

Cerebral and Limb Tissue Oxygenation During Peripheral Venoarterial Extracorporeal Life Support

Journal of Intensive Care Medicine
2020, Vol. 35(2) 179-186
© The Author(s) 2017



Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/0885066617735270
journals.sagepub.com/home/jic



Nousjka P. A. Vranken, BSc¹, Anouk A. M. A. Lindelauf, BAsc¹,
Antoine P. Simons, EKP, PhD², Marcel J. H. Ariës, MD, PhD³,
Jos G. Maessen, MD, PhD¹, and Patrick W. Weerwind, CCP, PhD¹

Abstract

Femoral access in extracorporeal life support (ECLS) has been associated with regional variations in arterial oxygen saturation, potentially predisposing the patient to ischemic tissue damage. Current monitoring techniques, however, are limited to intermittent bedside evaluation of capillary refill among other factors. The aim of this study was to assess whether cerebral and limb regional tissue oxygen saturation (rSO₂) values reflect changes in various patient-related parameters during venoarterial ECLS (VA-ECLS). This retrospective observational study included adults assisted by femorofemoral VA-ECLS. Bifrontal cerebral and bilateral limb tissue oximetry was performed for the entire duration of support. Hemodynamic data were analyzed parallel to cerebral and limb rSO₂. A total of 23 patients were included with a median ECLS duration of 5 [1-20] days. Cardiac arrhythmias were observed in 12 patients, which was associated with a decreased mean rSO₂ from 61% ± 11% to 51% ± 10% during atrial fibrillation and 67% ± 9% to 58% ± 10% during ventricular fibrillation (*P*<0.001 for both). A presumably sudden increase in cardiac output due to myocardial recovery (*n*=8) resulted in a significant decrease in mean cerebral rSO₂ from 73% ± 7% to 54% ± 6% and from 69% ± 9% to 53% ± 8% for the left and right cerebral hemisphere, respectively (*P*=0.012 for both hemispheres). Also, right radial artery partial gas pressure for oxygen decreased from 15.6 ± 2.8 to 8.3 ± 1.9 kPa (*P*=0.028). No differences were found in cerebral desaturation episodes between patients with and without neurologic complications. In six patients, limb rSO₂ increased from on average 29.3 ± 2.7 to 64.0 ± 5.1 following insertion of a distal cannula in the femoral artery (*P*=0.027). Likewise, restoration of flow in a clotted distal cannula inserted in the femoral artery was necessary in four cases and resulted in increased limb rSO₂ from 31.3 ± 0.8 to 79.5 ± 9.0; *P*=0.068. Non-invasive tissue oximetry adequately reflects events influencing cerebral and limb perfusion and can aid in monitoring tissue perfusion in patients assisted by ECLS.

Keywords

extracorporeal life support, noninvasive monitoring, near-infrared spectroscopy, regional tissue oximetry

Introduction

Despite the increasing experience and continuously improving technology applied in extracorporeal life support (ECLS), femoral access is still associated with regional variations in arterial saturation driven by an impaired oxygen delivery.¹ Specifically, femoral artery cannulation may compromise perfusion of the lower limbs, causing limb ischemia and concomitant tissue damage.^{2,3} Besides impaired limb perfusion, veno-arterial ECLS (VA-ECLS) is linked with the delivery of hypoxic blood to the brain (i.e., differential hypoxia or two-circulation syndrome), resulting in an increased risk of brain damage.⁴ Although maintaining adequate tissue oxygenation is vital in critically ill patients, current monitoring techniques are often limited to bedside observation of capillary refill, limb temperature, and limb color. Continuous non-invasive tissue oximetry could be of added value to monitor regional tissue

oxygen saturation (rSO₂) in patients supported by ECLS. This monitoring method is based on the Beer-Lambert law and uses near-infrared spectroscopy (NIRS) to assess local tissue

¹Department of Cardiothoracic Surgery, Maastricht University Medical Center, Maastricht, The Netherlands

²Department of Kardiotechnik, University Hospital Basel, Basel, Switzerland

³Department of Intensive Care, Maastricht University Medical Center, Maastricht, The Netherlands

Received June 09, 2017. Received revised August 23, 2017. Accepted September 14, 2017.

Corresponding Author:

Nousjka P. A. Vranken, Department of Cardiothoracic Surgery, Maastricht University Medical Center, P. Debyelaan 25, PO Box 5800, 6202 AZ Maastricht, The Netherlands.

Email: nousjka.vranken@mumc.nl

oxygenation.⁵ Tissue oximetry readings are proposed to reflect hemodynamic parameters in real-time, serving as a potential early marker for distal limb and cerebral ischemia.⁵⁻⁷ The literature describing the application of this monitoring technique in patients supported by VA-ECLS, however, remains scarce.⁸⁻¹⁰ The aim of this study was to assess the efficacy of cerebral and limb tissue oximetry during VA-ECLS.

Materials and Methods

Patients

In this retrospective study, data from adult patients assisted by peripheral femorofemoral VA-ECLS were consulted. Institutional approval was granted based on a retrospective quality analysis of our patient database (trial number 14-4-194). Due to the retrospective nature of the study, informed consent was waived.

