

ORIGINAL ARTICLE

Neonatal cerebral oximetry monitoring during ECMO cannulation

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Objective: Neonates were monitored with a cerebral oximeter before, during, and after cannulation for ECMO to determine the direct effects of ligation of the right internal jugular vein and right carotid artery on cerebral oxygenation.

Study Design: After obtaining informed consent, we used the FORE-SIGHT Cerebral Oximeter (CAS Medical Systems, Branford, CT, USA) to monitor neonates undergoing surgical preparation for veno-arterial (VA) or veno-venous (VV) extracorporeal membrane oxygenation (ECMO).

Result: A total of 17 subjects were monitored pre-ECMO for at least 48 h after cannulation. Of the 17 subjects, 12 experienced low cerebral tissue oxygen saturation (SctO₂) <60% during pre-ECMO surgery, with most exhibiting the lowest SctO₂ values between cannulation to the onset of ECMO. Two subjects received cardiopulmonary resuscitation (CPR) during surgery and experienced very low SctO₂ (5 and 36%). Pulse oximetry was found to be unreliable during CPR because of diminished pulsatile flow. SctO₂ increased above 60% after the onset of ECMO for all subjects and remained stable.

Conclusion: Neonates are vulnerable to SctO₂ during the pre-ECMO surgical period.

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Introduction

Several studies in the past showed that cerebral oxygenation can be compromised during surgery to prepare the neonatal patient for extracorporeal membrane oxygenation (ECMO) therapy from

noninvasive near infrared spectroscopy (NIRS) techniques, now commonly called cerebral oximetry.^{1–4} During this time, the carotid artery and/or the internal jugular vein are ligated to allow for ECMO support, but the procedure may temporarily impair cerebral perfusion. However, the data collected from the cerebral oximetry monitors used in these past studies were not validated and/or provided only trending cerebral oxygenation information.

The purpose of this study was to monitor physiologic changes in cerebral perfusion using the FORE-SIGHT cerebral oximeter (CAS Medical Systems, Branford, CT) a recently validated and FDA approved monitor,⁵ before, during and after cannulation for ECMO. In doing this, we hoped to identify any transient decrease in cerebral saturations with the ligation of the carotid artery and/or the internal jugular vein. As the number of subjects studied in the earlier studies^{1–4} was small, our data will further verify or refute the past findings. In addition, we hoped to show improvement in cerebral oxygenation with the commencement of ECMO.

Extracorporeal membrane oxygenation background

Extracorporeal membrane oxygenation involves using a membrane oxygenator attached to a heart-lung bypass machine to provide cardiopulmonary support to patients who have already failed conventional medical therapies. This type of support is offered in the neonatal intensive care unit to the newborns that have a reversible cause for pulmonary and/or cardiac failure. There are two types of ECMO bypass, veno-arterial (VA) and veno-venous (VV). In VA bypass, deoxygenated blood is removed through a cannula placed in the right internal jugular vein and oxygenated blood is returned to the aortic arch through a cannula placed in the carotid artery. Use of this technique allows the ECMO pump to take over approximately 60% of the function of both the heart and the lungs. If a patient has isolated pulmonary disease and does not require additional cardiac support, he/she would be a candidate for VV-ECMO. In this case, a double lumen catheter is placed in the right atrium through the right internal jugular vein and blood is both removed and replaced in the right atrium. This allows the ECMO membrane oxygenator to provide the needed pulmonary support without sacrificing the carotid artery. In addition, VV-ECMO maintains the normal pulsatility to the systemic flow.

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In addition to the double lumen catheter placed in the internal jugular vein toward the heart, patients on VV-ECMO have a second catheter placed in a cephalad direction in the jugular vein. This catheter augments cerebral venous outflow and allows access to blood draining from the cerebral circulation to measure cerebral oxygen saturations. It was through the use of this catheter that Rais-Bahrani *et al.*⁵ were able to validate the FORE-SIGHT cerebral oximeter.

