The influence of systemic hemodynamics and oxygen transport on cerebral oxygen saturation in neonates after the Norwood procedure

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Supplemental material is available online.

Objectives: Ischemic brain injury is an important morbidity in neonates after the Norwood procedure. Its relationship to systemic hemodynamic oxygen transport is poorly understood.

Methods: Sixteen neonates undergoing the Norwood procedure were studied. Continuous cerebral oxygen saturation was measured by near-infrared spectroscopy. Continuous oxygen consumption was measured by respiratory mass spectrometry. Pulmonary and systemic blood flow, systemic vascular resistance, oxygen delivery, and oxygen extraction ratio were derived with measurements of arterial, and superior vena cava and pulmonary venous gases and pressures at 2- to 4-hour intervals during the first 72 hours in the intensive care unit.

Results: Mean cerebral oxygen saturation was 66% $\pm$ 12% before the operation, reduced to 51% $\pm$ 13% on arrival in the intensive care unit, and remained low during the first 8 hours; it increased to 56% $\pm$ 9% at 72 hours, still significantly lower than the preoperative level ($P < .05$). Postoperatively, cerebral oxygen saturation was closely and positively correlated with systemic arterial pressure, arterial oxygen saturation, and arterial oxygen tension and negatively with oxygen extraction ratio ($P < .0001$ for all). Cerebral oxygen saturation was moderately and positively correlated with systemic blood flow and oxygen delivery ($P < .0001$ for both). It was weakly and positively correlated with pulmonary blood flow ($P = .001$) and hemoglobin ($P = .02$) and negatively correlated with systemic vascular resistance ($P = .003$). It was not correlated with oxygen consumption ($P > .05$).

Conclusions: Cerebral oxygen saturation decreased significantly in neonates during the early postoperative period after the Norwood procedure and was significantly influenced by systemic hemodynamic and metabolic events. As such, hemodynamic interventions to modify systemic oxygen transport may provide further opportunities to reduce the risk of cerebral ischemia and improve neurodevelopmental outcomes.

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There has been a dramatic reduction in mortality after surgery for complex congenital heart defects. Consequently, much attention is now being directed to neurologic outcomes among survivors.¹ The incidence of measurable neurologic sequelae is as high as 25%, including both early postoperative seizures^{2,3} and long-term neurodevelopmental impairment such as cognitive, attentional, behavioral, and neuromuscular disabilities.⁴⁻⁸ Studies on neurologic outcomes have largely focused on specific intraoperative risk factors, such as hemodilution, pH management,⁹ and deep hypothermic circulatory arrest.^{2-5,8,10} Others have reported preoperative reduction of cerebral blood flow and ischemic injury (in turn related to anatomic and functional features), being most severe in neonates with hypoplastic left heart syndrome.¹¹⁻¹⁴ Postoperative hemodynamic instability may further affect

Abbreviations and Acronyms

CPB	= cardiopulmonary bypass
Do ₂	= oxygen delivery
ERO ₂	= oxygen extraction ratio
ICU	= intensive care unit
NIRS	= near-infrared spectroscopy
PaO ₂	= arterial oxygen tension
Qp	= pulmonary blood flow
Qs	= systemic blood flow
ScO ₂	= cerebral oxygen saturation
SVR	= systemic vascular resistance
Vo ₂	= oxygen consumption

the vulnerable brain. Prolonged stay in the intensive care unit (ICU) has been found to be associated with poorer neurologic outcomes.¹⁵ Ischemic lesions early after cardiac surgery, in the form of periventricular leukomalacia, have been seen in more than 50% of neonates and have been attributed to postoperative hypoxia and diastolic hypotension.^{16,17}

