Published in final edited form as:

ASAIO J. 2017 ; 63(5): e52–e59. doi:10.1097/MAT.0000000000000453.

Regional Cerebral Abnormalities Measured by Frequency-Domain Near-Infrared Spectroscopy in Pediatric Patients During Extracorporeal Membrane Oxygenation

FENGHUA TIAN^{*}, CHRISTOPHER JENKS^{†,‡}, DONALD POTTER[‡], DARRYL MILES^{†,‡}, and LAKSHMI RAMAN^{†,‡}

^{*}Department of Bioengineering, University of Texas at Arlington, Arlington, Texas;

[†]Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, Texas;

[‡]Children's Health, Dallas, Texas.

Abstract

Extracorporeal membrane oxygenation (ECMO) is a form of advanced cardiorespiratory support provided to critically ill patients with severe respiratory or cardiovascular failure. While children undergoing ECMO therapy have significant risk for neurological morbidity, currently there is a lack of reliable bedside tool to detect the neurologic events for patients on ECMO. This study assessed the feasibility of frequency-domain near-infrared spectroscopy (NIRS) for detection of intracranial complications during ECMO therapy. The frequency-domain NIRS device measured the absorption coefficient (μ_a) and reduced scattering coefficient (μ_s') at six cranial positions from seven pediatric patients (0–16 years) during ECMO support and five healthy controls (2–14 years). Regional abnormalities in both absorption and scattering were identified among ECMO patients. A main finding in this study is that the abnormalities in scattering appear to be associated with lower-than-normal μ_s' values in regional areas of the brain. Because light scattering originates from the intracellular structures (such as nuclei and mitochondria), a reduction in scattering primarily reflects loss or decreased density of the brain matter. The results from this study indicate a potential to use the frequency-domain NIRS as a safe and complementary technology for detection of intracranial complications during ECMO therapy.

Keywords

extracorporeal membrane oxygenation; frequency-domain near-infrared spectroscopy; intracranial complications; absorption; scattering

Extracorporeal membrane oxygenation (ECMO) is a form of advanced cardiorespiratory support provided to critically ill patients with severe respiratory or cardiovascular failure.¹ Venovenous ECMO (VV-ECMO) bypasses the diseased lungs by draining the deoxygenated blood from and returning the oxygenated blood to the heart. Venovenous

Correspondence: Lakshmi Raman, Department of Pediatrics, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390. Lakshmi.Raman@UTSouthwestern.edu.

Disclosure: The authors have no conflicts of interest to report.

ECMO (VA-ECMO) is used in combined cardiopulmonary disease by draining the deoxygenated blood from the venous side and returning the oxygenated blood to the arterial side. Extracorporeal membrane oxygenation is typically used as a rescue therapy for potentially reversible, life-threatening conditions, such as severe shock states, severe respiratory failure such as acute respiratory distress syndrome (ARDS), postcardiac surgery, and neonates with persistent pulmonary hypertension (PPHN). It is also used as part of cardiopulmonary resuscitation (CPR) when conventional CPR has failed to stabilize the cardiopulmonary system. The use of ECMO support has increased steadily since the early 1990s.² With advancement in the intensive care unit (ICU) and ECMO technologies, the survival rate with ECMO has steadily improved. With the improved survival rate, neurologic complications have become an important cause for morbidity.^{3,4} Intracranial complications are the most common causes of death in ECMO-treated patients and are associated with poor neurodevelopmental outcomes and long-term disabilities in survivors.^{5–8} Pre-ECMO factors, such as hypoxemia, acidosis, and hypotension, and ECMO-related factors such as hemodynamic alterations resulting from the nonpulsatile flow, complications of systemic anticoagulation, and microthrombi from the extracorporeal circuit are potential contributors to brain injury.

Currently there is no reliable bedside tool to detect the neurologic events in patients on ECMO therapy. Head ultrasound has limited utility beyond the neonatal period.⁹ Computed tomography (CT) scan¹⁰ on ECMO and magnetic resonance imaging (MRI) after completion of ECMO require transport of critically ill patients to the radiology suite. New bedside tools for detection of neurologic events during ECMO therapy are needed.