Cerebral oximetry background

The FORE-SIGHT cerebral oximeter measures cerebral tissue oxygen saturation (SctO₂) as an absolute value, which does not require a baseline measurement like trending cerebral oximeters.⁶ Because the blood in the cerebral microvasculature is a mix of arterioles, venuoles and capillaries, the FORE-SIGHT monitor uses an algorithm that approximates the contribution of venous blood to arterial blood of 70 to 30% ratio.^{5,7,8} This leads SctO₂ measurements to be less than pulse oximetry measurements (pulse oximeter arterial oxygen saturation (SpO₂)), less than arterial oxygen saturation (SaO₂), but higher than brain venous oxygen saturation SjvO₂ (cephalad catheter internal jugular oxygen saturation; i.e., blood measured from a cephalad catheter of a VV-ECMO patient) by approximately 10%.^{5,6}

Besides the obvious benefit of noninvasive, direct measurement of cerebral oxygenation, cerebral oximetry also offers the benefit of working even in cases of nonpulsatile flow. Pulse oximetry requires pulsatile flow to determine oxygen saturation, and therefore does not work in instances where this is compromised, such as in the case of circulatory arrest or cardiopulmonary bypass. The cerebral oximeter can continue to be used in these cases and will display a continuous measurement of cerebral tissue oxygen saturation.

Methods

This study was approved by the Institutional Review Board at Children's National Medical Center. After obtaining parental informed consent, patients that were being placed on either VA or VV-ECMO were enrolled in the study. Before right carotid/internal jugular vein cannulation, the FORE-SIGHT Cerebral Oximeter neonatal size sensor (light source to detector separation of 25 mm) was affixed to the neonate's right forehead using a custom-made adhesive pad and was further secured with Hypafix tape (BSN Medical GmbH & Co. Hamburg, Germany). A laptop computer displayed and stored data every 3 s from the cerebral oximeter along with pulse oximetry SpO₂ data (N395, Tyco/Nellcor, Pleasanton, CA USA). Significant event markers were documented for analysis including the start time of surgery, the time of ligation of the jugular vein, the time of ligation of the carotid artery (if patient was going on VA ECMO), the time that the patient was placed on bypass, 30 and 60 min, and 6 h after the onset of ECMO. The data were then analyzed by multiple category repeated

measures nonparametric testing (Friedman two-way analysis of variance by SPSS software) to determine significant changes in SctO₂ between events.

Low cerebral desaturation is defined by SctO₂ < 60%, which would approximate brain venous or jugular bulb saturation SjvO₂ < 50% based on the estimation that SctO₂ is 10% higher than SjvO₂.⁶ A review of the literature revealed that a SjvO₂ < 44 to 55% exposed the patient to increased risk of complications, with most institutions recommending keeping SjvO₂ > 50%.^{9–16}

Results

Data were successfully collected for 17 ECMO neonatal subjects (13 VA/4 VV) during the surgical period. Demographic information: 7 male/10 female, 7 Caucasian/5 African American/3 Hispanic/2 unspecified, gestation age 38 to 41 weeks, and weight 2.3 to 4.4 kg. Diagnosis included left or right congenital diaphragmatic hernia, primary pulmonary hypertension, sepsis, hypertrophic cardiomyopathy and/or meconium aspiration syndrome.

Figure 1 is a box plot showing the SctO₂ median, 25th/75th percentiles, maximum/minimum range, and outlier data points for the 17 subjects for Pre-ECMO events (Pre-Surgery, Surgery Start, common carotid artery (CCA) Ligation, Internal Jugular Vein (IJV) Ligation, and Pre-ECMO (i.e., 2 min before ECMO onset), and ECMO events (ECMO + 30 min, ECMO + 60 min and ECMO + 6 h). Median SctO₂ data from each event consists of 17 data points except CCA ligation, which consists of 13 data points because CCA ligation is not performed for VV ECMO subjects. The three outlier points are from two subjects (see Figures 4 and 5), who experienced very low SctO₂ values, and needed cardiopulmonary

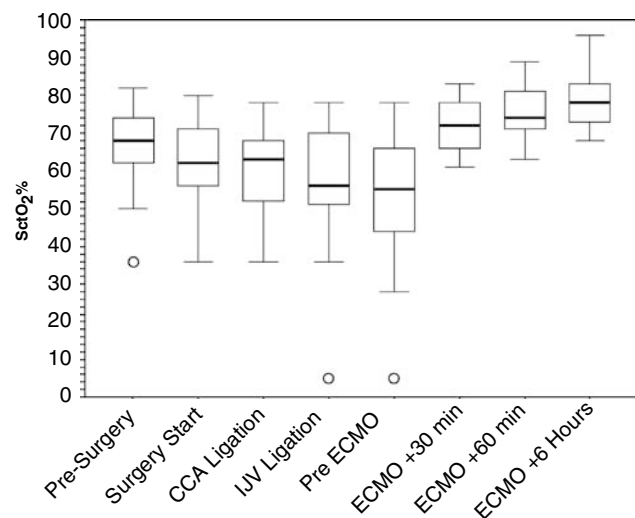


Figure 1 Box plot of cerebral tissue oxygen saturation percentage of SctO₂ (median, 25th and 75th percentile, range and outliers) based on ECMO events for all 17 subjects. ECMO, extracorporeal membrane oxygenation; SctO₂, cerebral tissue oxygen saturation.