Patients were fully sedated and on mechanical ventilation. Support was provided by either a Permanent Life SupportSystem (Maquet Cardiopulmonary AG, Hirrlingen, Germany) or a CardioHelp-mounted HLS Advanced 7.0 module (Maquet Cardiopulmonary), both Bioline-coated. Extracorporeal cardiopulmonary resuscitation patients were actively cooled to a rectal temperature of 33°C for 24 hours and thereafter gradually rewarmed to 37°C using a heater-cooler unit (HCU 30, Maquet Cardiopulmonary). Arterial cannulation was performed using a 19Fr. or 21Fr. HLS cannula (Maquet Cardiopulmonary), whereas venous cannulation was performed using a 26Fr. or 29Fr. multi-stage HLS cannula (Maquet Cardiopulmonary). An additional 8Fr. or 10Fr. cannula (Super Arrowflex percutaneous sheath introducer set, Teleflex Medical Europe Ltd, Westmeath, Ireland) was used to provide distal limb perfusion via antegrade cannulation of the femoral artery if necessary. Heparinization was monitored by activated partial thromboplastin time (targeted between 50 and 70 seconds), and at a hematocrit value less than 25% patients received transfusion of packed red blood cells (PRBCs).

Data Collection

Bi-frontal cerebral and bilateral limb rSO₂ were routinely monitored using non-invasive tissue oximetry using NIRS (INVOS 5100C Cerebral/Somatic Oximeter, Medtronic, Minneapolis, MN, USA). Immediately upon initiation of VA-ECLS, patients' forehead (left and right side) as well as the medial site of the musculus gastrocnemius (of both limbs) were fitted with a disposable self-adhesive sensor. All sensors were replaced once every seven days during the entire period of ECLS.

Data concerning systolic, diastolic, and mean radial artery blood pressure, pulse pressure, cardiac rhythm, pulse oximetry, limb temperature, blood loss, and number of transfused PRBCs were retrieved from a critical care and anesthesia data system (Philips ICIP Intellispace version F.00.01, Philips, Eindhoven, the Netherlands). Arterial blood gas analyses were executed using blood samples drawn from the right radial artery during

the full period of intensive care unit stay according to hospital protocol. Pulse oximetry was performed at the left index finger. All data acquisition and analyses were performed anonymously and in accordance with the Dutch law for approving medical research.

Data Processing

Raw data files retrieved from the clinical oximeter contain one data point every six seconds, i.e. ten data points per minute. The output files were exported to Microsoft Excel (Microsoft Office 2010) for further analysis.

To assess the effect of cardiac rhythm (sinus rhythm, atrial fibrillation (AF), and ventricular fibrillation (VF)) on cerebral rSO₂, data were analyzed as follows: first, all cerebral rSO₂ data points per patient were clustered in successive groups of 300 data points (30 minutes). For every group, a mean rSO₂ value was calculated. A relative difference of 5% between two subsequent data points was marked as an event. Second, cardiac rhythm and rSO₂ data were aligned. In case of an event identified in the cerebral rSO₂ data, the cardiac rhythm was consulted to see if any arrhythmias occurred. In case of a cardiac arrhythmia, the lowest mean cerebral rSO₂ value was derived for the duration of the particular arrhythmia. Also a mean cerebral rSO₂ was derived from a 300 data point sample during normal sinus rhythm, resulting in a rhythm-specific mean cerebral rSO₂ per patient. When a difference of $\geq 5\%$ was found between the left and right cerebral hemisphere rSO₂, values of both hemispheres were used for data presentation. In case of no difference between the left and right cerebral hemisphere, rSO₂ data were presented as one mean value for both hemispheres.

The effect of distal limb perfusion on limb tissue oxygenation was determined by comparison of mean rSO₂ values before (pre-event) and after (event) placement of a distal cannula in the femoral artery. Mean rSO₂ values were determined by averaging 300 data points before and after placement of the distal cannula. The latter sample was selected immediately following limb rSO₂ stabilization. For comparison of tissue oxygenation values prior to (pre-event) and following (event) distal cannula clot removal, mean rSO₂ values were calculated in a similar fashion using 300 data points per sample.

To study the difference in cerebral desaturations between patients who did and did not suffer from neurologic complications, a mean cerebral rSO₂ was calculated for 30-minute intervals in both cerebral hemispheres for the entire duration of ECLS. A desaturation episode was defined as a mean unilateral cerebral rSO₂ below 50% over a period of 30 minutes. Consecutively, the sum of desaturation episodes was compared between patients with and without neurologic complications.

Statistical Analysis

Numerical variables are depicted either in mean \pm standard deviation or as median [interquartile range] depending on data