Near-infrared spectroscopy (NIRS)¹¹ broadly describes a noninvasive technology that probes biological tissues based on the absorption and scattering of near-infrared light (650–950 nm). The near-infrared light can penetrate a couple of centimeters into the brain.^{12,13} The primary tissue absorbers in the near-infrared range are the oxygenated hemoglobin (HbO₂) and deoxygenated hemoglobin (Hb) in the blood. Hence the light absorption measured by NIRS mainly reflects the blood concentration and tissue oxygenation. Traditional NIRS cerebral oximeters (such as the INVOS, EQUANOX, FORE-SIGHT, etc.) extract the information of tissue oxygenation from light absorption and have been widely used during ECMO in the last decade.^{14,15} However, the tissue oxygenation saturation provided by the traditional NIRS cerebral oximeters is a ratio of oxygenated hemoglobin to total hemoglobin ($Hb_{total} = HbO_2 + Hb$).

In this case series, we propose to use frequency-domain NIRS technology¹¹ that can quantify the absolute value of light absorption. This value mainly reflects the amount of blood present in the tissues, which is a valuable parameter in ECMO patients with their increased risk for intracranial bleeding. Furthermore, frequency-domain NIRS can also quantify the absolute value of light scattering. The light scattering occurs because of mismatches in refractive index of the different tissue components. The most important cellular components involved in light scattering are cellular nuclei and mitochondria.¹⁶ Hence this value can help us determine the tissue mass in the brain.

Thus, the current study assessed the feasibility of frequency-domain NIRS technology for detection of intracranial complications during ECMO therapy, by measuring both the absorption and scattering properties in regional areas of the brain.

Methods

Participants

This study included patients 0 to 18 years of age, who had undergone ECMO therapy at Children's Medical Center of Dallas from 2013 to 2015. Pediatric patients who were placed on ECMO in the pediatric ICU (PICU) were eligible. Exclusion criteria were underlying congenital heart disease or cardiac surgery because of known predisposition to pre-ECMO cerebral injuries.^{17–19} The study protocol was approved by the institutional review board (IRB) at University of Texas Southwestern Medical Center at Dallas. Informed consent was obtained from the patients' parents or legal guardians.

To obtain normal values of cerebral absorption and scattering, a small cohort of healthy children were also recruited from the local community and measured by the same frequency-domain NIRS device. Informed consent was obtained from their parents or legal guardians before the measurements.

Instrument

Measurement of the absorption and reduced scattering coefficients of cerebral tissues was performed using a commercially available OxiplexTS tissue oximeter (ISS Inc., Champaign, IL; Figure 1). This device is based on multidistance frequency-domain NIRS. It consists of eight laser diodes as the light sources, four at 785 nm and four at 811 nm, and one photomultiplier tube (PMT) as the detector. The eight laser diodes are arranged into four source pairs (one 785 and one 811 nm laser per pair) that have different distances from the detector. The light from different sources passes through the tissues and is then detected by the PMT detector. Then, the absorption coefficient (μ_a) and reduced scattering coefficient (μ_s') of the sampled tissues are calculated by employing a linear fitting of the light attenuations and phase shifts as a function of the four source-detector distances.²⁰

Near-Infrared Spectroscopy Measurements

For each patient, the NIRS measurements were performed at six cranial positions, namely the FP1, FP2, F3, F4, C3, and C4 points in reference to the electroencephalography (EEG) 10–20 system (Figure 2). At each point, the NIRS probe was placed on the scalp firmly and the hair under the probe was combed out before the data were taken. To reduce the variations of data because of probe placement, each cranial position was measured three times by putting the probe on and off the scalp to derive a mean value.

For each patient, the NIRS measurements were performed on multiple dates during the ECMO support while the patient was clinically stable.

Data Analysis

The results from each measurement include μ_a and μ_s' readings at two wavelengths, namely 785 and 811 nm. Both wave-lengths are close but on different sides of the isosbestic point (=800 nm), where HbO₂ and Hb have the same molar extinction coefficient.²¹ Therefore to simplify the data analysis, the μ_a values were averaged over these two wavelengths. In this way, the averaged μ_a value was primarily sensitive to the total blood concentration in the sampled tissues. Similarly, the μ_s' values were also averaged over the two wavelengths.

