Optimization of extracorporeal membrane oxygenation therapy using near-infrared spectroscopy to assess changes in peripheral circulation: A pilot study

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Abstract
Near-infrared spectroscopy (NIRS) has been proposed as a noninvasive modality for detecting complications in patients undergoing extracorporeal membrane oxygenation (ECMO), and it can simultaneously reveal the global circulatory status of these patients. We optimized ECMO therapy on the basis of real-time peripheral NIRS probing. Three patients underwent venoarterial (VA) ECMO and one patient underwent venovenous (VV) ECMO. All patients received peripheral ECMO cannulation with routine distal perfusion catheter placement. We designed an experimental protocol to adjust ECMO blood flow over 1 hour. Hemodynamic responses were measured using NIRS devices attached to the calf at approximately 60% of the distance from the ankle to the knee. HbO₂ levels change substantially with adjustments in ECMO flow, and they are more sensitive than HHb levels and the tissue saturation index (TSI) are. NIRS for optimizing ECMO therapy may be reliable for monitoring global circulatory status.

KEYWORDS
extracorporeal membrane oxygenation, near-infrared spectroscopy, oxyhemoglobin, peripheral circulation, vasoactive medicine

1 | INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) is frequently used for critically ill patients as an advanced cardiopulmonary support to stabilize hemodynamic status and respiratory failure [1–3]. It provides survival benefits even for patients receiving cardiopulmonary resuscitation (CPR) with acceptable outcomes [4]. Although the care and outcomes of patients receiving ECMO have substantially improved over the past four decades, many problems remain unsolved. For instance, severe and life-threatening complications remain a major concern.
Meta-analyses have revealed that pooled estimated complications can reach 13.3% for neurologic complications, 5.9% for stroke, 46.0% for renal replacement therapy, and 30.4% for significant infection [5, 6]. Prolonged intensive care unit (ICU) and hospital stays are common among patients undergoing ECMO, and the technique’s costs and efficacy are other major concerns [3, 7].

Researchers have attempted to predict the success or mortality rate of patients receiving ECMO by using SAVE, PRESET, or ENCOURAGE scores to enable clinicians to evaluate patient status [8–10]. However, no guidelines or reliable clinical parameters are available for adjusting ECMO treatment in terms of machine settings or even vasoactive or inotropic agents [11]. Therefore, ECMO treatment or adjustment methods for these patients differ by doctor and hospital. We addressed this basic problem by using near-infrared spectroscopy (NIRS) to monitor real-time changes in peripheral tissue oxygenation in patients receiving ECMO. NIRS is a noninvasive and nonradiative method for measuring local oxygen-dependent metabolism based on diffuse optics. In addition, the high temporal resolution of NIRS allows physicians to monitor changes in blood oxygen concentration in real time. By using this new method, we can change ECMO settings with precision. Moreover, we can effectively adjust the doses of vasoactive and inotropic agents. This method may improve treatment for patients, wean them off ECMO more rapidly, reduce complications, and improve outcomes.

2 | METHODS

2.1 | Study population

The Institutional Review Board of Taipei Veterans General Hospital approved this study (TVGHIRB-2019-02-007AC). A prospective pilot study was conducted on adult patients (age > 20 years) undergoing ECMO at Taipei Veterans General Hospital from September 2018 to February 2019. Patients undergoing venoarterial (VA) and venovenous (VV) ECMO were included in this study. The exclusion criteria were as follows: (a) patients receiving ECMO with central cannulation; (b) patients for whom both distal-limb monitoring with NIRS oximetry was unsuitable. Here, we report the preliminary results of three patients receiving VA-ECMO and one receiving VV-ECMO.