Neonates with hypoplastic left heart syndrome undergoing the Norwood procedure, which involves reconstruction of the aortic arch to maintain unobstructed systemic blood flow (Qs) and limiting pulmonary blood flow (Qp) with a modified Blalock–Taussig shunt, may be particularly prone to neurologic insult, with hypoxic–ischemic lesions seen preoperatively in nearly half of these neonates.^{12,17} Intraoperatively, the already vulnerable neonatal brain will be exposed to the effects of prolonged cardiopulmonary bypass (CPB), circulatory arrest, and variable hemodynamic and metabolic events. The effects of regional brain perfusion strategies remain to be demonstrated, but it is likely that intraoperative neuroprotection is less than complete.¹⁸ In addition to these preoperative and intraoperative risk factors, our group has shown that the early postoperative period after the Norwood operation is characterized by hemodynamic instability with marginal systemic oxygen delivery (Do₂), with the injured neonatal single right ventricle supplying the parallel circulations and arterial oxygen desaturation.^{19,20} At the same time, systemic oxygen consumption (Vo₂) increases,^{19,20} thus further impairing systemic oxygen transport and placing the cerebral circulation at risk. It has been recently reported that low systemic venous oxygen saturation is associated with childhood neurodevelopmental abnormality.²¹ Clearly, a systematic assessment of the effects of systemic hemodynamics and oxygen transport on cerebral oxygenation during the early postoperative period is needed to understand the mechanisms of neurologic ischemic injury and to improve postoperative management and long-term neurologic outcomes.

Near-infrared spectroscopy (NIRS) provides a noninvasive, continuous method to monitor regional tissue oxyhe-

moglobin saturation.^{22,23} It has been extensively used during CPB to determine the risk factors for poor cerebral perfusion.^{16,18,24} In the present study, we hypothesized that cerebral oxygen transport might be influenced by systemic hemodynamics and oxygen transport during the early postoperative period after the Norwood procedure. We used NIRS to continuously measure cerebral oxygen saturation (ScO₂) and respiratory mass spectrometry to continuously measure Vo₂ and to derive measurements of Qp and Qs, Do₂, and oxygen extraction ratio (ERO₂). We examined the effects of each of the systemic hemodynamic indices and oxygen transport variables on ScO₂ during the first 72 hours after the Norwood procedure.

Patients and Methods**Patients**

This study was approved by the Research Ethics Board at the Hospital for Sick Children, Toronto, Canada. Written informed consent was obtained from the parents of 16 neonates (14 boys, age range 4–16 days, median 7 days) undergoing the Norwood procedure between April 2004 and November, 2006. Patient demographics are shown in Table E1. Data from some of these patients were reported previously on systemic hemodynamics and oxygen transport early after the Norwood procedure.^{19,20}

Operative Procedure

Neonates were intubated with a cuffed endotracheal tube (Microcuff–Heidelberg–Pediatric; Microcuff GmbH, Weinheim, Germany). General anesthesia was maintained with inhaled isoflurane, intravenous fentanyl, and pancuronium bromide. A standard Norwood procedure with regional cerebral circulation was used. All neonates had a 3.5-mm right modified Blalock–Taussig shunt with the distal anastomosis placed centrally on the intramediastinal pulmonary artery. CPB management consisted of a target flow of 125 mL · min⁻¹ · kg⁻¹ and a hematocrit value of 25% to 30% with modified pH-stat blood gas management for uniform cooling (18°C–20°C) at the esophageal site. Selected cerebral perfusion was performed in all neonates at pump flows of 30 to 35 mL · min⁻¹ · kg⁻¹. All neonates received aprotinin 1.7 × 10⁶ KIU/m² and methylprednisolone 10 mg/kg before CPB. Phenoxybenzamine 0.25 mg/kg was added to the pump prime. Separation from CPB occurred after initiation of infusions of milrinone (0.66 μg · min⁻¹ · kg⁻¹) and dopamine (5 μg · min⁻¹ · kg⁻¹). Modified ultrafiltration was used in all neonates immediately after separation from CPB. A pulmonary venous line was inserted into the orifice of the right upper pulmonary vein. The sternal incision was left open routinely in all the patients.

Critical Care

Infants received time-cycled pressure control/pressure support ventilation. Sedation and analgesia were given as a continuous intravenous infusion of morphine (20–40 μg · h⁻¹ · kg⁻¹), intermittent injections of lorazepam (0.1 mg/kg), and pancuronium (0.1 mg/kg). Pancuronium was discontinued when the patient achieved satisfactory hemodynamic stability.

