomy by means of simultaneous transcranial and lower torso NIRS monitoring.¹⁴ This investigation was performed to assess systematically the utility of regional oxygenation monitoring by NIRS relative to that of S $\bar{v}$ O₂ measurements during CPB in neonates and small infants undergoing surgical correction of CHD.

Materials and Methods

After approval was obtained from the local ethics committee and informed consent was obtained from the parents, 20 neonates and small infants (body weight <10 kg) undergoing surgical correction of CHD were enrolled in this prospective study. Patients with a diagnosis of persistent left upper caval vein were excluded from participation.

Near-infrared Spectroscopy

A near-infrared spectrometer (NIRO-200; Hamamatsu Photonics KK, Hamamatsu City, Japan) equipped with two independent emitter-sensor pairs was used for simultaneous measurement of regional oxygenations in the brain and in skeletal muscle of the lower torso. After induction of anesthesia, the first pair of NIRS optodes was positioned noninvasively on the patient's forehead with a spatial separation of 4 cm and an estimated optical path length of 15.4 cm between the emission and detection probes.¹⁵ A second pair of optodes was placed on the right thigh with an estimated optical path length of 14.4 cm. Light was generated by three pulsed laser diodes at wavelengths of 775, 810, and 850 nm, respectively, and emitted into the tissue through the source optode. Backscattered light from the tissue was collected by the detection probe equipped with a dual-segmented photodiode chip. With the spatially resolved spectroscopy method, the tissue oxygenation index (TOI) was calculated from measured changes of light attenuation along the intersegmental distance of the chip.^{16,17} The TOI is the ratio of oxygenated to total hemoglobin and thus reflects mean hemoglobin oxygen saturation within the scanned tissue section.

CPB and Surgery

In all cases, CPB was performed with a S3 mast-mounted roller pump console (Stöckert Instrumente GmbH, Munich, Germany), which provided short tubing connections in our circuit consisting of tubing with 4.76 mm (16 inch) inner diameter in the entire system, with the exception of the roller pump segment of the arterial pump, which consisted of silicone rubber tubing with 6.35 mm (0.25 inch) inner diameter. The entire extracorporeal circuit, incorporating the Capiox RX05 hollow-fiber membrane oxygenator (Terumo Deutschland GmbH, Eschborn, Germany) and an arterial line filter (Dideco D736; Dideco SpA, Mirandola, Italy), had a total priming volume of 200 mL.¹⁸

The patients' CHD diagnoses and the surgical procedures are summarized in Table 1. During CPB, a systemic hemoglobin concentration less than 8 g/L, corresponding to a hematocrit of approximately 24%, was considered the critical trigger for the transfusion of red blood cells.

Data Acquisition and Statistical Analysis

During CPB, TOI was continuously recorded at the forehead and the right thigh by spatially resolved NIRS. Blood samples (0.3 mL each) were obtained at 30-minute intervals from both the inferior and the

TABLE 1. Diagnoses and surgical procedures

Diagnosis	Procedure	No.
Atrial septal defect	Patch closure	1
Ventricular septal defect	Patch closure	5
Complete atrioventricular channel	2-patch reconstruction	4
Transposition of great arteries	Arterial switch operation	2
Tetralogy of Fallot	Correction	3
ALCAPA	Correction	3
Double-outlet right ventricle	Correction	2

ALCAPA, Anomalous origin of left coronary artery from pulmonary artery.

Figure 1. Oxygenation in upper and lower body compartments during CPB in neonates. Group data of venous oxygen saturation (SvO_2 , A) and lactate (C) determined in blood drawn from superior cannula (black bars), inferior cannula (white bars), or mixed venous line (gray bars) show higher oxygen extraction and lactate levels in upper body than in lower torso. Similarly, tissue oxygenation index (TOI, B) determined in lower limb exceeded simultaneously measured value in brain. Each bar is mean $\pm$ SEM from 55 measurements in 20 patients; asterisk represents $P < .05$; triple asterisk represents $P < .001$.

superior venous lines near the patient and in parallel from the mixed venous line of the CPB circuit. All samples were immediately analyzed for blood gas values (Rapidlab 865; Siemens Healthcare Diagnostics Inc, Deerfield, Ill), venous oxygen saturation (SvO_2), hemoglobin level, and lactate concentration.

