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Predictive value of microcirculation for pediatric extracorporeal membrane oxygenation weaning test: A monocentric prospective observational study

Violette Suc¹  | Julie Starck¹ | Yael Levy^{1,2} | Yohan Soreze^{1,2} |
Jerome Rambaud^{1,2} | Pierre-Louis Léger^{1,2}

¹Neonatal and Pediatric Intensive Care Unit, Trousseau Hospital, AP-HP, Paris, France

²Medicine Department, Sorbonne University, Paris, France

Correspondence

Violette Suc, Neonatal and Pediatric intensive care unit, Trousseau Hospital, AP-HP, Paris, France.

Email: violette.suc@gmail.com

Abstract

Background: Extracorporeal membrane oxygenation (ECMO) is widely used for children treated for refractory respiratory failures or refractory cardiogenic shock. Its duration depends on organ functions recovery. Weaning is decided using macro-circulatory tools, but microcirculation is not well evaluated. Sidestream dark-field video imaging is used to assess the perfusion of the sublingual microvascular vessels. The aim of this study was to assess the predictive value of microcirculatory indices in ECMO weaning.

Methods: This prospective monocentric study examined pediatric patients at Trousseau Hospital between March 2017 and December 2020. The study included all patients from 35 weeks of gestational age to 18 years old who were treated with ECMO. Children were divided into two groups: one with stability after weaning and the other with instability after weaning. We collected clinical and biological data, ventilation parameters, extracorporeal membrane oxygenation parameters, and drugs used at admission and after the weaning test. Microcirculations videos were taken after weaning trials with echocardiography and blood gas monitoring.

Results: The study included 30 patients with a median age of 29 days (range: 1–770 days) at admission, including 18 patients who received venoarterial ECMO (60%). There were 19 children in the stability group and 11 in the instability group. Macrocirculatory and microcirculatory indices showed no differences between groups. The microvascular flow index was subnormal in both groups (2.3 (1.8–2.4) and 2.3 (2.3–2.6), respectively; $p = 0.24$). The microvascular indices were similar between cases of venovenous and venoarterial ECMO and between age groups.

Conclusion: Microcirculation monitoring at the weaning phase did not predict the failure of ECMO weaning.

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**KEYWORDS**

extracorporeal membrane oxygenation, microcirculation, pediatric intensive care unit, sidestream dark field, weaning

1 | INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) is used in neonatal and pediatric cases of refractory respiratory or hemodynamic failures. The mortality risk increases with the duration of ECMO due to complications such as bleeding, ischemic events, infections, or neurological complications.¹ Weaning from ECMO is a critical step during patient care, and the decision for weaning requires daily tests. Pediatric weaning protocols are based on both macrocirculatory functions (heart rate, arterial pressure, and cardiac output) and organ functions (urine output, lactatemia, and skin perfusion).

The microcirculation is composed of micro-vessels with diameters of 5 to 20 micrometers, which allow tissue perfusion and oxygenation in each organ.² Devices are available to assess microcirculation perfusion at the bedside using sidestream dark field and orthogonal polarization imaging. The microcirculation is altered during the early stages of sepsis or septic shock in those who do not survive.³ Dysregulation of microvascular flow also correlates with severe organ dysfunction.⁴⁻⁷ Top et al. have also shown that persistent microcirculatory alterations are associated with unfavorable prognostic factors for survival among children with septic shock.⁸

The microcirculation improves during the first 24 h after an ECMO cannulation⁹⁻¹¹ and after weaning ECMO.¹² To our knowledge, there are no data on microcirculation and ECMO weaning in a pediatric population. Thus, the aim of this study was to determine whether the microcirculation perfusion indices can predict the risk of instability after weaning in pediatric ECMO patients.

2 | METHODS

2.1 | Population settings

We performed this prospective observational study at the Pediatric Intensive Care Unit (PICU) of Armand Trousseau Hospital in Paris between March 2017 and December 2020. This study was conducted in accordance with the STROBE guidelines. The study included all patients from 35 weeks of gestational age to 18 years old who were treated with venoarterial ECMO (VA-ECMO) for refractory shocks or venovenous ECMO (VV-ECMO) for refractory respiratory disease in the ECMO weaning

phase. The exclusion criteria were palliative care or parent opposition.