2.2 | ECMO cannulation and management

In the VA-ECMO group, a femorofemoral heparin-coated cannula (Medtronic, Minneapolis, Minnesota) was surgically implanted using the cutdown or percutaneous Seldinger technique. Antegrade 8-Fr perfusion catheters (Medtronic, Minneapolis, Minnesota) were routinely placed in the proximal superficial femoral artery to prevent limb ischemia. In the VV-ECMO group, heparin-coated cannulas were implanted percutaneously via the internal jugular and femoral veins, as depicted in Figure 1. The cannulas were connected to the ECMO circuit, which consisted of an oxygenator, heat exchanger, and centrifugal blood pump (Revolution blood pump, Sorin, Milano, Italy) (Rotaflow centrifugal pump, MAQUET, Cardiovascular LLC, Wayne, New Jersey). An anticoagulant with intravenous heparin (5000 units bolus) was administered during ECMO implantation and at a rate of 300 units per hour after ECMO initiation. The heparin dose was adjusted according to a partial thromboplastin time measured every 4 hours, with a goal of 40 to 45 seconds.

FIGURE 1  A, Veno-venous (VV) cannulation of ECMO. B, Veno-arterial (VA) cannulation of ECMO. ECMO, extracorporeal membrane oxygenation.
2.3 | Data collection

2.3.1 | Patient data

Baseline characteristics, indications for ECMO, and duration of ECMO support were retrieved from electronic medical records. The vasoactive–inotropic score (VIS) was calculated as $\text{VIS} = \text{dopamine dose (µg kg}^{-1} \text{min}^{-1}) + \text{dobutamine (µg kg}^{-1} \text{min}^{-1}) + 100 \times \text{epinephrine dose (µg kg}^{-1} \text{min}^{-1}) + 50 \times \text{levosimendan dose (µg kg}^{-1} \text{min}^{-1}) + 10 \times \text{milrinone dose (µg kg}^{-1} \text{min}^{-1}) + 10,000 \times \text{vasopressin (units kg}^{-1} \text{min}^{-1}) + 100 \times \text{norepinephrine dose (µg kg}^{-1} \text{min}^{-1}) \text{when NIRS monitoring was initiated [12]. Postoperative outcomes and complications were classified according to the Extracorporeal Life Support Organization registry definitions, which include vascular complications, neurologic complications, renal injury, bleeding, infection, and additional complications.}

2.3.2 | NIRS recording and analysis

Hemodynamic responses were measured using two PortaLite systems (Artinis, Netherlands), which emit near-infrared rays at two wavelengths (750 and 850 nm) to tissues through optical fibers attached to both calves of the patient at approximately 60% of the tibia length (Figure 2B). The instrument features three pairs of intensity-modulated laser diodes (each pair emits two wavelengths, 750 and 850 nm) and one gain-modulated photomultiplier tube detector that simultaneously uses the modified Beer–Lambert law to measure the relative concentration change of oxyhemoglobin (HbO$_2$, µM min$^{-1}$) and deoxyhemoglobin (HHb, µM min$^{-1}$) in the region of interest. Additionally, we use spatially resolved spectroscopy (SRS) methods to estimate the tissue saturation index (TSI%). The distances between the three pairs of light sources and the detector are 30, 35, and 40 mm, respectively (Figure 2A). All data were obtained using Oxysoft (Artinis, Netherlands) with a sampling rate of 25 Hz. The data were then normalized before additional calculations were performed to develop a common scale for the variables. Subsequently, the mean and SD of the concentrations of HbO$_2$ and HHb and the tissue saturation index (TSI) were obtained.

2.3.3 | Measurement protocol

The PortaLite system continuously monitored each patient for 55 minutes. At initiation, the ECMO flow rate was maintained for 5 minutes to obtain reference values and NIRS signal stability. In case of the VA-ECMO group, the flow rate was reduced by 500 revolutions per minute (rpm) for 10 min and was then returned to the original flow rate for the next 10 min. Subsequently, the flow rate was increased by 500 rpm for 10 min and then by another 500 rpm for the next 10 min. Finally, the flow rate was returned to the original rate for the final 10 min (Figure 2C). In the case of the VV-ECMO group, the adjustment protocol was the same as that for the VA-ECMO group, but adjustments of 300 rpm were made in each step.