To characterize the regional abnormalities in cerebral absorption and scattering, we assumed the normal brain should have approximately same μ_a and μ_s' values between the symmetrical positions on the two cerebral hemispheres (*i.e.*, FP1 vs. FP2, F3 vs. F4, and C3 vs. C4 in Figure 2) on basis of their structural similarity. In contrast, intracranial complications would result in different blood concentration or brain structure between two symmetrical positions, which could be reflected by the difference in corresponding μ_a and μ_s' values. To quantify the degree of lateral difference in μ_a and μ_s' , two lateralization factors, L_a and L_s , were defined as follows:

$$L_a = \frac{|\mu_{a_{\text{left}}} - \mu_{a_{\text{right}}}|}{|\mu_{a_{\text{left}}} + \mu_{a_{\text{right}}}|} \quad (1)$$

$$L_s = \frac{|\mu'_{s_{\text{left}}} - \mu'_{s_{\text{right}}}|}{|\mu'_{s_{\text{left}}} + \mu'_{s_{\text{right}}}|} \quad (2)$$

For each of L_a and L_s , a value of 0 indicated two symmetrical positions had same μ_a or μ_s' , a value of ~1 indicated one hemi-sphere had a much higher μ_a or μ_s' than the other hemisphere.

Neuroimaging Assessments

As part of the clinical protocol at the Children's Medical Center of Dallas, neuroimaging assessments were performed if clinically feasible for evidence of neurological abnormalities and injuries. This included head ultrasound during the ECMO run for neonates and 3 Tesla MRI scan for post-ECMO survivors. Emergent head imaging (CT scan) was also conducted during ECMO run when deemed clinically appropriate by the attending intensivist.

Results

Seven pediatric patients (one male and six females, 0–16 years) who received ECMO therapy were measured during the study period. One had veno-arterial ECMO (VA-ECMO), four had veno-venous ECMO (VV-ECMO), and the other two initially had VV-ECMO and then were converted to VA-ECMO. Individual characteristics and clinical outcomes of these patients are detailed in Table 1. Neuroimaging findings are described in Table 2.

Five healthy controls (two males and three females, 2–14 years) were measured for normal values of the brain. For healthy controls, both absorption and reduced scattering coefficients were similar between the laterally symmetrical positions (FP1 vs. FP2, F3 vs. F4, and C3 vs. C4. All p values are >0.05).

Thus, the quantified lateralization factors L_a and L_s were close to zero (all values <0.06). In contrast, the L_a and L_s values from the ECMO patients are largely variable. Figure 3, A and B shows the cumulative distribution function of L_a and L_s at the group level, respectively. In each figure, all of the values from healthy controls are within a narrow range of 0–0.06. The dash line indicates three standard deviations (single-sided normal distribution) of data from the control group, which constrains 99.7% probability of data variation from the normal brains. Thus, it was used as a threshold to identify the abnormalities among ECMO patients. As a result, 24% of L_a values and 16% of L_s values from the ECMO patients exceeded this threshold. Results from individual ECMO patients are described below.

Patient 1 was a 1 year old female who was a premature infant born at 28 weeks of gestation and placed on VV-ECMO for ARDS secondary to H1N1 pneumonia. She stayed on VV-ECMO for 12 days and was then weaned off ECMO support. Very thick hair resulted in NIRS measurements being feasible only at the FP1/FP2 points on three dates (days 1, 2, and 4). No regional abnormality was seen in either absorption or scattering although the post-ECMO MRI demonstrated volume loss of the white matter in bilateral thalami and cerebellar hemispheres (Figure 5, top-left panel), which were thought to be from underlying prematurity.

Patient 2 was a 9 month old female who was placed on VV-ECMO for pulmonary hypertensive crisis. During the ECMO run, she was converted to VA-ECMO due to hemodynamic instability. She stayed on VV/VA-ECMO for totally 6 days and was then weaned off. The NIRS measurements were conducted on three different dates (days 1, 2, and 4) during ECMO. Large variations in absorption coefficient were seen over time, especially at F3/F4, which therefore led to large lateralization difference ($L_a > 0.1$) between F3 vs. F4 and C3 vs. C4. These variations corresponded to the areas of large subdural fluid accumulation demonstrated by MRI, which were indicated pre-ECMO and significantly worsened post-ECMO, as shown in Figure 4C. For this patient, the reduced scattering coefficient was more stable over time and more consistent laterally.