The study was approved by the SRLF ethics committee (April 27, 2021, reference CE SRLF 21-35). Procedures were performed in accordance with the ethical standards of the SRLF committee and the Declaration of Helsinki of 1975. In accordance with our clinical research center, our study followed the criteria of a non-interventional routine-care study and did not have to be declared on clinical trial. An information letter was given to the parents, and biological and clinical data were collected from medical files and the ECMO database (n° 2121127v0) of Trousseau Hospital. Registration to APHP data manager made with the number 20210413140736.

2.2 | Study design

Two groups were defined in the study protocol. The first group comprised patients with instability after weaning who required re-initiation of ECMO within 24 h after ECMO clamping or hemodynamic failure. This was based on at least one of the follow criteria after ECMO clamping: introduction or an increase of vasopressive drugs, cardiac dysfunction requiring introduction or an increase of inotropic drugs, increased arterial pulmonary hypertension requiring an increase in the level of vasodilator drugs, increased ventilation parameters (peak inspiratory pressure > 28–30 cm H₂O), severe hypoxemia (SpO₂ < 94% with FiO₂ > 75%) or severe hypercapnic acidosis (pH < 7.30). The second group comprised patients with stability after weaning who did not present any of these criteria.

The weaning protocol was standardized for patients who received VA-ECMO and VV-ECMO (Supporting information Appendix 1). We performed a 1-h weaning test based on our department protocol. Microcirculation was always assessed by the same physician at the same time in the 1-h weaning test. The test was performed in sublingual regions of interest using a Microscan® device (Microvision Medical, Amsterdam, Netherland) with sidestream dark-field (SDF) technology (Supplemental Files 1 and 2). Four sublingual regions were examined for each patient with a duration of 30 s.

If the quality criteria were not reached according to the consensus on the assessment of sublingual microcirculation,² videos were excluded from the analysis. The ECMO weaning was performed with blinding from the results of the microcirculatory tests. The video analysis was carried out a posteriori.

2.3 | Data collection

Data were collected on age, weight, sex, medical background, etiology of PICU admission, severity score (PELOD for children and SNAPPE II for newborns), ventilation parameters (peak pressure, plateau pressure, median pressure, positive end expiratory pressure, respiratory rate, and FiO_2), ECMO parameters (ECMO flow, sweep gas flow, and FiO_2), routine biological and clinical data, hemodynamic parameters, echocardiography parameters, length of stay in the ICU, and mortality rate. The weaning test chosen for analysis was the first positive one.

A second investigator who was blinded to the patient conditions analyzed the microcirculation videos using the semi-automated software AVA3[®] (Automated Vascular Analysis, Microvision Medical, Amsterdam, Pays Bas). Several scores and indices were used to describe the microvascular flow. The De Backer score is a grid-based score based on 3 horizontal and vertical equidistant lines and the total number of vessel crossings per grid length. The total vessel density (TVD) is obtained through software-supported measurement of the total vessel area per surface area. The microvascular flow index (MFI) is a grid-based score per quadrant where 0 indicates no flow, 1 indicates intermittent flow, 2 indicates sluggish flow, 3 indicates continuous flow, and 4 indicates very high continuous flow.

2.4 | Statistical analysis

Statistical analysis was performed using PRISM software. The means of each microcirculation parameter (four regions) were calculated. Continuous data are presented as the median and interquartile range, and categorical data

are presented as frequencies and percentages. Fisher tests were used for the qualitative variables, and the Mann-Whitney-Wilcoxon test was used for quantitative variables. The level of significance was set at $p < 0.05$.

3 | RESULTS

During the study period, there were 2805 admissions to the PICU, of which 165 patients (5%) were supported with ECMO. The study included 34 patients on ECMO (20%) with available microcirculatory and microcirculatory indexes (Figure 1 shows the initial flowchart). Four patients were excluded because of poor video quality. Table 1 shows the general demographic data of the population. There were 13 newborn patients (43%) and 17 infants (57%), and the median age was 29 days (1–770 days).

The median PELOD score and SNAPPE II score for newborns at admission were 13.2 (3.8–29.3) and 50 (43–63), respectively. There were 18 patients who were put on VA-ECMO and 12 patients on VV-ECMO. The median length of ECMO was 8 (5–13) days. The survival rate was 80%, and six patients did not survive during the study period, who were all on VA-ECMO (with lung development anomaly, atypical pulmonary dysplasia, congenital diaphragmatic hernia, infectious lung disease, or hemodynamic failure). There were 19 patients who reached the criteria for stability after weaning group and 11 patients with instability after weaning.

No significant difference was identified between the groups in terms of demographic, clinical, and biological data. The median SNAPPE II score at admission was significantly higher in the instability group (63 (50–89) versus 34 (14–50), $p = 0.015$). Table 2 shows the initial hospitalization patterns.