The central esophageal temperature was monitored continuously and maintained at 36°C–37°C. Vasoactive agents (milrinone,

Figure 1. Mean $\pm$ SD values of cerebral oxygen saturation (ScO_2) and hemodynamics including systolic, diastolic, and mean arterial pressures, systemic vascular resistance (SVR), arterial oxygen saturation (SaO_2), arterial partial oxygen pressure (PaO_2), hemoglobin (Hb), pulmonary (Q_p) and systemic blood flows (Q_s), and oxygen transport including systemic oxygen consumption (VO_2), oxygen delivery (DO_2), and oxygen extraction ratio (ERO_2) during the first 72 hours after arrival in the intensive care unit. *After polynomial transformation, with time indicating the coefficient of the early trend, and time 2 indicating the later trend. **Data were entered after logarithmic transformation.

dopamine, phenoxybenzamine, and vasopressin) and ventilatory settings were adjusted according to our standard protocol to achieve arterial carbon dioxide tension around 45 to 50 mm Hg and pH 7.3 to 7.4, mean arterial blood pressure 40 to 45 mm Hg with systolic pressure in the range of 55 to 65 mm Hg, arterial oxygen saturation 70% to 80%, and superior vena caval saturation of 44% to 55%.²⁵ Intravenous volume infusions (5% albumin or blood) were given to maintain filling pressures of 7 to 10 mm Hg. Transfusions were given for a hemoglobin of less than 14 mg/dL, and hemoglobin was generally maintained between 14 and 16 mg/dL (Figure 1).

Methods of Measurements

ScO_2 . A NIRS probe, consisting of a near-infrared light emitter optode and a receiver optode with a distance of 5 cm, was placed on the patient's midline forehead. The recordings were monitored by a dual-detector device (Somanetics INVOS 5100A, Troy, Mich) and recorded at 1-minute intervals.

VO_2 . VO_2 was measured continuously with an AMIS2000 respiratory mass spectrometer (Innovision A/S, Odense, Denmark). This is a sensitive and accurate method that allows simultaneous measurements of multiple gas fractions. The detailed methodology used in this protocol has been published previously by our group.²⁰

Calculations of hemodynamic and oxygen transport variables. Blood samples were taken from the arterial line, superior vena cava, and pulmonary vein lines for the measurements of blood gases and saturations. Q_p and Q_s were then calculated by the direct Fick method:

$$Q_p = VO_2 / (Cp_{vO_2} - Ca_{O_2})$$

$$Q_s = VO_2 / (Ca_{O_2} - Cv_{O_2})$$

Systemic vascular resistance (SVR) was calculated by the following equation:

$$SVR = (MAP - MVP) / Q_s$$

Do₂ and ERO₂ were calculated by standard equations:

$$\text{Do}_2 = \text{Qs} \times \text{Cao}_2$$

$$\text{ERO}_2 = \text{Vo}_2 / \text{Do}_2$$

where Cao₂, Cpvo₂, and Cvo₂ indicate systemic arterial (which is pulmonary arterial), pulmonary venous, and superior vena cava oxygen contents, respectively; MAP and MVP indicate the mean arterial and superior vena cava pressures. All values were indexed to body surface area as calculated before the operation.

Study Protocol

Sco₂ was continuously monitored after anesthesia introduction, during the operation, and 72 hours after the operation. Intraoperative clinical data (including esophageal temperature, systemic arterial blood pressure, and blood gases) were collected before the operation as baseline, before selective cerebral perfusion (CPB cooling), during selective cerebral perfusion, before separation from CPB (CPB rewarming), and at the end of the operation. Postoperative study recordings were prospectively performed during the first 72 hours after arrival in the ICU. Values of hemodynamic and oxygen transport variables and central body temperature were collected at 2-hour intervals during the first 24 hours and at 4-hour intervals in hours 25 through 72. Sampling was avoided if a change in sedation, paralysis, ventilatory, or hemodynamic treatment was made within 15 minutes. The treating physicians were blinded to NIRS values during the postoperative period.