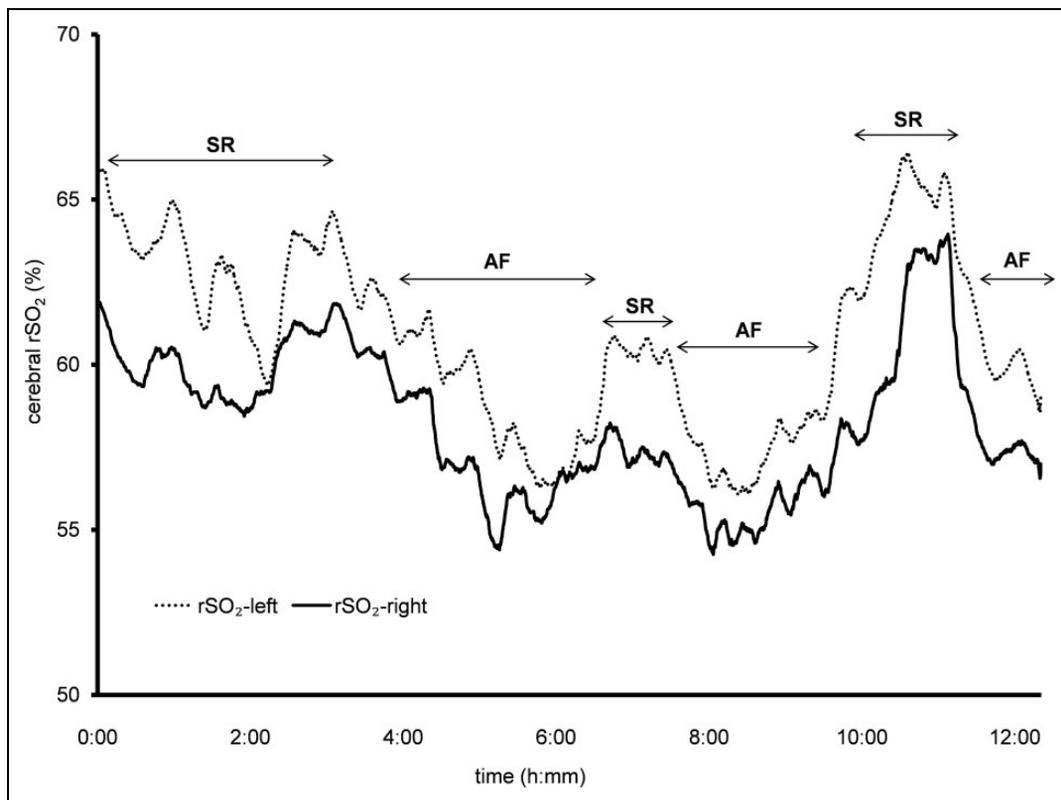


Figure 1. Example of a decrease in bi-frontal cerebral oxygen saturation during consecutive periods of atrial fibrillation and sinus rhythm. AF, atrial fibrillation; ECLS, extracorporeal life support; rSO_2 , regional tissue oxygen saturation; rSO_2 -left, regional tissue oxygen saturation left cerebral hemisphere; rSO_2 -right, regional tissue oxygen saturation right hemisphere; SR, sinus rhythm.

distribution. Comparison of rSO_2 values between the different cardiac rhythms, pre-event samples and event samples was performed using the related samples Wilcoxon signed-rank test. A P value <0.05 was considered statistically significant. All analyses were performed using the Statistical Package for Social Sciences version 22.0 (SPSS Inc., Chicago, IL, USAo).

Results

Twenty-three adult patients assisted by femorofemoral VA-ECLS were included in this retrospective study. Mean age was 59 ± 13 years and a total of 18 females and 5 males were included. The median duration of ECLS was 5 [1-20] days with a mean full ECLS pump flow of 4.5 ± 0.9 L/min.

Of the 23 patients, 16 were assisted by femorofemoral VA-ECLS upon resuscitation following an out-of-hospital cardiac arrest. Assistance by VA-ECLS was provided in three postcardiotomy cases. In the remaining four cases, life support was initiated following detection of, for example, pulmonary embolism. Distal cannulation was provided in six cases. Nine patients developed AF, whereas in three patients VF was observed. Development of abnormal cardiac rhythm was immediately followed by a decrease in mean rSO_2 from $61\% \pm 11\%$ to $51\% \pm 10\%$ during AF and from $67\% \pm 9\%$ to $58\% \pm 10\%$ during VF ($P < 0.001$ for both). No significant

differences were found between the left and right cerebral hemisphere rSO_2 ($P = 0.750$). An example of a decrease in bifrontal cerebral rSO_2 during AF is shown in Figure 1.

In case of a presumably increased cardiac output resulting from myocardial recovery during full ECLS ($n = 8$, mean flow 4.45 ± 0.6 L/min), a decrease in cerebral rSO_2 was observed from 73% to 54% and from 69% to 53% for the left and right cerebral hemisphere, respectively ($P = .012$ for both), as depicted in Table 1. Concomitant partial gas pressure for oxygen (PO_2) decreased from 15.6 ± 2.8 to 8.3 ± 1.9 kPa ($P = 0.012$). Arterial saturation values derived from blood gas analyses showed a significant decrease from $99\% \pm 1\%$ to $85\% \pm 8\%$ ($P = 0.028$), while pulse oximetry decreased from $99\% \pm 1\%$ to $97\% \pm 5\%$ ($P = 0.075$). In Figure 2 the change in cerebral rSO_2 values is shown in case of a sudden increased cardiac output during ECLS without concomitant adjustment of ventilator settings. After approximately one hour, the ventilatory settings were adjusted, resulting in gradual rSO_2 normalization.

In the current study, a total of 11 patients (47.8%) died while on VA-ECLS due to neurologic complications, deep cardiogenic shock, sepsis, pneumonia, lung edema, myocarditis, multi-organ failure, or intestinal ischemic damage. The total number of cerebral desaturation episodes did not differ between patients who did or did not survive until ECLS weaning (19 versus 12 episodes, respectively, $P = 0.695$).

Five patients (21.7%) developed neurological complications while on VA-ECLS, which included intracerebral hematoma or extensive ischemic damage diagnosed with computed tomography imaging, critical illness neuropathy, and absence of the direct light pupil reflex. Three out of five patients died due to the consequences of neurologic complications while in the remaining two cases one patient died due to lung edema and another survived weaning from ECLS. In the five patients with neurological complications, a median of 13 cerebral

desaturation episodes (sum of left and right hemisphere) were observed, while in patients without neurological complications a median of 14.5 desaturation episodes were found ($P=1.000$). In patients with neurologic complications, the median number of desaturation episodes per day on VA-ECLS was 6.5, while the median number of desaturation episodes in patients without neurologic complications amounted to 3.0 ($P=0.914$).

