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Assessing the brain using near-infrared spectroscopy during postoperative ventricular circulatory support

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Due to many innovative techniques and technologies, the overall rate of survival for infants undergoing surgical repair of congenital cardiac malformations is excellent. Despite these excellent outcomes, neonates with hypoplasia of the left heart represent a very unique population, and pose difficult challenges for the entire team involved in care. Despite some centers reporting outstanding outcomes, overall rate of survival rate is reported at only 53 percent,[1] and survivors often show neurodevelopmental deficits. Many attempts have been made to identify predictors of neurologic outcomes, with heavy concentration around the pre- and peri-operative periods. Little attention has been paid, however, to assessing how attempts at balancing the systemic and pulmonary circulation affect neurodevelopmental outcomes. In the past, we have reported excellent rates of survival with use of routine postoperative circulatory support to augment cardiac output.[2,3] This strategy, nonetheless, is still widely debated. It seems plausible that, by augmenting cardiac output in the immediate postoperative period, cerebral perfusion and oxygenation can be optimized, thereby improving neurologic outcomes. In this review, we describe our experience to date in assessing neurological outcomes, and discuss whether outcomes are associated with cerebral saturation and extraction of oxygen during the period of postoperative circulatory assist.

There have been many strategies employed in attempts at reducing neurological injury over the past several years. Among these are the rate and duration of cooling and re-warming, the use of alpha-stat as opposed to pH-stat strategies for perfusion, reducing haemodilution and optimizing the haematocrit, pharmacologic management, and postoperative circulatory support. It is apparent, nonetheless, that as yet we have failed to meet the challenge, as the neurological outcomes are still often impaired.[4–6] Direct monitoring of the delicate balance between supply and consumption of cerebral oxygen may be of great clinical significance. There are three monitors or measures of cerebral oxygenation currently in practice today:

- saturation of oxygen at the jugular venous bulb
- oxygen tension in the cerebral tissues
- trans-cranial cerebral oximetry.[7]

The saturation measured at the jugular venous bulb demonstrates the relationship between global cerebral supply of and demand for oxygen. This method, therefore, may fail to detect cerebral hypoxia.[8,9] Monitors of cerebral tension of oxygen measure directly the supply and demand of oxygen in the brain, a miniaturized detector being placed directly over or into the cerebral parenchyma. The third method of assessing this balance is by transcranial cerebral oximeter. This provides continuous, noninvasive, and organ-specific measures of the availability of oxygen. Because of its availability in the United States of America, its ease of use, and its noninvasive ability to estimate regional saturations of oxyhaemoglobin in the tissues, we have chosen to use the Somanetics INVOS 5100B (Troy, Michigan) device to aid in our study.

The device predominantly measures the saturation of oxygen in the capillaries, and does not discriminate between venous and arterial blood. It does not need, therefore, to rely on the flow of blood to make a measurement. In addition, because the ratio of venous to arterial blood in the brain is three to

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one,[10,11] the measurement is primarily venous. The device uses near-infrared spectroscopy, and therefore differentiates between oxygenated and deoxygenated haemoglobin based on their specific characteristics of absorption of light. There are few biological substances that can absorb near-infrared. Haemoglobin, and cytochrome aa,[3] are the only chromophores that show a detectable change in near-infrared absorption in response to hypoxia or ischaemia. Because measurement is confined to only a small region of the frontal cortex, however, it is not able to measure focal events in areas further away from the sensor. And, because it measures the saturations of oxygen in the blood capillaries, the results obtained may not correlate with global oxygenation, especially during arteriovenous shunting.

It is our belief that augmenting postoperative cardiac output by routine use of mechanical circulatory assist for patients undergoing the initial stage of palliation for hypoplastic left heart syndrome can be a useful strategy to improve overall hospital survival, as well as neurological outcome. In an earlier study, we reported an overall hospital survival rate of 92 percent in 13 patients when employing this strategy.[12] In addition, at the time of the report, 7 of the 12 survivors had undergone the Glenn procedure, and all 7 tested normal for cognitive and motor function and development. As a result, we decided to expand on this theme even further to try and address some very specific questions. A multi-institutional study was undertaken, collaborating with an institution that does not routinely use ventricular assist in the postoperative period. The results reported below, however, are exclusively those obtained to date from our own institution.