resuscitation (CPR) during ECMO surgery. Three observations from the Figure 1 results are (1) increase in intersubject variability of SctO₂ during ECMO surgery; (2) decrease of SctO₂ for most subjects during ECMO surgery, particularly just before ECMO; and (3) increase of SctO₂ gradually for the first few hours of ECMO, with less intersubject variability. The pattern of SctO₂ changes during ECMO surgery for 6 h after ECMO onset is statistically significant ($P < 0.001$) from the Friedman multiple category repeated measures nonparametric test.

This result was supported by comparison of SctO₂ values between pairs of events using the nonparametric Wilcoxon signed-rank test: The decrease of SctO₂ between presurgery and surgery start to Pre-ECMO were statistically significant ($P < 0.001$). The increase of SctO₂ from presurgery, surgery start and Pre-ECMO to ECMO (+30 and +60 min, and +6 h after start) were statistically significant ($P < 0.01$). The increase of SctO₂ from ECMO +30 min to ECMO +60 min and ECMO +6 h were statistically significant ($P < 0.05$).

Table 1 shows the time duration in minutes (mean ± s.d.) that SctO₂ was below 40, 50 and 60%, along with range and the number of subjects experiencing SctO₂ below these thresholds for Pre-ECMO surgery and ECMO for 48 h. It was found that during the period of time between IJV Ligation and pre-ECMO onset, most subjects (14/17) experienced the lowest SctO₂ values. During this apparent vulnerable period, the minimum mean SctO₂ was $49.2 \pm 17.3\%$ (range: 5 to 71%). From Table 1, SctO₂ events are less frequent once the subject is on ECMO. During ECMO, drops of SctO₂ below 60% were transitory, with SctO₂ recovering rapidly.

The pulse oximeter occasionally failed to measure SpO₂ (three subjects) or was not reflective of cerebral desaturations (one subject) during ECMO surgery. The time in minutes when the pulse oximeter was deemed not reliable or not reflective of cerebral oxygenation was 10 to 29 min for the four subjects. The percentage of pulse oximetry measurement of SpO₂ failed while two subjects were undergoing CPR during ECMO surgery likely because of

diminished pulsatile perfusion. Cerebral oximetry measured very low SctO₂ values of 5 and 36% during CPR.

Figures 2–5 show notable recordings of SctO₂ and SpO₂ from different subjects. Figure 2 shows an example of a SctO₂ event that was undetected by pulse oximetry. Here, SctO₂ dropped to 44%, whereas SpO₂ remained near 100% at the onset of ECMO. Figure 3 shows multiple desaturation events during Pre-ECMO surgery, where SctO₂ and SpO₂ track each other. Figure 4 shows a CPR case. Here, at the start of cerebral oximetry monitoring, the subject was being sustained by CPR during pre-ECMO surgery with an SctO₂ of 36%. Pulse oximetry was intermittent during this time, likely because of low pulsatile perfusion to the extremities. Once ECMO was started, SctO₂ increased to 60% and normal pulse oximetry function returned. Figure 5 shows another CPR case where very low

Table 1 Analysis of low cerebral oximetry SctO₂ values recorded during Pre-ECMO surgery and ECMO for 48 h

Parameter	Mean (s.d.)	Range	Observations
<i>Pre-ECMO surgery</i>			
SctO ₂ < 40% (min)	4.5 (9.6)	0–29	4/17 subjects
SctO ₂ < 50% (min)	9.8 (15.5)	0–48	9/17 subjects
SctO ₂ < 60% (min)	27.0 (26.7)	0–78	12/17 subjects
<i>ECMO to 48 h</i>			
SctO ₂ < 40% (min)	0	0	0/17 subjects
SctO ₂ < 50% (min)	0.1 (0.4)	0–1.5	1/17 subjects
SctO ₂ < 60% (min)	2.5 (5.7)	0–21	4/17 subjects

Data are presented as time in minutes when SctO₂ was below 40, 50 and 60%. The number of subjects experiencing low SctO₂ values for these thresholds is indicated in the observations.