Table 1. Cerebral Tissue Oxygen Saturation Values in Case of an Im Promptu Increase in Cardiac Output While on Extracorporeal Life Support.^{a,b}

	Before Increased CO	During Increased CO	P Value
Cerebral rSO ₂ (%)			
Left	73 ± 7	54 ± 6	0.012
Right	69 ± 9	53 ± 8	0.012
Arterial oxygen saturation (%)	99 ± 1	85 ± 8	0.028
Arterial PO ₂ , kPa	15.6 ± 2.8	8.3 ± 1.9	0.012
Pulse oximetry (%)	99 ± 1	97 ± 5	0.075
Mean pressure (mm Hg)	70 ± 7	80 ± 15	0.012

Abbreviations: CO, cardiac output; Left, left cerebral hemisphere; Right, right cerebral hemisphere; rSO₂, regional tissue oxygen saturation; PO₂, partial gas pressure for oxygen.

^an=8

^bValues presented as mean ± standard deviation.

Regarding tissue oximetry performed at the distal limb, rSO₂ values of the non-cannulated limb amounted to 65% ± 6% (mean value) and remained constant throughout the entire duration of ECLS. In six patients (26%), additional cannulation of the femoral artery proved necessary to ensure adequate blood flow to the limb. Following insertion of a distal cannula in the femoral artery, limb rSO₂ increased from 29.3 ± 2.7 to 64.0 ± 5.1 ($P=0.027$) as shown in Table 2. An example of a limb rSO₂ pattern is provided in Figure 3.

Complications with distal cannulation of the femoral artery were observed in four patients (17.4%) following insertion of the distal cannula, including bleeding and thrombus formation. Due to clotting of the distal cannula, which was the most common complication associated with distal cannulation, limb rSO₂ values decreased (Table 2). Blood flow in the distal cannula restored following clot removal by aspiration using a syringe, as reflected by the increase in limb rSO₂ (from 31.3 ± 0.8 to 79.5 ± 9.0, $P=0.068$). Furthermore, a decrease in temperature was noted in the cannulated limb.

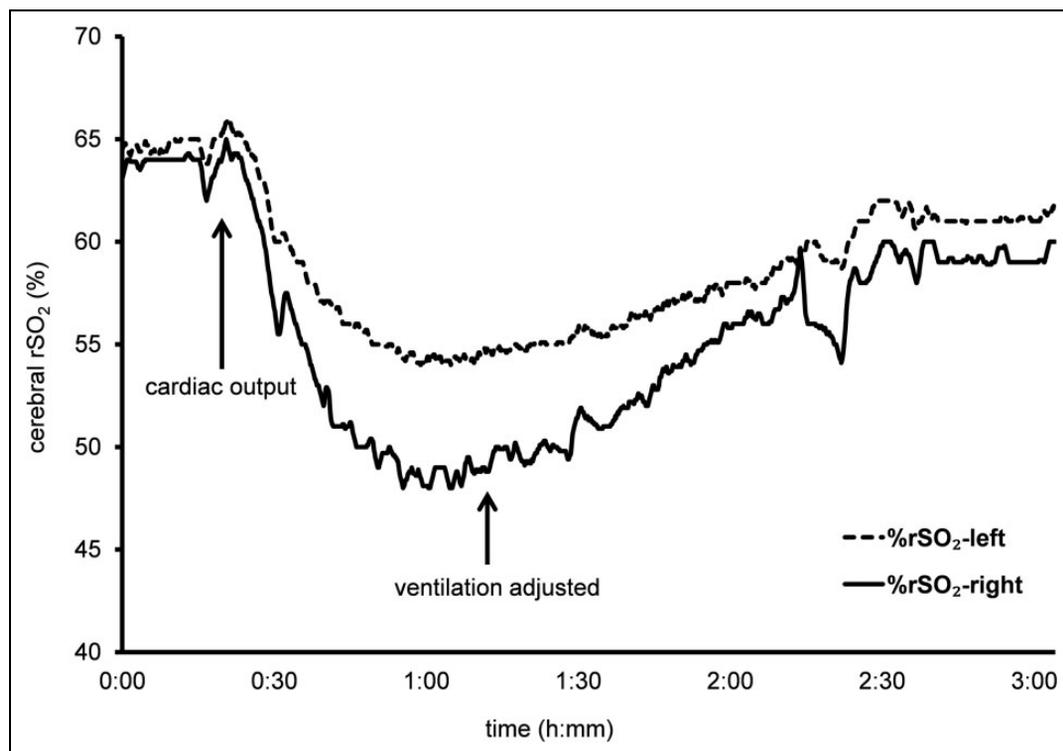


Figure 2. Example of a decrease in bi-frontal cerebral tissue oxygen saturation with an im promptu increase in cardiac output during full extracorporeal life support. rSO₂, regional tissue oxygen saturation; rSO₂-left, regional tissue oxygen saturation left cerebral hemisphere; rSO₂-right, regional tissue oxygen saturation right hemisphere.

Notably, changes in limb temperature became evident after a clear time delay as compared to changes observed in limb rSO₂ (Figure 4).

All patients received PRBC transfusion or infusion of fluids (e.g., Ringer lactate and/or Gelofusin 4%). Transfusion of 38 PRBC units (275 mL per unit) for 13 anemic patients did not result in a significant change in cerebral rSO₂. In contrast, rSO₂ levels increased >10% after infusion of >1000 mL of fluids within one hour (*P*<0.001, Table 3).