Patient 3 was a 3 day old full-term female who was placed on VV-ECMO for PPHN and meconium aspiration. She stayed on VV-ECMO for 4 days and was then weaned off. For this patient, only the FP1/FP2 points were measured by NIRS on two dates (days 1 and 3) due to the presence of thick hair at all the other positions. On day 1, both absorption and reduced scattering coefficients showed significant reduction on the left cerebral hemisphere. On day 3, both coefficients returned to normal. The early abnormality seen in the NIRS corresponded to abnormal signal intensity within the white matter of the same region shown in the post-ECMO MRI (Figure 5, top-right panel).

Patient 4 was a 14 year old female who was placed on VV-ECMO for ARDS secondary to H1N1, as well as methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonias. During

her ECMO run, she was converted to VA-ECMO due to hemodynamic instability. She stayed on VV/VA-ECMO for 20 days and was then weaned off. For this patient, the FP1/FP2 and F3/F4 points were measured by NIRS (the C3/C4 points were blocked by cannulas) on three successive dates (days 1–3). All results were normal. However, the post-ECMO MRI did have some evidence of mild atrophy and small area of hemorrhage in the right centrum semiovale (Figure 5, bottom-left panel).

Patient 5 was a 6 month old female who was placed on VV-ECMO for ARDS secondary to H1N1. She was on VV-ECMO for 12 days before her death. Near-infrared spectroscopy measurements were conducted on two successive dates (days 1 and 2) in the late course of her ECMO run. While the absorption coefficient was relatively stable over time, a decrease in reduced scattering coefficient from day 1 to day 2 was seen in all six positions, especially in F3 and C3. As a result, the corresponding lateralization difference between F3 vs. F4 and C3 vs. C4 were very large ($L_s > 0.2$) in day 2. Patient died from right atrial perforation from cannula malpositioning during her ECMO run.

Patient 6 was a 16 year old female who was placed on VV-ECMO, with a femoral drainage cannula, for ARDS secondary to respiratory syncytial virus (RSV) septic shock. She stayed on VV-ECMO for 26 days and was then weaned off. The NIRS measurements were conducted on three dates (days 1, 4, and 5) and all of the results were normal. There was no available post-ECMO imaging as the patient was diagnosed of incurable cancer during her ECMO therapy.

Patient 7 was a 2 day old full-term male who was placed on VA-ECMO for PPHN and meconium aspiration. He was on VA-ECMO for 3 days and then weaned off. For this patient, the FP1/FP2 and F3/F4 points were measured by NIRS (the C3/C4 points were blocked by cannulas) on three successive dates (days 1–3). Significant reduction in reduced scattering coefficient was seen in the left cerebral hemisphere (Fp1 on day 1 and F3 on day 3), which corresponded to the area of restricted diffusion involving the superior cerebellar peduncles shown in MRI. This indicates that ischemic injury to the involved area could lead to decrease in white and grey matter within the central mid brain (Figure 5, bottom-right panel).

At the group level, it was observed that lower-than-normal values of reduced scattering coefficient (μ_s') in one side of the brain were consistently associated with large lateralization difference (L_s), such as patient 5 above, whereas the relationship between absorption coefficient (μ_a) and lateralization difference (L_a) was not apparent. Thus, linear regressions were further conducted to assess the relationships between L_s and μ_s' as well as between L_a and μ_a' , and the results are shown in Figure 6, A and B, respectively. Because each nonzero lateralization factor corresponded to a higher μ_a or μ_s' value on one side of the brain and a lower value on the other side of the brain, each of the $L_a - \mu_a$ or $L_s - \mu_s'$ relationship was analyzed based on its corresponding higher-value brain side and lower-value brain side separately. These analyses demonstrated that the μ_a values had little correlation with L_a on both higher-value brain side ($R^2 = 0.05$, $p = 0.18$) and lower-value brain side ($R^2 = 0.03$, $p = 0.32$). Similarly, μ_s' on the higher-value brain side also had little correlation with L_s ($R^2 = 0.07$, $p = 0.12$). However, μ_s' on the lower-value brain side had a significant descending

correlation with L_s ($R^2 = 0.35$, $p < 0.01$). Therefore, it appears that the large lateral difference in scattering was caused by a reduction of scattering in one side of the brain.

Discussion

The current study assessed intracranial abnormalities in neonatal and pediatric patients on ECMO support by measuring the regional light absorption and scattering with frequency-domain NIRS technology. The precision of the NIRS measurements enabled identification of regional abnormalities in both absorption and scattering based on comparisons between healthy controls and ECMO patients, as well as between the laterally symmetrical positions (FP1 vs. FP2, F3 vs. F4, and C3 vs. C4 in Figure 2). The results from this study indicate a potential to use the frequency-domain NIRS for detection of intracranial complications during ECMO therapy.