Data Analysis

Data are expressed as mean $\pm$ standard deviation. Mixed linear regression analysis for repeated measures was used to determine the nature of any time trend of the measures over the 72-hour study period. For some measures, various transformations of time (logarithmic and polynomial) were tested regarding the best fit for the time course. Correlations between the variables were sought also using mixed linear regression analysis for repeated measures. The extent of correlation was indicated by the intercept, parameter estimate, and *P* value. Further comparisons of the extents of correlations between the 2 periods in the first 24 hours and the following 48 hours were made and indicated by the parameter estimates of the interactions of time period and the variables and *P* values. All data analyses were performed with SAS statistical software version 9.2 (SAS Institute, Inc, Cary, NC).

Results

Patients

There was no incidence of circulatory collapse or death during the study period. All neonates survived to hospital discharge except for one who died of cardiac failure on the 25th postoperative day (patient 13). Complete data sets were collected in all neonates for 72 hours except in one (patient 8) owing to weaning from mechanical ventilation at 48 hours. The standard neonatal physical examination at the time of discharge did not demonstrate abnormal neurologic findings.

Intraoperative Changes of Sco₂

Sco₂ values differed markedly between the different periods of perfusion and surgical repair. Preoperative baseline Sco₂ was 66% $\pm$ 12%. Sco₂ increased to 88% $\pm$ 6% at the end of cooling and was 90% $\pm$ 7% during selective cerebral perfusion. It decreased to 64% $\pm$ 9% during rewarming, and further to 54% $\pm$ 6% after separation from CPB, significantly lower than the preoperative baseline level (*P* = .02).

Postoperative Changes of Sco₂ and Systemic Hemodynamic and Oxygen Transport Variables

Table E2 and Figure 1 show the results of Sco₂ and its temporal relationship with systemic hemodynamic, and oxygen transport variables during the 72 hours after arrival in the ICU. All the variables showed substantial intraindividual and interindividual variations over the study period, with marked differences in the time course and extent of change.

Sco₂. Sco₂ further decreased to 51% $\pm$ 13% on arrival in the ICU and remained at the low level in the initial 8 hours. Over the first 72 hours, Sco₂ was significantly related to time in a complex polynomial function, with an increase in the first 48 hours (*P* < .0001) and a subsequent small but significant decrease in 48 to 72 hours (*P* < .0001). The mean value of Sco₂ at 72 hours was 56% $\pm$ 9%, significantly lower than the preoperative baseline level (*P* = .02). When all data were pooled together, the values ranged from 27% to 79%, with 28% of the measurements lower than the reported critical level of 48%.²⁶⁻²⁸

Systemic hemodynamics and oxygen transport. Systolic and mean arterial pressures were significantly related to time after a logarithmic transformation, being initially low in the first 24 hours, followed by a rapid increase between 24 and 48 hours, and remained at that level thereafter (*P* < .0001 for both). Diastolic arterial pressure significantly and linearly increased over the study period (*P* = .004). SVR was significantly related to time in a complex polynomial function, being initially high in the first 8 hours, followed by a rapid decrease in the first 24 hours (*P* < .0001), and a subsequent small but significant increase (*P* = .0001). Hemoglobin showed a small linear decrease over time (*P* < .0001). Sao₂ and arterial oxygen tension (Pao₂) were significantly related to time after logarithmic transformation, with a rapid increase in the first 24 hours and thereafter a slow increase (*P* < .0001). Qp showed a linear significant increase over time (*P* < .0001). Qs and Do₂ were significantly related to time in a complex polynomial function, with an initial rapid increase in the first 24 hours followed by a slow increase (*P* < .0001 for both), and a subsequent small but significant decrease at around 28 hours (*P* = .0001 for Qs and *P* < .0001 for Do₂). Vo₂ and ERO₂ were significantly related to time after logarithmic transformation, showed a rapid decrease in the first 8 hours, and a

Figure 2. Correlations between cerebral oxygen saturation (ScO_2) and systemic hemodynamic and oxygen transport variables of systolic, diastolic, and mean arterial pressures, systemic vascular resistance (SVR), arterial oxygen saturation (SaO_2), arterial partial oxygen pressure (PaO_2), Hemoglobin (Hb), pulmonary (Qp) and systemic blood flows (Qs), systemic oxygen consumption (VO_2), oxygen delivery (DO_2), and oxygen extraction ratio (ERO_2) in neonates during the first 72 hours after arrival in the intensive care unit (ICU).

subsequent slow decrease ($P = .0005$ for VO_2 , and $P < .0001$ for ERO_2).