Methods and materials

We have studied 8 consecutive patients undergoing either the first stage of palliation for hypoplastic left heart syndrome, or the Damus-Kaye-Stansel reconstruction of the aortic arch with augmentation for variations of hypoplastic heart syndrome, at Doernbecher Children's Hospital at the Oregon Health & Sciences University, Portland, Oregon. We report here only on the first 5 patients studied thus far. Institutional Review Board approval and parental consent were obtained for all patients. All patients were cooled on cardiopulmonary bypass to 18°C for a minimum of 20 to 30 minutes. Cardiopulmonary bypass was managed using pH stat cooling, switching to alpha- stat cooling just prior to circulatory arrest and for the duration of the procedure. Our target haematocrit was 30 percent during the periods of cooling and arrest, increasing to 35 percent during re-warming. We employed bypass flows of 150 to 200 milliliters per kilogram per minute, using intermittent cerebral reperfusion through the brachiocephalic arterial shunt every 20 minutes at 40 to 50 milliliters per kilogram per minute for 2 minutes during reconstruction of the aorta and the neoaortic arch. All patients received bolus infusions of aprotinin at 1.7×10^6 kilointernational units per meter squared, and a similar dose in the extracorporeal circuit prime, followed by a continuous infusion of 4×10^5 kilounits per meter squared throughout the procedure,[13] and intravenous decadron at 2 milligrams per kilogram at 8 hours, and again at 2 hours, prior to surgery. All patients were placed on infusions of milrinone at 0.5 micrograms per kilogram per minute, and dopamine at 5 micrograms per kilogram per minute prior to separation from bypass, continuing these doses into the postoperative period. Once separated from cardiopulmonary bypass, all patients underwent a period of modified ultrafiltration. Protamine sulfate was administered to achieve full heparin reversal. Once haemostasis was achieved, atrial and neoaortic cannulas were then attached to a roller ventricular assist device, and the rate of flow was slowly increased to 150 to 200 milliliters per kilogram per minute. Sternums were left open, covered with Esmark (Allegiance Health Corporation, McGraw Park, IL), and the patients were transferred to the pediatric intensive care unit. Once haemostasis was achieved, usually within 1 to 2 hours, an infusion of heparin was started. Activated clotting times were maintained at 160 to 180 seconds for the first 24 hours, and increased to 180 to 200 seconds thereafter. All patients remained with their systemic-to-pulmonary shunt open whilst undergoing ventricular assistance and ventilation was maintained to achieve an arterial tension of oxygen between 30 and 45 millimetres of mercury, and partial pressures of carbon dioxide between 35 and 45 millimetres of mercury. Continuous mixed venous saturations were measured from the venous drainage of the ventricular assist device with an in-line saturation monitor (Terumo CDI500, Ann Arbor, Michigan), and maintained between 60 and 80 percent saturation. Once systemic perfusion was deemed adequate as measured by physical examination, with adequate output of urine, and normalized levels of lactate of less than 2 millimoles per litre, the rate of flow through the pump was gradually diminished and the patient removed from the assist device. All infants underwent routine pre-operative assessment, which included baseline electroencephalogram, head ultrasound, and neurological examination. Infants will undergo neurodevelopmental evaluations at 6 months, 1 year, and 2 years. Continuous monitoring of cerebral saturations of oxygen was performed during surgery, and for the first 48 hours of postoperative ventricular

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assistance. Blood was drawn for proteomic analysis preoperatively, after initiation of, and on the first postoperative day of, ventricular assistance. Systemic mixed venous oxygen saturations, patient mean arterial pressures, and cardiopulmonary bypass flows were captured at one-minute intervals while on bypass with a computerized data management system (JOCAP® XL; Jostra Marquet, Hirllingen, Germany). These same values were collected at hourly intervals upon arrival on the intensive care unit. The near-infrared probe was placed on the right frontal cortex immediately after entry into the operating room, and was monitored by a cerebral saturation monitor (Somanetics INVOS 5100B, Troy, Michigan). These values were trended at one-minute intervals throughout the entire period of study. Values of lactate were obtained at normal intervals as dictated by the protocol and/or at clinically appropriate times (Radiometer ABL, Copenhagen, Denmark). All data are presented as mean plus or minus the standard deviation, along with the range.

All members of the team were blinded to the values for regional cerebral saturation, and therefore no interventions were made based on these values. All postoperative care was performed following our usual protocol. The specific questions we sought to address were:

- Is survival of infants supported with postoperative mechanical circulatory different than those who are not supported by assist devices?
- Are neurodevelopmental outcomes improved, and can outcomes be associated with cerebral oxygen saturation and extraction during mechanical ventricular assist?
- Are there specific gene or protein markers of survival of neurological outcome?