Group data are given as mean $\pm$ SEM. Differences between dependent variables were analyzed by Wilcoxon signed rank test (SigmaStat; Systat Software Inc, San Jose, Calif). The Spearman coefficient of correlation (r_s) was calculated to test correlations between parameters, and linear regression analysis was performed (SigmaPlot; Systat).

Results

Regional tissue oxygenations during CPB were determined in 9 female and 11 male patients with a mean age of 5.3 ± 3.1 months (range 3 days–10 months) and a mean body weight of 5.4 ± 1.8 kg (range 3.2–9.5 kg). Eight procedures were performed under conditions of normothermia, 7 under conditions of mild hypothermia at a core temperature of 32°C , and the remaining 5 under conditions of moderate hypothermia at a core temperature of 28°C . The mean duration of CPB was 98 ± 25 minutes (range 35–185 minutes). For each measurement, regional TOI recordings were performed and three blood samples were obtained simultaneously from the inferior, the superior, and the mixed venous lines of the CPB circuit. On average, 2.75 ± 0.22 measurements were performed for each patient, depending on the duration of CPB, yielding a total of 55 measurements overall.

Direct comparison of SvO_2 values revealed a significantly lower SvO_2 in blood samples retrieved from the superior relative to the inferior venous line (Figure 1, A). The notion that

average blood oxygenation is lower in the upper than in the lower body compartment was confirmed by NIRS measurements yielding higher TOI values at the thigh than at the forehead (Figure 1, B). This regional heterogeneity in oxygenation is directly reflected in the metabolic level by higher lactate concentrations in venous blood from the upper than in the lower torso (Figure 1, C). Thus regional oxygen extraction during CPB is higher in the upper body than in the lower body, and direct measurements of SvO_2 or lactate in blood sampled from the mixed venous line of the CPB may overestimate the critical oxygenation status of the cerebral compartment.

To assess whether $S\bar{v}O_2$ measurements yield an adequate estimate of the quality of perfusion and oxygenation in the different body compartments, we compared SvO_2 data derived from the superior and inferior venous lines with simultaneously measured $S\bar{v}O_2$ values (Figure 2). Although $S\bar{v}O_2$ values were correlated linearly ($r_s = 0.90$, $P < .001$) with SvO_2 measurements from the inferior venous line, no correlation was found between $S\bar{v}O_2$ and SvO_2 values determined simultaneously in the superior venous line of the CPB circuit. Thus $S\bar{v}O_2$ yields a good estimate of the oxygenation status in the lower body but is of little predictive value regarding the upper body. This notion was further substantiated by the finding that lactate concentrations in mixed venous blood correlated significantly ($r_s = 0.32$, $P = 0.018$) with SvO_2 values from the inferior but not the superior venous line.

A similar pattern of correlation was observed when $S\bar{v}O_2$ values were compared with data on regional tissue oxygenation as determined by NIRS (Figure 3). Whereas $S\bar{v}O_2$ was correlated linearly ($r_s = 0.47$, $P < .001$) with regional

Figure 2. Correlations of mixed venous oxygen saturation (SvO_2) with values measured simultaneously in blood drawn from either superior cannula (open circles) or inferior cannula (closed circles) of cardiopulmonary bypass circuit. In 55 measurements each from 20 patients, mixed venous oxygen saturations were correlated significantly with values from inferior venous cannula ($r_s = 0.897$, $P < .001$) but not from superior venous cannula.

Figure 3. Correlations of mixed venous oxygen saturation (SvO_2) in cardiopulmonary bypass circuit with tissue oxygenation index (TOI) values measured simultaneously in either brain (open circles) or lower limb (closed circles) by regional near-infrared spectroscopy. In 55 measurements each from 20 patients, mixed venous oxygen saturation was correlated significantly with regional tissue oxygenation of lower limb ($r_s = 0.47$, $P < .001$) but not of brain.