Table 2. Restoring Limb Tissue Oxygen Saturation by Inserting a Distal Cannula in the Femoral Artery (n=6) and Clotting of the Distal Cannula (n=4).^a

Patient #	Limb rSO ₂ Prior Cannulation (%)	Limb rSO ₂ Post Cannulation (%)	Limb rSO ₂ Clotted Cannula (%)	Limb rSO ₂ After Clot Removal (%)
4	24 ± 2	63 ± 3	32 ± 3	66 ± 4
5	28 ± 1	60 ± 3	31 ± 2	89 ± 5
10	32 ± 2	70 ± 4	—	—
11	30 ± 1	59 ± 2	30 ± 1	86 ± 1
16	31 ± 2	72 ± 2	—	—
28	31 ± 3	60 ± 5	32 ± 2	77 ± 3

Abbreviation: rSO₂, regional tissue oxygen saturation.
^aData presented as mean ± standard deviation. Difference between limb rSO₂ prior to distal cannulation and limb rSO₂ post cannulation (n=6): *P*=0.027. Difference between limb rSO₂ in case of a clotted distal cannula and limb rSO₂ after clot removal (n=4): *P*=0.068.

Discussion

This observational study focused on the application of continuous non-invasive tissue oximetry in patients supported by peripheral VA-ECLS. Our results showed cerebral and limb tissue oximetry readings adequately reflect both hemodynamic instability and compromised limb perfusion.

Fluctuations in mean arterial pressure, pulse oximetry values, arterial PO₂, and oxygen saturation reflect variations in cardiac output and are often the first signs of hemodynamic instability in patients on ECLS.^{11,12} Maintaining adequate cardiac output is important to prevent ischemic episodes, which can potentially result in complications such as congestive heart failure, neurocognitive impairment, renal dysfunction, infections, and irreversible multi-organ failure.¹²⁻¹⁶ A decreased cardiac performance resulting in lowered cardiac output has been associated with decreased cerebral and microvascular perfusion, which is reflected by lowered rSO₂ values.¹⁷ As a compensatory mechanism, brain oxygen extraction has shown to increase in the case of reduced cardiac performance with concomitant lowered rSO₂.^{18,19} A possible cause of reduced cardiac performance can be an abnormal cardiac rhythm such as AF.²⁰ In the current study, AF was noted in nine patients, whereas in three patients VF was observed. Our results confirm that cerebral tissue oxygenation is lowered during episodes of AF and VF. These results indicate a high positive predictive value, suggesting that tissue oximetry can aid in timely recognition of

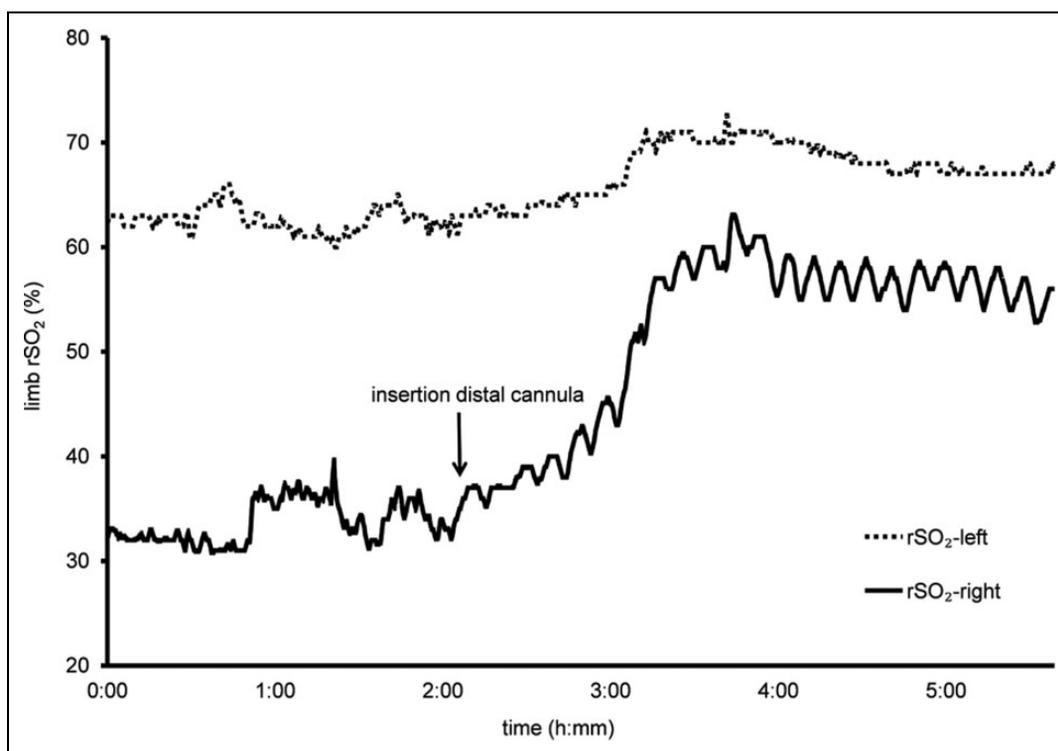


Figure 3. Example of an increase in limb tissue oxygen saturation after restoring blood flow by inserting a distal cannula in the femoral artery. rSO₂, regional tissue oxygen saturation; rSO₂-left, regional tissue oxygen saturation left limb; rSO₂-right, regional tissue oxygen saturation right limb.