Correlations of ScO_2 With Systemic Hemodynamics and Oxygen Transport

The statistical analysis results of the correlations between ScO_2 and systemic hemodynamics and oxygen transport during the whole study period are seen in Table E3 and Figure 2.

ScO_2 was closely and positively correlated with systolic, diastolic, and mean arterial pressures (parameter estimate 0.31, 0.26, and 0.48, respectively; $P < .0001$, $P = .0003$,

and $P < .0001$, respectively) and with SaO_2 and PaO_2 (parameter estimate 0.41 and 0.69, respectively; $P < .0001$ for both). ScO_2 was also closely and negatively correlated with ERO_2 (parameter estimate -31.0 ; $P < .0001$). It was moderately and positively correlated with Qs (parameter estimate 2.1; $P < .0001$) and DO_2 (parameter estimate 0.023; $P < .0001$). It was weakly but significantly and positively correlated with Qp (parameter estimate 1.8; $P = .001$) and negatively with SVR (parameter estimate -0.15 ; $P = .003$). It was not correlated with VO_2 ($P > .05$).

Additionally, PaO_2 and SaO_2 were weakly correlated with Qp (parameter estimate 0.05; $P < .0001$ for both), Qp/Qs

(parameter estimate 0.03 and 0.04, respectively; $P < .0001$ for both), and Do_2 (parameter estimate 3.7, $P = .002$ for PaO_2 ; parameter estimate -0.16 ; $P > .05$ for Sao_2). The extents of correlations of Sco_2 with hemodynamics and oxygen transport variables were not significantly different between the period of the first 24 hours and that of the later period ($P > .05$ for all).

Discussion

This is the first study to examine the consequences of postoperative systemic hemodynamics and oxygen transport on cerebral oxygenation in neonates with hypoplastic left heart syndrome after the Norwood procedure. We found that Sco_2 fell during the first 8 hours after surgery and then increased in neonates during the first 72 hours after the Norwood procedure. Critically low levels of Sco_2 occurred frequently. The changes in Sco_2 were significantly related to the changes in systemic hemodynamics and oxygen transport variables.

NIRS was used to estimate cerebral oxygenation in our study. The dual-path length device we used measures the percentage of oxyhemoglobin to total hemoglobin in the mixture of arteries, capillaries, and veins in a slice of tissue approximately 1.5 to 2.5-cm deep.²² Because the predominant venous portion may account for approximately 70% to 80% in NIRS signals,²⁹ the changes in Sco_2 can estimate the cerebral flow–metabolism relationships. In heavily sedated subjects, as in these neonates, in whom aerobic metabolism of the brain is relatively low and stable, Sco_2 may act as surrogate for cerebral blood flow and Do_2 .

Evidence from adult humans²⁶ and neonatal piglets²⁸ indicates that aerobic metabolism may be impaired when Sco_2 decreases below 44% to 47%. In a recent study of neonates after the Norwood procedure, prolonged exposure to low postoperative Sco_2 ($<45\%$ for >180 minutes) was associated with the development of ischemic lesions on magnetic resonance imaging.²⁷ In our neonates, the preoperative baseline Sco_2 was $66\% \pm 12\%$, similar to the range reported by Hoffman and associates.¹⁸ The intraoperative changes also showed a similar pattern.¹⁸ Sco_2 increased during cooling, was well maintained during selective cerebral perfusion, and decreased after rewarming and separation from bypass to be lower than preoperative baseline values, at an average of $54\% \pm 6\%$. There was a further decrease in Sco_2 in the first 8 hours after arrival in the ICU. Despite the subsequent increase, at 72 hours Sco_2 was still significantly lower than preoperative baseline levels.