TOI determined at the right thigh, no correlation with cerebral TOI values measured at the forehead was detectable. Thus $S\bar{v}O_2$ may reflect the oxygenation status in the lower torso but is a poor indicator of cerebral perfusion and oxygenation during CPB in neonates.

Cerebral oxygenation status can be adequately reflected by SvO_2 if measurements are performed in venous blood from the upper body (Figure 4). This was evident from a linear correlation of cerebral tissue oxygenation determined by NIRS with SvO_2 values determined simultaneously in the superior venous line ($r_s = 0.70$, $P < .001$). Similarly, SvO_2 values in the inferior venous line were correlated significantly with TOI data from the lower limb ($r_s = 0.56$, $P < .001$). These findings confirm the validity of NIRS as a non-invasive technique for monitoring regional tissue oxygenation during CPB in neonates.

Discussion

We assessed regional differences in oxygenation in neonates and small infants during CPB for the correction of CHD with online-measured $S\bar{v}O_2$, regional SvO_2 , and regional TOI obtained with NIRS. Our data demonstrate that even with standard surgical and CPB procedures, considerable variations in tissue oxygenation exist between different body compartments. Importantly, $S\bar{v}O_2$, which is widely used as a measure of adequacy of perfusion and oxygenation on CPB,¹⁹ was shown to reflect poorly the oxygenation status of the upper body compartment, including the brain. In contrast, noninvasive regional monitoring of tissue oxygenation by transcran-

ial and lower-torso NIRS revealed significant correlations with SvO_2 values measured in blood from the superior and inferior caval lines, respectively, thus yielding reliable information about the quality of regional perfusion and oxygenation during CPB.

Our data demonstrate that in neonates and small infants undergoing surgery with CPB for the correction of CHD, $S\bar{v}O_2$ represents predominantly the oxygenation status in the lower body compartment drained by the caval vein inferior line of the CPB circuit, whereas the oxygenation status of the upper body, and particularly the brain, is poorly reflected. This deficiency in monitoring is even more detrimental because relative perfusion is on average worse in the upper body during CPB, as reflected by lower SvO_2 and higher lactate concentration. $S\bar{v}O_2$ thus systematically overestimates the adequacy of oxygenation and perfusion in the most critical organ, the brain, and serious cerebral malperfusion may remain unrecognized with the standard monitoring techniques.

Previous clinical studies evaluating the value of postoperative $S\bar{v}O_2$ monitoring in neonates and infants have shown conflicting results. In several independent studies, regional cerebral oxygenation assessed by NIRS was correlated significantly with SvO_2 measured through a central venous or pulmonary arterial catheter.^{12,20,21} Surprisingly, the correlation between cerebral TOI and $S\bar{v}O_2$ was particularly high when the central venous catheter was placed with the tip in the inferior as opposed to the superior caval vein or the right

Figure 4. Correlations of regional venous oxygen saturation (SvO_2) determined in superior (closed circles) or inferior (open circles) cannula of cardiopulmonary bypass circuit with regional tissue oxygenation index (TOI) measured simultaneously by regional near-infrared spectroscopy in either brain (closed circles) or lower limb (open circles), respectively. In 55 measurements each from 20 patients, regional venous oxygen saturation was correlated significantly with regional tissue oxygenation index in both upper body ($r_s = 0.70$, $P < .001$) and lower torso ($r_s = 0.56$, $P < .001$).

atrium.²¹ Moreover, a Bland–Altman comparison between $S\bar{v}O_2$ and regional oxygen saturation revealed wide limits of agreement, suggesting that despite a significant correlation $S\bar{v}O_2$ was of poor predictive value for cerebral oxygenation.¹²