ECMO is associated with a relatively high incidence of substantial complications, of which intracranial injuries are the most important and most devastating.⁹ These injuries consist of hemorrhagic and nonhemorrhagic, ischemic lesions. The existence of intracranial injuries and the classifications of severity are the major predictors for neurodevelopmental outcomes in survivors. In general, head ultrasound is used for detection of intracranial abnormalities in ECMO-treated newborns and infants with open fontanels. It is sensitive in the evaluation of large intracranial hemorrhage,²² but less useful for the detection of ischemic lesions.

Several studies have demonstrated that CT and MRI scans can identify intracranial lesions that earlier were not seen with head ultrasound. For instance, a recent study by Rollins *et al.*²³ studied 50 neonates with MRI done after ECMO, before discharge, and compared the results with head ultrasound completed during ECMO. Head ultrasound was abnormal in 24% neonates during ECMO, whereas post-ECMO MRI was abnormal in 62% neonates. Most of the lesions unrecognized on head ultrasound were nonhemorrhagic. While MRI appears to be ideal for post-ECMO evaluation, its application during ECMO therapy is not possible. CT imaging is limited by the difficulty in transport of these patients to the radiology suite and the potential risks, such as accidental decannulation and death. Thus, we currently lack a reliable tool for early detection of intracranial injuries during ECMO therapy, especially for the patients with closed fontanels where head ultrasound cannot be used.

Near-infrared spectroscopy has been widely accepted as a noninvasive, portable technology in critical care unit that has demonstrated sensitivity to changes in cerebral tissue oxygenation.^{14,15} Compared with head ultrasound, NIRS can be used for all age groups because the near-infrared light can easily pass through the skull. A main drawback of NIRS is its limited penetration depth. The depth sensitivity of NIRS increases with the source-detector distance. With an achievable source-detector distance of 3 to 5 cm, NIRS has sufficient sensitivity to the cortical sulci and superficial white matter.¹³ On the other hand, a study by Bulas *et al.*²² found that hemorrhages in ECMO-treated newborns are mainly within the brain parenchyma. Thus, we suggest NIRS could still be a complementary tool to the existing technologies for bedside evaluation during ECMO therapy.

The frequency-domain NIRS used in this study determined absolute absorption and reduced scattering coefficients of cerebral tissues based on the incremental changes of light attenuation and phase shift at four source-detector distances. In this way, the light attenuation and phase shift caused by the extracerebral tissues (*i.e.*, the scalp and skull) were represented as the base values at the shortest source-detector distance, and therefore had minimal influence on the cerebral readings. This mechanism limited the measurement variations in both absorption and scattering, which allowed us to investigate their abnormal changes by comparing readings between healthy controls and ECMO patients, as well as between the laterally symmetrical positions. A main finding in this study is that the identified abnormalities in scattering among ECMO patients appear to be associated with lower-than-normal values of reduced scattering coefficient seen in regional areas of the brain. Because light scattering originates from the intracellular structures (such as nuclei and mitochondria),¹⁶ a reduction in scattering primarily reflects loss or decreased density of the brain matter. Loss of brain volume can be because of several different factors, such as resolving hemorrhage, hypoxic ischemic lesions, and injury secondary to stroke, all of which can occur in patients undergoing ECMO therapy. Furthermore, we have also seen the consistent changes in the scattering corresponding to changes in post-ECMO neuroimaging. However, this correspondence was seen only if the injury was in the parietal or frontal regions of the brain. The NIRS measurement was not sensitive enough to pick up changes in the water shed areas of the brain, such as hippocampi and the deep cerebral and cerebellar nuclei.

Because none of the ECMO patients in this study developed significant intracranial bleeding during the therapy, we did not see any consistent changes in the absorption pattern. Large intracranial bleeding would certainly cause significant changes of blood volume in the area of the brain that is involved, which would lead to abnormalities in the absorption pattern. However, further studies on larger groups of patients during ECMO are needed for confirmation. Furthermore, frequency-domain NIRS was done during the course of the ECMO run when patients were much sicker and had significant disturbances in their cerebrovascular functions.²⁴ The neuroimaging done is much later in the course of their hospitalization when they are less sick and stable. This can be one of the significant reasons why the frequency-domain NIRS changes did not always correlate with the changes seen on neuroimaging.