Results

The characteristics of all 5 patients are summarized in Table 1. Regional cerebral saturation was markedly variable between patients during the pre cardiopulmonary bypass period, with a mean of 62.2 percent plus or minus 6.7 percent. Each patient established his or her own control value. We used this value to establish the baseline for cerebral saturation, including the time frame of pre-induction just up until the onset of cardiopulmonary bypass. During cooling on bypass, the cerebral saturations increased as expected, and peaked at 80.2 percent plus or minus 16.5 percent. During deep hypothermic circulatory arrest, the cerebral saturations fell to 66.2 percent plus or minus 15.6 percent, but remained above baseline value. Cerebral saturations peaked at 80.4 percent plus or minus 18.5 percent during each intermittent period of reperfusion while under circulatory arrest. Upon re-warming on cardiopulmonary bypass, regional cerebral saturations fell slightly from the time frames obtained during cooling and intermittent reperfusion to 78.8 percent plus or minus 8.2 percent, but again remained above baseline values. During the period subsequent to bypass, which included the time from modified ultrafiltration up to the initiation of ventricular circulatory support, the cerebral saturations dropped most significantly to 42.8 percent plus or minus 9.8 percent. They did not recover to near baseline values of 57.2 percent plus or minus 11 percent, and 60.6 percent plus or minus 11.9 percent, respectively, until after 24 and 48 hours of ventricular support (Figs 1 and 2). The mean arterial pressures were targeted to be maintained at greater than 30 millimeters of mercury pressure, and the haematocrit maintained at 40 percent at all times while on ventricular support. Flows through the pump were increased as necessary

Table 1. Demographics of our 5 patients.

Age in days	17 ± 18.9
Weight in kilograms	3.2 ± 1.2
Body surface area in meters squared	0.21 ± 0.1
Duration of cardiopulmonary bypass in minutes	155 ± 9.5
Duration of cardiac arrest in minutes	57.6 ± 8.3
Reperfusion events	3 ± 1
Time to ventricular assistance in minutes	22.6 ± 6.9

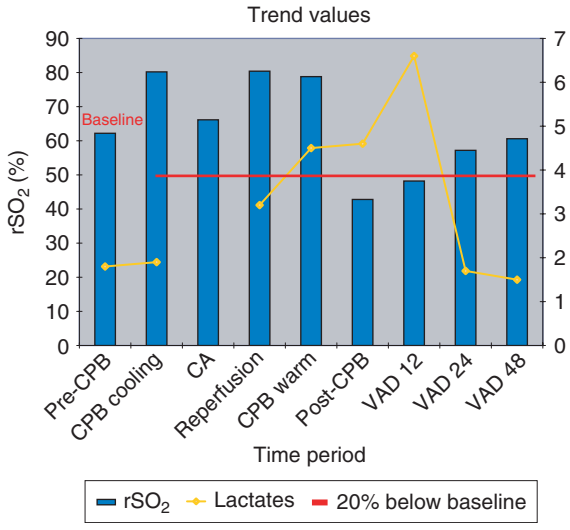


Figure 1.
Regional cerebral saturations (rSO_2) and values showing the trend for lactate divided into 9 major periods of time. Data shown is the mean for each period of time. rSO_2: regional cerebral saturation; CPB: cardiopulmonary bypass; CA: circulatory arrest; VAD 12: ventricular assist device at 12 hours; VAD 24: ventricular assist device at 24 hours; VAD 48: ventricular assist device at 48 hours.

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in the event of increasing levels of lactate during the postoperative period. These levels returned to less than 2 millimoles per liter within 24 hours of ventricular support. Despite maintenance of adequate mixed venous saturations of oxygen, mean arterial pressure, flows through the pump, and decreasing levels of lactate, cerebral saturations remained below 20 percent of baseline until after 24 hours of ventricular support, and did not increase to just below baseline until after 48 hours of ventricular support. A summary of these findings is shown in Table 2.

Discussion

The risk of regional variations in cerebral saturation was most significant immediately following separation from cardiopulmonary bypass, and slowly started to improve over the next 24 to 48 hours, returning to values just below baseline after 48 hours of ventricular support. This desaturation occurred despite maintaining haematocrits of 40 percent, mean arterial pressures of greater than 50 millimeters of mercury pressure, and mixed venous saturations greater than 72 percent. Even as the levels of lactate began rapidly to normalize, cerebral saturations were slower to return to baseline. Low cerebral saturations can indicate a serious imbalance, but not necessarily an injury. The relationship between the absolute lowest allowable cerebral saturation values and outcomes in neonates is complex and not known.[13,14] Very likely it is dependent upon variables such as the duration of desaturation, temperature,[15] and/or the presence of neuroprotective drugs.[16] The ability and ease of augmenting cardiac output, and providing haemodynamic stability by mechanical circulatory assistance as shown above, should thereby also presumably be expected to favour increases in cerebral saturation and delivery of oxygen. These results may show that regional cerebral oxygenation is still vulnerable despite the postoperative use of mechanical circulatory assistance, and that cerebral desaturation may not be a result of decreased systemic delivery of oxygen. Several authors have show cerebral vascular resistance to be increased after deep hypothermic circulatory arrest,[17,18] as well as cerebral autoregulation to be impaired.[19] During cooling, there is a linear decrease in flow and an exponential decrease in metabolism. As cooling occurs, the cerebral saturation rises, reflecting the reduced metabolic need. Although we report regional cerebral saturation of 80.4 percent during reperfusions at a pump flow rate of 45 millimeters per kilogram per minute, extremely high values may signify luxuriant flow of blood through the brain, and may also prove to be deleterious to neurological outcome.