This study shows that the vulnerable brain is dependent on unstable hemodynamics and oxygen transport seen in the early postoperative period after the Norwood procedure. Do_2 is characteristically low and highly variable. Qs and Do_2 are most depressed during the first 12 to 24 hours; at the

same time, Vo_2 is high, further compounding the imbalance of oxygen transport.^{19,20} Thus the first 12 to 24 hours represents a critical period for not only cardiovascular but also neurologic morbidity. Low Sco_2 was associated with depressed hemodynamics and impaired balance of oxygen transport, as seen in the low arterial blood pressure, Sao_2 , PaO_2 , Qp , Qs , and Do_2 and a high Vo_2 and ERO_2 . Thereafter, Sco_2 improved with the gradual recovery in hemodynamics and oxygen transport.

Sco_2 showed wide interindividual and intraindividual variations throughout the study period (27%–79%). The frequency of a critically low level ($<48\%$) was substantial, representing about 28% of all the measurements. Correlation analysis revealed that the changes in Sco_2 were influenced by the different elements of systemic hemodynamics and oxygen transport measurements to different degrees. The close and positive correlation between Sco_2 and Sao_2 may be expected because of the intrinsic arterial contribution to the NIRS signals. An arterial contribution of $16\% \pm 21\%$ to the NIRS signals has been reported by Watzman and associates²⁹ in a group of children with congenital heart disease of varied arterial oxygen saturations. The explanation for the close positive correlation with PaO_2 may be less clear-cut. Arterial hypoxemia is known to increase cerebral blood flow when PaO_2 is reduced to less than 30 to 50 mm Hg in models of acute hypoxemia.³⁰ This regulation may be impaired in subjects exposed to chronic hypoxemia³¹ and further compounded by anesthesia and hypothermic CPB. This may be the case in our patient population. Although speculative, with the loss of such compensation mechanism, a decrease in PaO_2 may lead to a direct decrease in cerebral Do_2 . Arterial oxygenation has little impact on Qp and Qp/Qs and little contribution to systemic Do_2 .²⁰ It does, however, appear to have significant impact on cerebral Do_2 . Therefore, limiting arterial oxygenation as a means of favorably balancing the parallel circulations may be suboptimal, but may have an unnecessary detrimental impact on the brain. Indeed, the judicious use of inspired oxygen may be beneficial to cerebral oxygenation and metabolism without compromising systemic circulation. Sco_2 was positively correlated with hemoglobin in these neonates. A positive correlation has been found between Sco_2 and hemoglobin during mild-to-moderate hemodilution^{32,33} and is further supported in our data in subjects with relatively high levels of hemoglobin.

The intercorrelations of Sco_2 , systemic arterial pressure, SVR, and Qs are also important to note for these neonates. Sco_2 was significantly and positively correlated with systolic, diastolic, and mean arterial pressures. This may indicate impaired cerebrovascular autoregulation or a pressure-passive cerebral circulation after CPB.^{34,35} The low diastolic pressure in the presence of a Blalock–Taussig shunt may further render the brain vulnerable to hypoper-

fusion or hypoxic insult. Loss of cerebrovascular autoregulation and low diastolic arterial pressure have previously been shown to be risk factors for the occurrence of severe periventricular leukomalacia in premature infants³⁴ and in neonates after cardiac surgery.¹⁶ Interestingly, the close and positive interrelationships between ScO_2 and arterial pressure and, in turn, between arterial pressure and SVR did not necessarily lead to positive correlation between ScO_2 and SVR. In fact, ScO_2 was negatively and significantly correlated with SVR. This is largely due to the negative correlation between SVR and Qs and Do_2 ; Qs and Do_2 were significantly and positively correlated with ScO_2 .

It is our routine management of these neonates to use phenoxylbenzamine and milrinone to sustain a relatively low SVR and to maintain an adequate Qs and Do_2 .^{25,36} The current study shows that this approach may also be beneficial to improve cerebral oxygenation. Furthermore, phenoxylbenzamine can cross the blood–brain barrier and may have a direct and important effect on reducing cerebral vascular resistance.³⁷ Phenoxylbenzamine may also contribute to maintaining cerebral blood flow during hypotension induced by bleeding³⁸ and enhance cerebrovascular response to carbon dioxide.³⁹ These properties of phenoxylbenzamine are appealing in the care of neonates after the Norwood operation, in whom the goal is to optimize both systemic and cerebral oxygen transport. Further studies are necessary to quantify the potential effect of redistribution of blood flow between cerebral and systemic vascular beds caused by this and other medications.