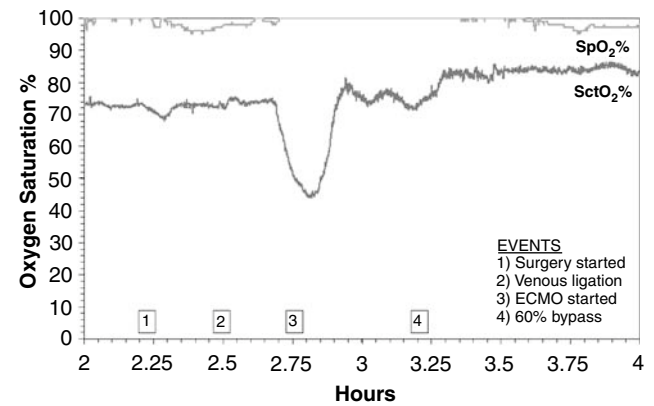


Figure 2 This representative result shows that occasionally pulse oximetry SpO₂ is insensitive to cerebral oxygen desaturation as indicated by SctO₂ for a neonate undergoing surgery for VV-ECMO (note the decrease of SctO₂ before and during the onset of ECMO, a common observation). ECMO, extracorporeal membrane oxygenation; SctO₂, cerebral tissue oxygen saturation; SpO₂, pulse oximeter arterial oxygen saturation.

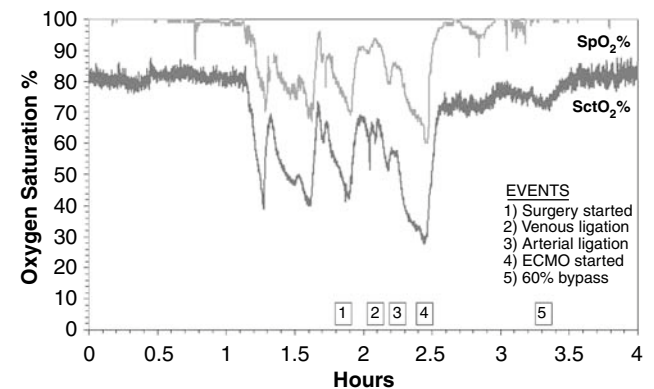


Figure 3 This representative result shows cerebral oximetry SctO₂ closely correlating to pulse oximetry SpO₂ for a neonate undergoing surgery for VA ECMO (note again the lowest SctO₂ values following cannulation to the onset of ECMO). ECMO, extracorporeal membrane oxygenation; SctO₂, cerebral tissue oxygen saturation; SpO₂, pulse oximeter arterial oxygen saturation; VA, veno-arterial.

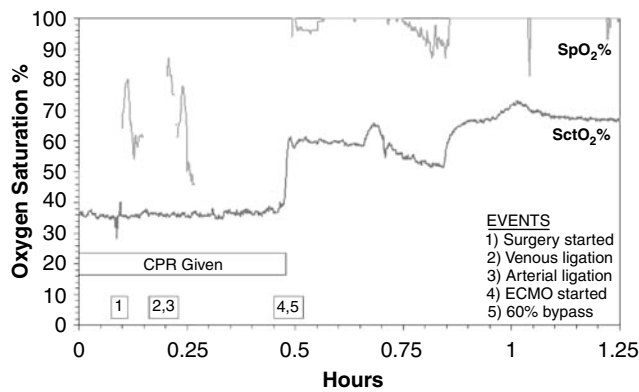


Figure 4 During this case, the neonate was sustained by cardiopulmonary resuscitation during surgery for VA ECMO. This case shows that cerebral oximetry $SctO_2$ is not disturbed by low pulsatile perfusion, as opposed to the intermittent pulse oximetry SpO_2 . $SctO_2$ recovered to 60% when ECMO was started. ECMO, extracorporeal membrane oxygenation; $SctO_2$, cerebral tissue oxygen saturation; SpO_2 , pulse oximeter arterial oxygen saturation; VA, veno-arterial.