Another limitation in this study was the light absorption by the hair, for which data from several cranial points (such as F3, F4, C3, and C4) could not be collected among subjects with thick hair. The hair absorption is a common issue in NIRS. This can be improved by better probe design, for example, letting the optical fibers have short tips (1–2 mm) out of the probe to pass through the hair. Furthermore, recently, we have reported the use of brush optodes to improve the optical contact on subjects with dense hair.²⁵ The brush optode is applicable for all kinds of NIRS probes, which can be regarded as the ultimate solution of this issue.

Conclusions

Regional abnormalities in both absorption and scattering were identified by frequency-domain NIRS among pediatric patients during ECMO therapy. The scattering abnormalities

appear to be associated with lower-than-normal μ_s' values in regional areas of the brain, which primarily reflects loss or decreased density of the brain matter. These results suggest that the frequency-domain NIRS potentially can be a complimentary bedside tool to help detect cerebral abnormalities for patients on ECMO. Future studies are needed to correlate these abnormalities with long-term outcomes.

Acknowledgments

This study was supported by American Heart Association (AHA) Beginning-Grant-in Aid (15BGIA25860045; PI Tian). The views expressed are those of the authors and not necessarily that of the AHA.

References

1. Lequier L: Extracorporeal life support in pediatric and neonatal critical care: A review. *J Intensive Care Med* 19: 243–258, 2004. [PubMed: 15358943]
2. ECLS Registry Report: International Summary 1 2014 <http://www.elsonet.org/index.php/registry/statistics/limited.html>.
3. UK Collaborative ECMO Trial Group: UK collaborative randomised trial of neonatal extracorporeal membrane oxygenation. *Lancet* 348: 75–82, 1996. [PubMed: 8676720]
4. Polito A, Barrett CS, Wypij D, et al.: Neurologic complications in neonates supported with extracorporeal membrane oxygenation. An analysis of ELSO registry data. *Intensive Care Med* 39: 1594–1601, 2013. [PubMed: 23749154]
5. Hofkosh D, Thompson AE, Nozza RJ, Kemp SS, Bowen A, Feldman HM: Ten years of extracorporeal membrane oxygenation: Neurodevelopmental outcome. *Pediatrics* 87: 549–555, 1991. [PubMed: 1707157]
6. Glass P, Wagner AE, Papero PH, et al.: Neurodevelopmental status at age five years of neonates treated with extracorporeal membrane oxygenation. *J Pediatr* 127: 447–457, 1995. [PubMed: 7544826]
7. Kasirajan V, Smedira NG, McCarthy JF, Casselman F, Boparai N, McCarthy PM: Risk factors for intracranial hemorrhage in adults on extracorporeal membrane oxygenation. *Eur J Cardiothorac Surg* 15: 508–514, 1999. [PubMed: 10371130]
8. Glass P, Bulas D: Neonatal ECMO: Neuroimaging and neurodevelopmental outcome. *Semin Perinatol* 29: 58–65, 2005. [PubMed: 15921154]
9. van Heijst AF, de Mol AC, Ijsselstijn H: ECMO in neonates: Neuroimaging findings and outcome. *Semin Perinatol* 38: 104–113, 2014. [PubMed: 24580766]
10. Lidegran MK, Mosskin M, Ringertz HG, Frenckner BP, Lindén VB: Cranial CT for diagnosis of intracranial complications in adult and pediatric patients during ECMO: Clinical benefits in diagnosis and treatment. *Acad Radiol* 14: 62–71, 2007. [PubMed: 17178367]
11. Ferrari M, Quaresima V: A brief review on the history of human functional near-infrared spectroscopy (fNIRS) development and fields of application. *Neuroimage* 63: 921–935, 2012. [PubMed: 22510258]
12. Cui X, Bray S, Reiss AL: Functional near infrared spectroscopy (NIRS) signal improvement based on negative correlation between oxygenated and deoxygenated hemoglobin dynamics. *Neuroimage* 49: 3039–3046, 2010. [PubMed: 19945536]
13. Dehghani H, White BR, Zeff BW, Tizzard A, Culver JP: Depth sensitivity and image reconstruction analysis of dense imaging arrays for mapping brain function with diffuse optical tomography. *Appl Opt* 48: D137–D143, 2009. [PubMed: 19340101]
14. Fenik JC, Rais-Bahrami K: Neonatal cerebral oximetry monitoring during ECMO cannulation. *J Perinatol* 29: 376–381, 2009. [PubMed: 19158806]
15. Wong JK, Smith TN, Pitcher HT, Hirose H, Cavarocchi NC: Cerebral and lower limb near-infrared spectroscopy in adults on extracorporeal membrane oxygenation. *Artif Organs* 36: 659–667, 2012. [PubMed: 22817780]