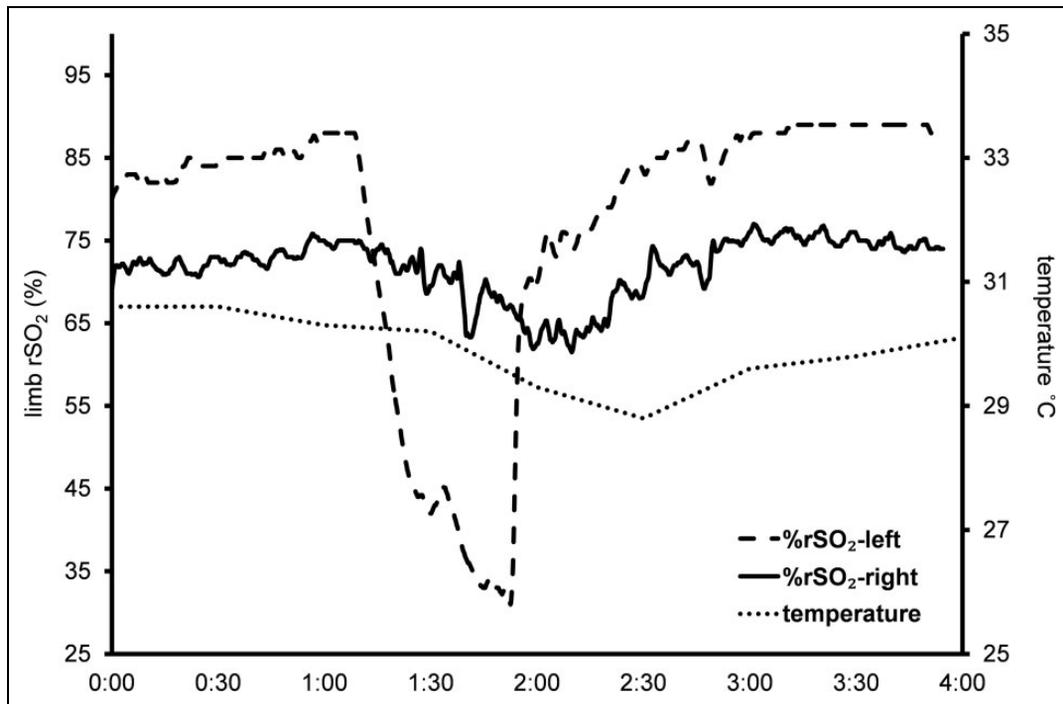


Figure 4. Example of a decrease in limb tissue oximetry values in case of a clotted distal cannula positioned in the left femoral artery. rSO₂ regional tissue oxygen saturation; rSO₂-left, regional tissue oxygen saturation left limb; rSO₂-right, regional tissue oxygen saturation right limb.

Table 3. Effect of Transfusion of PRBC and Fluid Infusion on Mean Bifrontal Cerebral Tissue Oxygen Saturation.^a

	Pre transfusion	Post transfusion	P Value
PRBC (n=13)	60 ± 13	60 ± 13	0.686
Infusion <1000 mL fluids (n=11)	62 ± 13	63 ± 13	0.102
Infusion >1000 mL fluids (n=10)	60 ± 15	70 ± 10	0<0.001

Abbreviation: PRBC, packed red blood cells.

^aFluid infusion concerns Ringer lactate or Gelofusin. Data are presented as mean ± standard deviation.

hemodynamic instability in VA-ECLS patients, contributing to early detection of impaired cerebral perfusion.

Femoro-femoral cannulation is a common access technique for VA-ECLS procedures.²¹ A consequence of this cannulation method specifically is the development of so-called “differential hypoxia” or “isolated hypoxia” in the upper body.^{22,23} The phenomenon of differential hypoxia can be explained as follows: during full ECLS, the right heart is fully unloaded, the resultant lung circulation is minimal, and mechanical lung ventilation is reduced accordingly. If under these circumstances an increase in cardiac output occurs due to, for example, cardiac recovery, blood ejected by the left ventricle remains hypoxic as a result of the reduced ventilatory settings. Blood pumped by the ECLS system via the arterial femoral cannula retrograde into the aorta is fully saturated with oxygen and encounters the desaturated blood ejected by the left

ventricle. When both blood flows meet in the near descending aorta, hypoxic blood will flow through the cervical arteries, whereas fully saturated blood will be diverted to, for example, the left subclavian artery. Subsequently, the brain suffers from an inadequate oxygen delivery, reflected by lowered cerebral rSO₂.^{9,22,23} One may assume that the phenomenon of differential hypoxia occurred in eight of our patients in whom a presumably sudden increase in cardiac output occurred without timely adjustment of mechanical lung ventilation settings (Table 3). In line with this hypothesis, a significant decrease in cerebral rSO₂ and right radial artery PO₂ values were found, while pulse oximetry values (measured at the left index finger) remained unaffected. However, due to the retrospective nature of this study, this could not be confirmed by echocardiographic imaging. Nonetheless, these results suggest that cerebral oximetry enables early identification of differential hypoxia in patients on ECLS. When cardiac recovery is confirmed and a patient becomes candidate for weaning from ECLS, immediate adjustment of mechanical lung ventilation is warranted to prevent differential hypoxia and minimize the risk of neurological complications resulting from cerebral desaturation. The current results indicate that increased lung perfusion without accompanying adapting ventilator settings might be detected by careful (multimodal) monitoring with tissue oximetry. After multidisciplinary discussion, additional treatments might be planned such as fluid unloading or inotropic support to further improve myocardial and lung recovery. In addition, an observed decrease in rSO₂ may indicate an increased oxygen extraction and thereby a relative decrease in cerebral perfusion, increasing the risk of poor neurologic outcome.²⁴ Future

studies should therefore focus on neurological outcome of patients weaning from VA-ECLS.