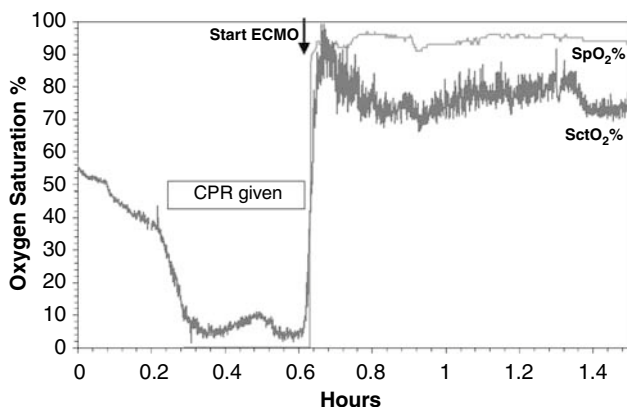


Figure 5 Another case where the neonate was sustained by cardiopulmonary resuscitation during surgery for VV-ECMO. $SctO_2$ dropped very low to 5%, then recovered after ECMO start, exhibiting a hyperemic response before settling to 70 to 80%. Pulse oximetry was nonfunctional until the start of ECMO. ECMO, extracorporeal membrane oxygenation; VA, veno-arterial.

$SctO_2$ values (5%) were recorded. Pulse oximetry did not function during this period. Once ECMO was started, $SctO_2$ increased dramatically to over 90% (hyperemia), then settled to 70 to 80%, and normal pulse oximetry function returned.

Discussion

These results show that neonates undergoing ECMO can be exposed to $SctO_2$ events during pre-ECMO surgery, especially between arterial and jugular venous cannulation to the onset of ECMO. Earlier studies using NIRS to monitor ECMO subjects also observed cerebral oxygenation decreases during ECMO surgery.^{1–4} Ejike *et al.*¹ reported that only the right cerebral hemisphere experienced $SctO_2$ following right carotid cannulation in three subjects using a

bilateral sensor NIRS system. In our study, the cerebral oximetry sensor was placed on the right forehead. We did not use a left forehead sensor. On the other hand, Van Heijst *et al.*⁴ observed bilateral decrease in cerebral oxygenation following right carotid cannulation in 10 subjects. Procedural differences in technique may explain these findings. Both Ejike *et al.*¹ and Van Heijst *et al.*⁴ observed a decrease of cerebral oxygenation primarily due to right carotid cannulation but not right internal jugular vein cannulation.^{3,4} Because carotid and internal jugular cannulation were performed about the same time, we did not distinctly see that $SctO_2$'s were primarily caused by carotid cannulation.

One possible explanation of the observation of decreased cerebral oxygenation following cannulation includes restricted circulatory flow caused by the cannulae. Venous return would be reduced leading to decreased stroke volume and cerebral blood flow. Once the ECMO pump is active, full flow is restored, and cerebral oximetry $SctO_2$ and pulse oximetry SpO_2 increases. If the cannulae do restrict flow, then initiating ECMO as soon as possible after cannulation may prevent possible prolonged $SctO_2$'s.¹

Positioning of the neonate during ECMO surgery is another possibility resulting in reduced cerebral blood flow and oxygen desaturation events. Repositioning the neonate after cannulation to restore cerebral blood flow to maintain $SctO_2 > 60\%$ is a possible solution. Other possibilities causing impaired cerebral oxygenation during ECMO surgery include arterial hypoxia, hypotension, pH and PCO_2 disturbances. All of these perturbations are possible and even common during cannulation surgery.

In some cases, cerebral desaturations may be unavoidable especially for emergency ECMO surgery. These neonates may be undergoing CPR to maintain cerebral perfusion as best as possible. Here, cerebral oximetry can be a tool to determine the effectiveness of CPR, especially when pulse oximetry fails because of the requirement of pulsatile flow to calculate an SpO_2 value. Cerebral oximetry does not need pulsatile flow to determine $SctO_2$; therefore, cerebral oximetry can be used reliably during nonpulsatile flow situations, such as cardiopulmonary bypass, deep hypothermia circulatory arrest, high blood loss/shock, CPR and regional low-flow cerebral perfusion.^{5,6,17–19}