3 | RESULTS

3.1 | Case description

The first patient was a 65-year-old man who was found unconscious (duration: 10 min). Coronary angiography

**FIGURE 2** A, Photograph and probe details of the continuous wave NIRS system. B, Measuring position in the lower limb. The blue line represents the length from the knee to the ankle; the orange line represents 60% of the length of the blue line. The probe was placed at the end of the orange line. C, Experimental flowchart. We controlled the speed of the ECMO system and observed hemodynamics during the experiment over six stages. ECMO, extracorporeal membrane oxygenation; NIRS, near-infrared spectroscopy.
indicated coronary artery disease with triple vessel disease. He experienced cardiogenic shock in the catheterization room, and emergency VA-ECMO cannulas were implanted via the right femoral artery and left femoral vein. Subsequently, percutaneous transluminal coronary angiography with a drug-eluting stent was achieved. VA-ECMO speed and pump flow were 2602 rpm and 2.64 L min\(^{-1}\), respectively. Mean arterial pressure was 102 mmHg, and the VIS was 7.18. After transferring the patient back to the ICU, we started our experimental protocol. The patient was weaned smoothly from VA-ECMO 2 days later, and he was discharged after 1 month of rehabilitation.

As shown in Figure 3B, in stage 1, HbO\(_2\) levels increased to +2 \(\mu\)M min\(^{-1}\) in the noncannulation side and +0.2 \(\mu\)M min\(^{-1}\) in the cannulation side. From stages 2 to 4, HbO\(_2\) levels increased from +2 \(\mu\)M min\(^{-1}\) to +4 \(\mu\)M min\(^{-1}\) in the noncannulation side and from +0.5 \(\mu\)M min\(^{-1}\) to +2 \(\mu\)M min\(^{-1}\) in the cannulation side. HbO\(_2\) levels changed considerably as the ECMO pump flow was adjusted. However, changes in HHb levels remained at approximately +1 \(\mu\)M min\(^{-1}\) in the noncannulation side and −1 \(\mu\)M min\(^{-1}\) in the cannulation side. As shown in Figure 3A, the TSI remained at approximately 63% in both sides. HHb level and TSI did not change substantially with adjustments in ECMO pump flow.

### 3.2 VA-ECMO group

A total of three patients were enrolled in this study. The indications for ECMO in each patient were acute myocardial infarction, postcardiotomy, and pulmonary embolism. Of the three patients, two were female, and their mean age was 64 years. Their mean VIS was 7.06, mean pump speed was 2243 rpm L\(^{-1}\), and mean pump flow was 1.89 L min\(^{-1}\) (Supporting Information) (Table A1). All three patients were successfully weaned from VA-ECMO. Two patients were discharged, and only one patient died because of multiorgan failure 1 week later.

As presented in Figure 4, in stage 1, average HbO\(_2\) levels increased to +2 \(\mu\)M min\(^{-1}\) in the noncannulation side and to +1 \(\mu\)M min\(^{-1}\) in the cannulation side. From stages 2 to 4, HbO\(_2\) levels increased from +2 \(\mu\)M min\(^{-1}\) to +4 \(\mu\)M min\(^{-1}\) in the noncannulation side and increased from +1 \(\mu\)M min\(^{-1}\) to +2 \(\mu\)M min\(^{-1}\) in the cannulation side. HbO\(_2\) levels changed considerably as the ECMO pump flow was adjusted. In addition, this phenomenon

**FIGURE 3** A, Hemodynamics of a patient receiving VA-ECMO. B, Average change in HbO\(_2\) concentration (\(\Delta\)HbO\(_2\)). ECMO, extracorporeal membrane oxygenation

**FIGURE 4** Hemodynamics of patients receiving VA-ECMO. ECMO, extracorporeal membrane oxygenation
was more sensitive in the noncannulation side rather than it was in the cannulation side.

3.3 | Patient receiving VV-ECMO on different measurement days

In addition to the VA-ECMO group, NIRS was applied in the VV-ECMO group. We report the first case of NIRS on different measurement days. As shown in Figure 5, a 62-year-old man was admitted to the ICU because of acute respiratory distress syndrome related to influenza A. Severe hypoxia was noted after endotracheal intubation. VV-ECMO cannulas were inserted via the right internal jugular vein and right femoral vein. The pump speed was 1717 rpm $L^{-1}$ and the pump flow was 2.6 $L \text{min}^{-1}$. The patient was weaned from VV-ECMO 11 days later, and he was discharged 1 month after VV-ECMO removal.