During CPB, the adequacy of $S\bar{v}O_2$ measurements to yield relevant information on the cerebral oxygenation status appears to be even further reduced. In our study, $S\bar{v}O_2$ was correlated neither with cerebral TOI values determined by NIRS nor with SvO_2 values from the superior venous line. This finding is in agreement with previous studies reporting a lack of correlation between $S\bar{v}O_2$ and jugular SvO_2 in both pediatric¹⁹ and adult²² patients undergoing CPB. The perception that $S\bar{v}O_2$ provides only an unsatisfactory estimate of the cerebral oxygenation status during CPB is also supported by data from an experimental CPB model in swine, in which oxygenation in the sagittal sinus decreased from $66\% \pm 3\%$ to $33\% \pm 2\%$, whereas $S\bar{v}O_2$ remained largely unchanged between 75% and 80%.¹⁰ Our finding that $S\bar{v}O_2$ represents primarily the lower body compartment during CPB is, furthermore, in agreement with a previous study by Lindholm and colleagues,¹⁰ who showed that $S\bar{v}O_2$ correlates well with hepatic but not jugular vein oxygen saturation in adults undergoing CPB. This study therefore shows, in line with previous reports, the existence of considerable regional heterogeneities in oxygenation in neonates and infants during CPB, thus stressing the need for direct monitoring of critical organs at a local level.

Noninvasive monitoring of regional tissue oxygenation by NIRS may provide such crucial information. In our study, cerebral TOI measured by NIRS was correlated significantly with SvO_2 determined simultaneously in the superior venous line, with a correlation coefficient of 0.70. This is in agreement with previous studies demonstrating significant correlations between jugular bulb oxygen saturation and cerebral oxygenation determined by transcranial NIRS in children.^{23,24} The validity of the transcranial NIRS approach in yielding adequate and reliable information on cerebral oxygenation is further supported by data from Al-Rawi and coworkers,²⁵ who demonstrated an 87.5% sensitivity and a 100% specificity of the TOI measurement with respect to changes in intracranial perfusion in the adult head.

The interpretation of NIRS data is limited, however, by the technical constraints of the technique and the lack of reliable reference values or critical thresholds in defined patient populations. Approximately 70% of the obtained NIRS signal is derived from the venous compartment, with capillaries and arterioles contributing 20% and 10%, respectively.²⁶ TOI thus reflects SvO_2 in the cerebral compartment only partially, varying not only with changes in tissue perfusion or oxygen extraction but also with changes in the relative distribution of blood volume among the arteriolar, capillary, and venous compartments within the scanned tissue section. Taking this into account, variations in TOI monitored by transcranial NIRS can still yield critical information on changes in the cerebral oxygenation status. The clinical relevance of NIRS monitoring is, however, further complicated by the lack of accepted and validated critical thresholds for cerebral TOI. This applies in particular to the patient population of neonates and small infants monitored in our study. In a recent clinical investigation of 143 infants and children undergoing CHD surgery, Fenton and coworkers²⁷ showed an association of baseline cerebral oxygenation values of less than 50% with perioperative death, suggesting that postponement of the surgical intervention or additional interventions such as red blood cell transfusions or hyperoxic ventilation might be warranted in cases with preoperative TOI values below this threshold. Under perioperative conditions including CPB, regional perfusion, and hypothermia, however, critical oxygenation thresholds in the brain remain largely unknown. This applies in particular to the patient population undergoing correction of CHD, in which individual susceptibility to tissue hypoxia may vary according to the underlying malformation and especially differs between cyanotic and noncyanotic malformations.

The high incidence and critical outcome of neurologic sequelae warrant optimization of cerebral monitoring during CPB in neonates and small infants.^{2–4} The results of our study demonstrate that the measurement of $S\bar{v}O_2$ is inadequate for this purpose and should be supplemented with additional monitoring systems with higher regional resolution. Currently, NIRS provides the only versatile noninvasive

technique for point-of-care monitoring during CPB. The extent to which improved regional monitoring of oxygenation in neonates and small infants with CHD undergoing CPB can serve as a perioperative guidance tool to optimize cerebral perfusion and improve clinical outcome remains to be determined in future studies.

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