16. Wang LV, Wu H-I: Biomedical Optics: Principles and Imaging. New Jersey, Wiley-Interscience, 2007.
17. Donofrio MT, Massaro AN: Impact of congenital heart disease on brain development and neurodevelopmental outcome. *Int J Pediatr* 359390, 2010.
18. Miller SP, McQuillen PS, Hamrick S, et al.: Abnormal brain development in newborns with congenital heart disease. *N Engl J Med* 357: 1928–1938, 2007. [PubMed: 17989385]
19. McQuillen PS, Barkovich AJ, Hamrick SE, et al.: Temporal and anatomic risk profile of brain injury with neonatal repair of congenital heart defects. *Stroke* 38(2 suppl): 736–741, 2007. [PubMed: 17261728]
20. Arri SJ, Muehleman T, Biallas M, Bucher HU, Wolf M: Precision of cerebral oxygenation and hemoglobin concentration measurements in neonates measured by near-infrared spectroscopy. *J Biomed Opt* 16: 047005, 2011. [PubMed: 21529095]
21. Pahl S: Tabulated molar extinction coefficient for hemoglobin in water. <http://omlc.ogi.edu/spectra/hemoglobin/summary.html>.
22. Bulas DI, Taylor GA, O'Donnell RM, Short BL, Fitz CR, Vezina G: Intracranial abnormalities in infants treated with extracorporeal membrane oxygenation: update on sonographic and CT findings. *AJNR Am J Neuroradiol* 17: 287–294, 1996. [PubMed: 8938301]
23. Rollins MD, Yoder BA, Moore KR, et al.: Utility of neuroradiographic imaging in predicting outcomes after neonatal extracorporeal membrane oxygenation. *J Pediatr Surg* 47: 76–80, 2012. [PubMed: 22244396]
24. Short BL: The effect of extracorporeal life support on the brain: A focus on ECMO. *Semin Perinatol* 29: 45–50, 2005. [PubMed: 15921152]
25. Khan B, Wildey C, Francis R, et al.: Improving optical contact for functional near-infrared brain spectroscopy and imaging with brush optodes. *Biomed Opt Express* 3: 878–898, 2012. [PubMed: 22567582]

Figure 1.

OxiplexTS tissue oximeter (ISS Inc., Champaign, IL) and its probe. This device consists of eight laser diodes, four at 785 nm and the other four at 811 nm, as light sources and one photomultiplier tube as detector. The eight lasers are arranged into four source pairs that are in different distances from the detector. Each source pair consists of one 785 nm laser and one 811 nm laser.

Figure 2.

Schematic positions of NIRS measurement on the head. For each patient, the NIRS measurements were performed at six cranial positions, namely the FP1, FP2, F3, F4, C3, and C4 points in reference to the EEG 10–20 system. EEG, electroencephalography; NIRS, near-infrared spectroscopy.

Figure 3.

Accumulated probability distributions of lateralization factors L_a and L_s . As shown in this figure, about 85% (indicated by the dotted line) of the L_a and L_s values are within a narrow range of 0 to 0.1, whereas the rest L_a and L_s values above this level vary widely.

Figure 4.

Frequency-domain NIRS and neuroimaging results from patient 2: **A:** Absorption coefficient μ_a (unit: cm^{-1}) measured at F3/F4. **B:** Lateralization factor L_a between F3/F4. **C:** T2-weighted MRI images 18 days before ECMO and 11 days post-ECMO, respectively. The patient developed increased right frontal parietal convexity subdural effusion post-ECMO (right panel, arrow). ECMO, extracorporeal membrane oxygenation; NIRS, near-infrared spectroscopy; MRI, magnetic resonance imaging.

Figure 5. Post-ECMO MRI images from patients 1, 3, 4, and 7. ECMO, extracorporeal membrane oxygenation; MRI, magnetic resonance imaging.

Figure 6.