On day 1, HbO$_2$ levels did not change in stage 1. However, from stages 2 to 4, HbO$_2$ levels decreased to $-0.4 \mu M \text{min}^{-1}$. On day 3, HbO$_2$ levels also did not change in stage 1. However, from stages 2 to 4, HbO$_2$ levels increased to $+0.7 \mu M \text{min}^{-1}$. On day 7, HbO$_2$ levels increased to $+2 \mu M \text{min}^{-1}$ in stage 1. In addition, from stages 2 to 4, HbO$_2$ levels increased to $+6 \mu M \text{min}^{-1}$(Figure 6). In this case, changes in HbO$_2$ levels differed widely as the ECMO pump flow was adjusted, even under the same experimental protocol.

4 | DISCUSSION

Measurements of HbO$_2$ level, HHb level, and TSI in the lower limbs through NIRS were analyzed to optimize ECMO therapy in this study. The preliminary results revealed a strong correlation between NIRS values and global circulatory status in patients undergoing ECMO. First, HbO$_2$ levels changed substantially as ECMO blood flow was adjusted, whereas HHb levels and TSI did not change as obviously as HbO$_2$ levels did. This phenomenon was more sensitive in the noncannulation side than in the cannulation side. Second, HbO$_2$ changes as ECMO blood flow is adjusted are probably entirely different in a

![FIGURE 5](image_url)  Hemodynamic changes in the patient receiving VV-ECMO on different measurement days. A, Day 1; B, Day 1 + 2; C, Day 1 + 6. ECMO, extracorporeal membrane oxygenation

![FIGURE 6](image_url)  Average change in HbO$_2$ concentration in the patient receiving VV-ECMO on different measurement days. A, Day 1; B, Day 1 + 2; C, Day 1 + 6. ECMO, extracorporeal membrane oxygenation
patient on different measurement days under the same experimental protocol.

NIRS has been proposed as a real-time noninvasive system for monitoring regional microcirculation and is based on different absorption and scattering coefficients of more than two wavelengths. Our study published in 2012 revealed a linear correlation in oxygenation dynamic signals between NIRS and an arterial occlusion test [13], implying that NIRS can be a tool for clinical diagnosis. We published a study comparing 44 healthy participants with 35 patients with sepsis in an ICU. HbO2 levels increased continually in healthy participants but plateaued after only 5 min in patients with sepsis [14]. In Australia, Stephen and colleagues [15] used NIRS to predict organ failure and outcomes in 323 patients with sepsis in an emergency department. NIRS devices are becoming crucial diagnostic tools in critically ill patients.

NIRS devices have been used to detect ECMO complications. Wong et al. [16] argued that NIRS with ECMO is crucial for detecting cerebral and peripheral ischemia. The authors analyzed 20 patients, all of which had significant decreases in bilateral cerebral oximetry tracings that resulted in them requiring hemodynamic interventions. Six patients had unilateral lower-limb oximetry events that resolved upon distal perfusion cannula replacement. Pozzebon et al. [17] studied 56 patients receiving ECMO who were monitored with a cerebral frontal NIRS device. Patients with acute cerebral complications were associated with cerebral desaturation (94% vs 68%), and they more frequently had high right–left saturation differences (33% vs. 8%). Lamb et al. [18] demonstrated the benefits of continual monitoring by using NIRS to identify limb ischemia in patients undergoing ECMO with or without a distal perfusion cannula. In addition to interest in complication detection, interest in NIRS monitoring of global circulatory status is increasing. In a retrospective study of 12 patients experiencing cardiogenic shock and undergoing VA-ECMO [19], both cerebral and peripheral regional oxygen saturations were significantly correlated with the total circulatory index, systemic vascular resistance index, and mean arterial pressure. However, commercial devices can monitor TSI. Porta Lite systems were used in the current study to monitor HbO2 and HHb levels to optimize ECMO therapy.