The number of desaturation episodes did not differ between patients with or without a diagnosis of neurologic complications. Although this finding might seem contradictory, one must take into account that the evidence for a causal relationship between cerebral oximetry derived measurement values and neurologic outcome is still lacking.²⁵ Obviously, the development of neurologic complications is a very complex process and not in all cases reflected by clear reduction in rSO₂ values. One explanation can be found in the fact that the cerebral autoregulatory activity is not considered when measuring regional rSO₂. In the case of cerebral hyperperfusion, for example, cerebral rSO₂ values may appear normal while the intrinsic neuroprotective mechanism of cerebral autoregulation is severely affected, predisposing the patient to an increased risk of neurologic complications.

Moreover, patients on VA-ECLS are subject to complex physiologic interactions including a whole-body inflammatory response, translating into high morbidity and mortality rates. This, in combination with the limitations inherent to the measurement technique of tissue oximetry using NIRS may be part of the explanation why a clear link between rSO₂ and clinical outcomes could not be established. Nevertheless, the results clearly indicate that cerebral tissue oximetry adequately reflects episodes of hemodynamic instability which is also a known factor contributing to postoperative morbidity and mortality.

A possible adverse effect of femoral cannulation is inadequate perfusion of the cannulated limb caused by occlusion of the femoral artery cannula. The limited antegrade flow in the distal artery is exacerbated due to the delayed use of a distal artery perfusion cannula.²⁶ This may result in lower extremity ischemia, fasciotomy, or even limb amputation.²⁷ In the current practice, capillary refill as well as temperature and color of the limb are systematically evaluated for detection of ischemia. Changes in these parameters, however, are subjective with a possible risk of delayed intervention in the case of circulatory compromise. The current study showed that limb rSO₂ adequately reflected distal cannula clotting as well as restoration of blood flow (Figure 4). Hence, tissue oximetry aids in early recognition of compromised limb perfusion and contributes to timely intervention by identifying the need for an additional distal cannula. This exemplification underlines the clinical benefit of using noninvasive tissue oximetry in patients assisted by VA-ECLS.

Packed red blood cell transfusion increases the oxygen content and improves tissue oxygen saturation.²⁸ Based on the fact that tissue oximetry enables rapid evaluation of tissue oxygenation, one can expect that transfusion of PRBCs result in an immediate increase in rSO₂ values.²⁸⁻³⁰ However, our data did not support this hypothesis. A possible explanation can be found in the critical hemodynamic conditions of our patients who received PRBC transfusion, since twelve patients had severe bleeding. In this case, transfusion of PRBCs may have compensated for the decrease in cardiac output due to blood

loss, resulting in a restored cardiac output and thereby preserving bi-frontal cerebral rSO₂ (Table 3). Another explanation for the lack of an increase in cerebral rSO₂ following PRBC transfusion can be found in the use of vasopressors, considering a study by Brassard et al. showing a decreased cerebral rSO₂ due to phenylephrine administration.³⁰ Nine of our patients received a relatively high dose of norepinephrine (1.94 µg/kg/min at maximum) that could have led to a decrease in cerebral rSO₂, masking the effect of PRBC transfusion on rSO₂ readings. The study of Brassard et al., in contrast, included young (26 [7] years) and healthy subjects. Our patients had co-morbidities including Q-fever, liver ischemia, pulmonary emboli, and an adenine nucleotide transporter deficiency. In addition, three patients in whom rSO₂ was unaffected by PRBC transfusion were diagnosed with either endocarditis or pericarditis. The limited effect of PRBC transfusion in infected patients has been described by Creteur et al. who attributed this effect to diminished microcirculation.³¹ Therefore, it remains debatable whether tissue oximetry is appropriate for assessing the effects of PRBC transfusion on tissue oxygenation in patients assisted by VA-ECLS. On the other hand, when fluid suppletion exceeded 1000 mL/h, cerebral rSO₂ did increase, which was most likely due to a concomitant increase in cardiac output together with timely adjustment of the ventilator settings.

One study limitation that needs to be considered when interpreting the current study results is the relatively small sample size. Despite this fact, the authors were able to show alterations in cerebral and limb rSO₂ as a reflection of changes in several patient-related factors including hemodynamic stability and limb perfusion. In addition, due to the retrospective design of the study, it was not possible to include data regarding blood flow in distal perfusion cannulae and hemoglobin.

In conclusion, non-invasive tissue oximetry is a viable monitoring method for assessing cerebral and distal limb tissue perfusion in patients assisted by ECLS and should therefore be part of routine monitoring.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Avgerinos DV, DeBois W, Voevidko L, Salemi A. Regional variation in arterial saturation and oxygen delivery during venoarterial extracorporeal membrane oxygenation. *J Extra Corpor Technol.* 2013;45(3):183-186.
2. Foley PJ, Morris RJ, Woo EY, et al. Limb ischemia during femoral cannulation for cardiopulmonary support. *J Vasc Surg.* 2010;52(4):850-853.
3. Gander JW, Fisher JC, Reichstein AR, et al. Limb ischemia after common femoral artery cannulation for venoarterial