A: Relationship between absorption coefficient μ_a and lateralization factor L_a at the group level. Since each nonzero L_a corresponded to a high μ_a value on one side of the brain and a low μ_a value on the other side, the $L_a - \mu_a$ relationship was analyzed based on the corresponding higher-value brain side ($\square$) and lower-value side ($\diamond$) separately. The lines indicate the linear regression curves in the two separate cases. **B:** Relationship between reduced scattering coefficient μ_s' and lateralization factor L_s at the group level. The $L_s - \mu_s'$ relationship was also analyzed based on the corresponding higher-value brain side ($\square$) and lower-value side ($\diamond$) separately. The lines indicate the linear regression curves in the two separate cases.

Table 1.
Individual Characteristics and Clinical Outcomes of the Pediatric ECMO Patients

Patient	Age	Diagnosis		ECMO Parameters			Neuroimaging Date	Outcome
		Primary	Secondary	Type	Duration (hours)			
1	1 year	ARDS	H1N1	VV	284	3 days post-ECMO		Survival to discharge
2	9 months	Pulmonary hypertension	Osteopetrosis s/p BMT	VV to VA	150	18 days pre- ECMO; 11 days post-ECMO		Survival to discharge
3	3 days	Persistent pulmonary hypertension	Meconium aspiration	VV	99	4 days post-ECMO		Survival to discharge
4	14 years	ARDS	H1N1 with MRSA pneumonia	VV to VA	473	37 days post-ECMO		Survival to discharge
5	6 months	ARDS	H1N1	VV	288	No imaging		Death
6	16 years	ARDS	Septic shock rsv, fluid overload	VV	632	No imaging		Survival to discharge
7	2 days	Persistent pulmonary hypertension	Meconium aspiration, sepsis	VA	76	2 days post-ECMO		Survival to discharge

ARDS, acute respiratory distress syndrome; BMT, bone marrow transplant; ECMO, extracorporeal membrane oxygenation; MRSA, methicillin-resistant *Staphylococcus aureus*; VA, veno-arterial; VV, veno-venous.

Table 2.

Neuroimaging Findings Among the ECMO Survivors

Patient	Intra-ECMO NIRS Findings	Neuroimaging Findings
1	FP1/FP2 points were measured on three dates (days 1, 2, and 4). No regional abnormality in either absorption or scattering was seen	Extensive white matter volume loss with prominence of the sulci. There is volume loss in the bilateral thalami. There is volume loss in the cerebellar hemispheres. MR spectroscopy demonstrates decreased NAA peak
2	All of the FP1/FP2, F3/F4, and C3/C4 points were measured on three dates (days 1, 2, and 4). Large variations in absorption coefficient were seen over time, especially at F3/F4, which led to large lateralization difference ($L_a > 0.1$) between F3 vs. F4.	Optic atrophy, a right parietal subdural effusion, and an enlarged third ventricle unchanged from the pre-ECMO MRI
3	FP1/FP2 points were measured on two dates (days 1 and 3). On day 1, both absorption and reduced scattering coefficients showed significant reduction on the left cerebral hemisphere. On day 3, both coefficients returned to normal	Abnormal signal intensity within the white matter of the left frontal region
4	FP1/FP2 and F3/F4 points were measured on three successive dates (days 1 to 3). All results were normal	Mild cerebral and cerebellar atrophy. Diminutive left hippocampus
5	All of the FP1/FP2, F3/F4, and C3/C4 points were measured on two successive dates (days 1 and 2) in the third week of ECMO run. A decrease in reduced scattering coefficient from day 1 to day 2 was seen in all six positions, especially in F3 and C3. The corresponding lateralization difference L_s between F3 vs. F4 and C3 vs. C4 were very large ($L_s > 0.2$) on day 2	No imaging
6	All of the FP1/FP2, F3/F4, and C3/C4 points were measured on three dates (days 1, 4, and 5). All results were normal	No imaging
7	FP1/FP2 and F3/F4 points were measured on three successive dates (days 1 to 3). Significant decrease in reduced scattering coefficient was seen in the left cerebral hemisphere (FP1 on day 1 and F3 on day 3)	Symmetric restricted diffusion involving the superior cerebellar peduncles and their decussation within the central mid brain

ECMO, extracorporeal membrane oxygenation; MRI, magnetic resonance imaging; NAA, N-acetyl aspartate; NIRS, near-infrared spectroscopy.