The lack of correlation between ScO_2 and Vo_2 is likely due to the deep sedation used to minimize cerebral Vo_2 . Nonetheless, the improvement in ScO_2 was most pronounced when Vo_2 was most rapidly decreased. As we have demonstrated, Vo_2 is the most important contributor to the improvement in the balance of oxygen transport during the early hours after the Norwood procedure.²² The close and negative correlation between ScO_2 and ERo_2 indicates the important influence of the balance of systemic oxygen transport on cerebral oxygenation during the early postoperative period after the Norwood procedure. Strategies to limit Vo_2 may therefore improve overall oxygen balance and may be particularly relevant to neonates after the Norwood procedure, in whom Do_2 is tenuous.

Of note, whereas the low ScO_2 during the first 24 hours was associated with depressed systemic hemodynamics and impaired balance of oxygen transport, the influence of the systemic hemodynamics and oxygen transport variables on ScO_2 was of equal significance between the period of the first 24 hours and the following 48 hours. This may indicate that cerebral oxygen transport is vulnerable to systemic hemodynamic and oxygen transport fluctuations during the early days after the Norwood procedure.

Limitations

The superior vena cava was used to measure systemic venous saturation for the calculations of Qs and Do_2 . This measure does not account for potential differences in the inferior vena cava saturation.⁴⁰ Conversely, it could be argued that by sampling upper body venous saturation, we have a more representative measurement, incorporating cerebral blood flow.

NIRS was used to estimate cerebral oxygenation in our study. As mentioned earlier, NIRS measures oxygen saturation in the mixture of arteries, capillaries, and veins in a small part of underlining cerebral tissue and thus may not precisely reflect overall balance of cerebral oxygen transport. The value of the critically low ScO_2 was derived from subjects with biventricular circulation^{26–28} and may not be generalizable to subjects with single ventricle and parallel circulations. Further assessments of cerebral oxygen and lactate extractions with a jugular bulb venous probe may be more precise to reflect cerebral oxygen transport. This, in combination with electroencephalography and cerebral magnetic resonance imaging, will provide further information about the influence of postoperative hemodynamics and oxygen transport on cerebral oxygen transport, ischemic injuries, and functional outcomes in this high-risk group of neonates.

Conclusions

ScO_2 decreases significantly in neonates during the early postoperative period after the Norwood procedure. A critically low level of ScO_2 occurs frequently and is significantly influenced by the systemic hemodynamic instability and the imbalance of systemic oxygen transport. Interventions to optimize hemodynamic stability and to achieve an adequate balance of oxygen transport, including maintaining a low SVR and adequate Qs and Do_2 , a relatively high hemoglobin, and in addition, judicious use of high inspired oxygen, may provide further opportunities to reduce the risk of cerebral ischemic injury and improve neurodevelopmental outcomes. Future studies correlating systemic hemodynamics and oxygen transport and cerebral oxygen transport to functional neurologic outcome may yield important insights of neurologic injury.

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TABLE E1. Clinical data for the 16 neonates

Patient	Age (d)	Weight (kg)	BSA (m ²)	CPB (min)	ACC (min)	Circulatory arrest (min)	Cerebral perfusion (min)	Diagnosis
1	4	3.7	0.25	151	100	35	53	HLHS, AS, MS
2	16	3.5	0.24	133	39	34	0	HLHS, AS, MS, endocardial fibroelastosis of LV
3	7	4.2	0.27	122	62	3	60	HLHS, AS, MS
4	12	3.5	0.23	165	75	13	59	DILV, TGA
5	6	3.5	0.23	172	82	9	70	HLHS, AA, MA
6	7	4.0	0.25	167	64	17	44	HLHS, AS, MS
7	6	2.9	0.20	142	62	1	62	HLHS, AS, MS
8	9	3.6	0.24	109	50	4	44	HLHS, AS, MS
9	7	2.8	0.19	66	59	17	20	HLHS, AS, MS
10	5	2.5	0.18	170	126	46	60	HLHS, AS, MS
11	4	4.2	0.27	124	99	44	49	HLHS, AA, MA TAPVC
12	5	3.9	0.26	98	50	12	37	HLHS, AA, MA
13	4	3.1	0.21	134	67	8	58	HLHS, AA, MA
14	7	3.2	0.21	164	66	9	54	TA, TGA, hypoplastic aortic arch
15	10	3.4	0.24	100	47	4	4	HLHS, AA, MS
16	4	3.6	0.23	143	68	6	60	HLHS, AA, MA