- extracorporeal membrane oxygenation: an unresolved problem. *J Pediatr Surg*. 2010;45(11):2136-2140.
4. Choi JH, Kim SW, Kim YU, et al. Application of veno-arterial-venous extracorporeal membrane oxygenation in differential hypoxia. *Multidiscip Respir Med*. 2014;9(1):55.
 5. Murkin JM, Arango M. Near-infrared spectroscopy as an index of brain and tissue oxygenation. *Br J Anaesth*. 2009;103(suppl 1):i3-i13.
 6. Cole AL, Herman RA Jr, Heimlich JB, Ahsan S, Freedman BA, Shuler MS. Ability of near infrared spectroscopy to measure oxygenation in isolated upper extremity muscle compartments. *J Hand Surg Am*. 2012;37(2):297-302.
 7. Olsson C, Thelin S. Regional cerebral saturation monitoring with near-infrared spectroscopy during selective antegrade cerebral perfusion: diagnostic performance and relationship to postoperative stroke. *J Thorac Cardiovasc Surg*. 2006;131(2):371-379.
 8. Ejike JC, Schenkman KA, Seidel K, Ramamoorthy C, Roberts JS. Cerebral oxygenation in neonatal and pediatric patients during veno-arterial extracorporeal life support. *Pediatr Crit Care Med*. 2006;7(2):154-158.
 9. Tyree K, Tyree M, DiGeronimo R. Correlation of brain tissue oxygen tension with cerebral near-infrared spectroscopy and mixed venous oxygen saturation during extracorporeal membrane oxygenation. *Perfusion*. 2009;24(5):325-331.
 10. Caicedo A, Papademetriou MD, Elwell CE, et al. Canonical correlation analysis in the study of cerebral and peripheral haemodynamics interrelations with systemic variables in neonates supported on ECMO. *Adv Exp Med Biol*. 2013;765:23-29.
 11. van Meurs K, Lally K, Peek G, Zwischenberger J. *ECMO: Extracorporeal Cardiopulmonary Support in Critical Care*. 3rd ed. Ann Arbor, MI: Extracorporeal Life Support Organization; 2007.
 12. Miller CE, Thompson S, Lozar J. A theoretical evaluation of cardiac output as a function of mean arterial pressure in the human cardiovascular system. *J Theor Biol*. 1976;63(1):89-98.
 13. Hoffman GM, Ghanayem NS, Tweddell JS. Noninvasive assessment of cardiac output. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu*. 2005:12-21.
 14. Mariscalco G, Klersy C, Zanobini M, et al. Atrial fibrillation after isolated coronary surgery affects late survival. *Circulation*. 2008;118(16):1612-1618.
 15. Mathew JP, Fontes ML, Tudor IC, et al. A multicenter risk index for atrial fibrillation after cardiac surgery. *JAMA*. 2004;291(14):1720-1729.
 16. Ganushchak YM, Fransen EJ, Visser C, De Jong DS, Maessen JG. Neurological complications after coronary artery bypass grafting related to the performance of cardiopulmonary bypass. *Chest*. 2004;125(6):2196-2205.
 17. Wutzler A, Nee J, Boldt LH, et al. Improvement of cerebral oxygen saturation after successful electrical cardioversion of atrial fibrillation. *Europace*. 2014;16(2):189-194.
 18. Madsen PL, Nielsen HB, Christiansen P. Well-being and cerebral oxygen saturation during acute heart failure in humans. *Clin Physiol*. 2000;20(2):158-164.
 19. Koike A, Itoh H, Oohara R, et al. Cerebral oxygenation during exercise in cardiac patients. *Chest*. 2004;125(1):182-190.
 20. Dong YX, Madhavan M, Wu JH, et al. Acute effects of atrial fibrillation on atrial and ventricular function: a simultaneous invasive-echocardiographic hemodynamic study. *Int J Cardiol*. 2013;169(6):e114-e119.
 21. Spurlock DJ, Toomasian JM, Romano MA, Cooley E, Bartlett RH, Haft JW. A simple technique to prevent limb ischemia during veno-arterial ECMO using the femoral artery: the posterior tibial approach. *Perfusion*. 2012;27(2):141-145.
 22. Kitamura M, Shibuya M, Kurihara H, Akimoto T, Endo M, Koyanagi H. Effective cross-circulation technique of venoarterial bypass for differential hypoxia condition. *Artif Organs*. 1997;21(7):786-788.
 23. Angleitner P RM, Laufer G, Wiedermann D. Watershed of veno-arterial extracorporeal life support. *Eur J Cardiothorac Surg*. 2016;50(4):785.
 24. Buckley E, Sidebotham D, McGeorge A, Roberts S, Allen SJ, Beca J. Extracorporeal membrane oxygenation for cardiorespiratory failure in four patients with pandemic H1N1 2009 influenza virus and secondary bacterial infection. *Br J Anaesth*. 2010;104(3):326-329.
 25. Zheng F, Sheinberg R, Yee MS, Ono M, Zheng Y, Hogue CW. Cerebral near-infrared spectroscopy monitoring and neurologic outcomes in adult cardiac surgery patients: a systematic review. *Anesth Analg*. 2013;116(3):663-676.
 26. 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*. 2012;36(8):659-667.
 27. Roberson RS, Bennett-Guerrero E. Impact of red blood cell transfusion on global and regional measures of oxygen. *Mt Sinai J Med*. 2012;79(1):66-74.
 28. Sandal G, Oguz SS, Erdeve O, Akar M, Uras N, Dilmen U. Assessment of red blood cell transfusion and transfusion duration on cerebral and mesenteric oxygenation using near-infrared spectroscopy in preterm infants with symptomatic anemia. *Transfusion*. 2014;54(4):1100-1105.
 29. Seidel D, Blaser A, Gebauer C, Pulzer F, Thome U, Knupfer M. Changes in regional tissue oxygenation saturation and desaturations after red blood cell transfusion in preterm infants. *J Perinatol*. 2013;33(4):282-287.
 30. Brassard P, Seifert T, Wissenberg M, Jensen PM, Hansen CK, Secher NH. Phenylephrine decreases frontal lobe oxygenation at rest but not during moderately intense exercise. *J Appl Physiol*. 2010;108(6):1472-1478.
 31. Creteur J, Neves AP, Vincent JL. Near-infrared spectroscopy technique to evaluate the effects of red blood cell transfusion on tissue oxygenation. *Crit Care*. 2009;13(suppl 5):S11.