Although our preliminary results involve only three patients undergoing VA-ECMO, we demonstrated that HbO2 levels change substantially as the ECMO pump flow is adjusted. HbO2 levels be used as a sensitive value for detecting global circulatory status in patients undergoing VA-ECMO. After we reduced ECMO blood flow to 500 rpm (stage 1), HbO2 levels increased in the non-cannulation side but were fair in the cannulation side. After we increased ECMO blood flow from 500 rpm to 1000 rpm (stages 3 and 4), HbO2 levels appeared to plateau in both the noncannulation and cannulation sides. All three patients undergoing VA-ECMO were weaned from the machine. We hypothesized that the patients were not strongly dependent on the ECMO machine on the experimental day. Therefore, HbO2 levels increased even though ECMO blood flow decreased. Moreover, tissue oxygenation demand was reached during stage 3; therefore, HbO2 levels plateaued in stage 4 even as we provided more oxygenated blood to the circulation system.

Based on these preliminary results, we conducted the same experimental protocol on different measurement days in a patient undergoing VV-ECMO. We consider that the initial change in this group was not so obvious. However, the data changed as the patient’s clinical condition improved. On the first day of VV-ECMO, HbO2 levels plateaued even as blood flow increased to 600 rpm. From days 3 to 7, the HbO2 level increased considerably as ECMO blood flow increased. The increase in oxygenated blood that was detected in peripheral NIRS indicated that peripheral tissue had large oxygenation absorption.

5 | LIMITATIONS

The current pilot study had several limitations. First, only three patients receiving VA-ECMO and one patient receiving VV-ECMO were enrolled. More patients should be monitored to determine whether outcomes can be predicted and how ECMO blood flow should be adjusted. Second, in the VA-ECMO group, we did not evaluate the same patients on different days. Third, HbO2 level is a relative value, whereas TSI is an absolute level. Defining meaningful changes in these values requires more experiments. Fourth, the measured blood oxygen changes can be caused by the change in metabolism or blood perfusion. However, in this study, all the measurement periods were completed in 1 hour. Therefore, we would say the change of blood oxygenation mainly affected by the change of ECMO blood flow rather than by the change in metabolism. Finally, indications for ECMO, cardiac index, and systemic vascular resistance index differed completely in each case; therefore, more data are required to evaluate the correlations among these hemodynamic parameters.

6 | CONCLUSION

NIRS to optimize ECMO therapy may enable the reliable monitoring of global circulatory status. Our preliminary results demonstrated that HbO2 level changes
considerably as ECMO blood flow is adjusted, and it is more sensitive than HHb level and TSI are. In addition, measurements in the noncannulation side are more precise than those in the cannulation side. Further research should be conducted to evaluate the same patient on different days with the aim of precisely adjusting ECMO blood flow and rapidly wean patients from the machine.

CONFLICT OF INTEREST
The authors have no conflict of interest to declare.

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| No. | Indication for ECMO | Mode | Age | Gender | Final outcome | BMI  | BSA  | VIS  | Pump speed (rpm) | Pump flow (L min⁻¹) | ECMO FiO₂ (%) | Gas flow (L min⁻¹) |
|-----|---------------------|------|-----|--------|---------------|------|------|------|------------------|---------------------|---------------|-------------------|
| 1   | AMI                 | VA   | 65  | M      | Discharge     | 27.327 | 1.846 | 7.18 | 2602             | 2.64                 | 100           | 3                 |
| 2   | Post-Cardiotomy     | VA   | 54  | F      | Discharge     | 19.471 | 1.415 | 11   | 1562             | 1.61                 | 100           | 0.96              |
| 3   | Others              | VA   | 73  | F      | Weaning (Mortality) | 18.984 | 1.414 | 3    | 2565             | 1.42                 | 20            | 4                 |
| 4   | ARDS                | VV   | 62  | M      | Discharge     | 25.584 | 1.803 | —    | 1676             | 2.63                 | 70            | 2                 |

25.947  1.815  —  1717  2.55  100  2
22.681  1.697  —  1657  2.6  80  2