AA, Aortic atresia; AS, aortic stenosis; ACC, aortic crossclamp; BSA, body surface area; CPB, cardiopulmonary bypass; DILV, double-inlet left ventricle; HLHS, hypoplastic left heart syndrome; LV, left ventricle; MA, mitral atresia; MS, mitral stenosis; TAPVC, total anomalous pulmonary venous connection; TGA, transposition of great arteries; TA, tricuspid atresia.

TABLE E2. Statistical analysis results of the changes of ScO_2 , systemic hemodynamics, and oxygen transport in the 16 neonates during the 72-hour study period using mixed linear regression method

Variables	Intercept	Parameter estimate	P values
ScO_2 (%)*	50	Time 0.35 Time ² - 0.004	<.0001 <.0001
SAP (mm Hg)†	54	3.4	<.0001
DAP (mm Hg)	33	0.03	.004
MAP (mm Hg)†	40	1.6	<.0001
SVR (Wood unit · m ²)*	21	Time -0.23 Time ² 0.003	<.0001 .0001
Hb (g/dL)	14.5	-0.009	.001
SaO_2 (%)†	69	2.0	<.0001
PaO_2 (mm Hg)†	33.5	2.5	<.0001
Q_p (L · min ⁻¹ · m ⁻²)	2.1	0.007	<.0001
Q_s (L · min ⁻¹ · m ⁻²)*	1.9	Time 0.03 Time ² - 0.0004	<.0001 .0001
Do_2 (mL · min ⁻¹ · m ⁻²)*	262	Time 5.00 Time ² - 0.06	<.0001 <.0001
Vo_2 (mL · min ⁻¹ · m ⁻²)†	96	-2.8	.0005
ER_{O_2} †	0.38	-0.03	<.0001

DAP, Diastolic arterial pressure; Do_2 , systemic oxygen delivery; ER_{O_2} , oxygen extraction ratio; Hb, hemoglobin; MAP, mean arterial pressure; PaO_2 , arterial oxygen tension; Q_p , pulmonary blood flow; Q_s , systemic blood flow; SaO_2 , arterial oxygen saturation; SAP, systolic arterial pressure; ScO_2 , cerebral oxygen saturation; SVR, systemic vascular resistance; Vo_2 , systemic oxygen consumption. *After polynomial transformation, with time indicating the coefficient of the early trend, and time² indicating the later trend. †Data were entered after logarithmic transformation.

TABLE E3. Statistical analysis results of the correlations of ScO_2 as the dependent variable with the systemic hemodynamics and oxygen transport as the independent variables in the 16 neonates during the first 72 hours after the Norwood procedure using mixed linear regression method

Independent variables	Intercept	Parameter estimate	<i>P</i> values
SAP (mm Hg)	34.9	0.31	<.0001
DAP (mm Hg)	46.3	0.26	.0003
MAP (mm Hg)	33.8	0.48	<.0001
SVR (Wood unit $\cdot$ m ²)	57.0	−0.15	.003
Hb (g/dL)	46.2	0.64	.02
SaO ₂ (%)	24.8	0.41	<.0001
PaO ₂ (mm Hg)	26.9	0.69	<.0001
Qp (L $\cdot$ min ^{−1} $\cdot$ m ^{−2})	51.0	1.8	.001
Qs (L $\cdot$ min ^{−1} $\cdot$ m ^{−2})	50.1	2.1	<.0001
DO ₂ (mL $\cdot$ min ^{−1} $\cdot$ m ^{−2})	47.8	0.023	<.0001
VO ₂ (mL $\cdot$ min ^{−1} $\cdot$ m ^{−2})	58.1	−0.03	.13
ERo ₂	64.4	−31.0	<.0001

For abbreviations see [Table 2](#).