Our results show that $SctO_2$ events occur more frequently before starting ECMO compared to after the onset of ECMO. Although ECMO has its known potential risks, we observed that cerebral oxygenation increases during ECMO, and the frequency of $SctO_2$ events dramatically decreases (assuming normal ECMO pump operation). Once ECMO was established, mean $SctO_2$ increased during the first 6 h of ECMO. With the exception of one CPR subject, we did not observe a large transient increase of $SctO_2$ indicative of hyperemia during the start of ECMO, as opposed to the results of Ejike *et al.*¹ Hyperemia may occur due to changes in ABP, pressor requirements and serum Hb, which are common in this period. Abrupt correction of hypotension and hypoxia cause transient hyperemia in animal models. During ECMO, $SctO_2$ was

consistently above the 60% threshold for all subjects with less variability compared to pre-ECMO. In the past, our institution's goal is to maintain a cephalad $SjvO_2 > 60\%$ for VV-ECMO cases, which would translate to maintaining cerebral oximetry $SctO_2 > 70\%$. For VA-ECMO, no cephalad catheter is used, so maintaining a $SctO_2 > 70\%$ is our only available guideline. Therefore, cerebral oximetry is the only oximeter useful to maintain safe cerebral oxygenation levels for VA-ECMO subjects. Many VA-ECMO circuits use an in-line mixed venous oxygen saturation monitor that can be useful in estimating cerebral oxygenation status. However, these monitors do not directly monitor the brain-like cerebral oximetry.

Although we define $SctO_2 > 60\%$ to be a safe level based on the best available information in the literature on brain/jugular bulb venous oxygen saturation $SjvO_2$, we do not know the safe upper limit of $SctO_2$ during ECMO. It is possible that ECMO pump flow could result in excessive flow to the brain. Other causes of very high $SctO_2$ values ($> 90\%$) include reduced brain metabolism, cerebral vasodilation and/or increased $PaCO_2$. On the other hand, during hypothermia, especially deep hypothermia, $SctO_2$ values commonly are $> 90\%$ because of purposeful reduced brain metabolism before surgeries requiring deep hypothermic cardiac arrest.^{18,19} Similar to high internal jugular vein/jugular bulb oximetry $SjvO_2$ values,²⁰ high $SctO_2$ values during deep hypothermia provide evidence to the clinician that brain metabolism is being suppressed with the advantage of being noninvasive.

In recent years, cerebral oximetry has begun to move from the research lab into clinical settings. However, routine use of the cerebral oximeter has been hampered by concerns of unreliability and inaccuracy. The FORE-SIGHT Cerebral Oximeter has been shown to be both a valid and reliable tool to be used in the clinical setting. However, there is a paucity of information on how to use the monitor in the clinic most effectively. The clinician's ability to interpret this monitor at the bedside is not as straight forward as previous modalities such as the pulse oximeter. With the pulse oximeter, the expected range for a healthy subject is 90 to 100%. When the patient is outside of this, the bedside physician knows how to respond. With the cerebral oximeter, there is a wide range for what is considered to be 'normal' cerebral oxygenation. $SctO_2$ values are expected to be below SaO_2 and above venous oxygen saturations. The expected range for a neonate is between 60 and 90%. However, there is not enough clinical follow-up data to tell us what it means for patients to be outside of this range, and therefore should the bedside physician take action to correct a patient outside this normal range. One of the benefits of this study was to identify a cohort of patients that had a wide range of $SctO_2$ measurements that will be able to be followed up in developmental clinic in the future.

Earlier studies looking at cerebral blood flow in ECMO patients, particularly animal studies, had shown that there was no decrease

in cerebral blood flow during cannulation. However, patients enrolled in this study showed that there was a transient drop in cerebral oxygenation during and postcannulation, particularly if there was a delay between cannulation and the start of bypass flow. The other unexpected finding was the effectiveness of the cerebral oximeter as a useful tool during cardiopulmonary arrest. During this state, there is a loss of pulsatile flow and a stagnation of the blood. Therefore, the measurements of pulse oximetry, cephalad, jugular bulb oximetry and arterial blood gas measurements are all compromised. Because cerebral oximetry relies on direct measurement of tissue saturation, pulsatile flow is not necessary for continued measurement. **It was found in multiple study patients that the $SctO_2$ measurements could be followed to determine the effectiveness of chest compressions during CPR.**

Conclusion

The use of cerebral oximetry to measure $SctO_2$ is a useful, noninvasive, rapid way to measure cerebral oxygenation. This monitor is now being recognized as a useful bedside tool for management of critically ill neonates. In the future, further studies will be needed to assess long-term outcomes for patients with low cerebral saturations.

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