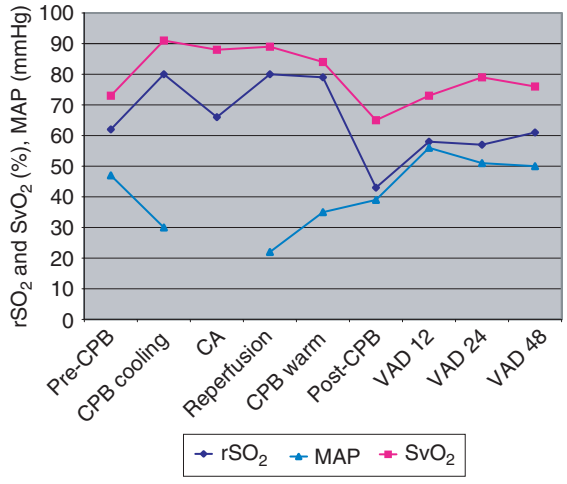


Figure 2.
Regional cerebral saturations, mixed venous saturations, and mean arterial pressure values divided into 9 major periods of time. Data shown is the mean for each period. SvO_2: systemic mixed venous oxygen saturation; MAP: mean arterial pressure. Other abbreviations as for Figure 1.

Our results are only preliminary, and all results were not available at the time of writing. The questions still needing fully to be addressed are:

- Is survival different in infants receiving ventricular support when compared to those not on support?

Table 2. Hemodynamic data at various intervals.

Time period	Cerebral saturation	Mixed venous saturation	Mean arterial pressure	Bypass flow	Lactate
Pre-bypass	62.2 ± 6.7 (51–67)	73 ± 16.1 (51–88)	47.4 ± 9.3		1.98 ± 0.9 (.7–2.5)
Cooling in bypass	80.2 ± 16.5 (55–94)	91.4 ± 4.8 (86–97)	31.4 ± 6.7	144.8 ± 17.5	1.88 ± .87 (.7–2.7)
Circulatory arrest	66.2 ± 15.6 (43–82)				
Intermittent reperfusion	80.4 ± 18.5 (48–95)	89.1 ± 6.3 (78–93.5)	23.3 ± 8.1	47.4 ± 5.8	3.18 ± 1.7 (1.5–5.4)
Rewarming in bypass	78.8 ± 8.2 (66–87)	83.6 ± 3.3 (79–88)	36 ± 6.7	136.8 ± 19.5	4.5 ± 1.6 (2.5–4.9)
After bypass	42.8 ± 9.8 (34–50)	65 ± 8.5 (57–78)	39.2 ± 11.1		4.6 ± .99 (3.7–5.9)
12 hours of assistance	48.2 ± 9.8 (37–59)	72.3 ± 7 (63–81)	56.2 ± 5.4	159.8 ± 39.6	6.5 ± 3.0 (3.1–10.7)
24 hours of assistance	57.2 ± 11 (47–75)	76.4 ± 4.4 (67–91)	51.2 ± 5.1	165.2 ± 32.9	1.68 ± 1.75 (1.1–3)
48 hours of assistance	60.6 ± 11.9 (48–72)	76.4 ± 4.4 (72–82)	50 ± 8.2	148.75 ± 38.2	1.42 ± .61 (.78–2.4)

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- Are there specific genes are protein markers of survival or neurological outcome
- Can improved neurological and developmental outcomes be associated with cerebral saturations of oxygen and its extraction during mechanical circulatory support?

It is important to emphasis that, during this study, no interventions were taken based on the values of cerebral saturation of oxygen, as these values were blinded to all members of the team. Cerebral oximetry may prove to be a useful adjunct in assessing delivery and extraction of oxygen, and monitoring these values may reveal additional opportunities to reduce the risk of cerebral ischaemia. We intend to continue to collect and evaluate neurodevelopmental data over the long term using this strategy. Perhaps routine use of postoperative mechanical circulatory assistance, in concert with suitable pharmacologic support and optimal strategies for ventilation, may prove to be useful in improving the outcomes in terms of quality in this very specific population of patients.

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