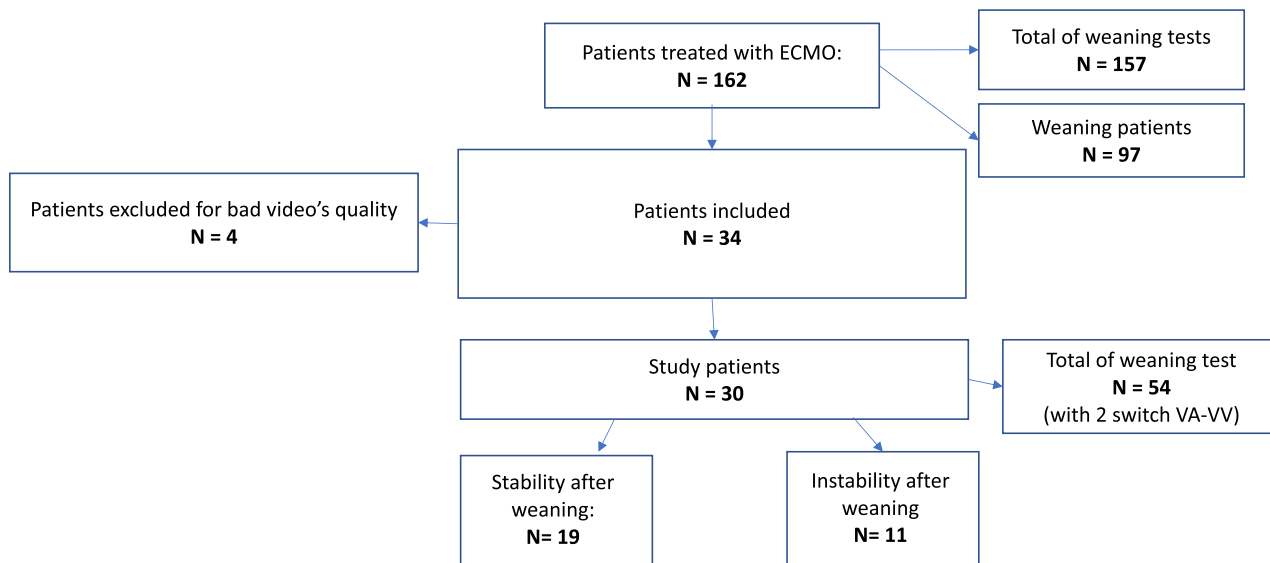


FIGURE 1 Flowchart.



TABLE 1 Patients' general characteristics.

| General characteristics | Total | Stability after weaning | Instability after weaning | p-value |
|---|-----------------|-------------------------|---------------------------|-------------------------------------|
| Patients <i>n</i> | 30 | 19 | 11 | |
| Males <i>n</i> (%) | 15 (50%) | 9 (47%) | 6 (54%) | OR 1.14 [0.26–4.8] <i>p</i> = 1 |
| Age (d) | 29 [1–770] | 48 [1–858] | 6 [1–231] | 0.87 |
| Neonates <i>n</i> (%) | 13 (43%) | 7 (37%) | 6 (54%) | OR 1.46 [0.31–6.68] <i>p</i> = 0.73 |
| Weight (kg) | 4 [3.3–11] | 5.2 [3.1–12] | 3.3 [3.5–4.4] | 0.53 |
| PELOD | 20.8 [10–26.1] | 20.8 [10–20.8] | 23.5 [0.7–44] | 0.8 |
| SNAPPE II | 50 [43–63] | 63 [50–89] | 34 [14–50] | 0.015* |
| Type ECMO, <i>n</i> (%) | | | | |
| Venoarterial-ECMO | 18 (60%) | 10 | 8 | OR 1.3 [0.35–5.3] <i>p</i> = 0.7 |
| Venovenous-ECMO | 12 (40%) | 9 | 3 | OR 0.5 [0.08–3] <i>p</i> = 0.7 |
| Hemodynamic Support at PICU admission | | | | |
| Norepinephrine | 25 (83%) | 16 (84%) | 8 (72%) | OR 1.9 [0.21–18] <i>p</i> = 0.6 |
| Milrinone | 3 (10%) | 2 (10%) | 1 (9%) | OR 1.17 [0.05–76] <i>p</i> = 1 |
| Prostacycline | 5 (16%) | 4 (21%) | 1 (9%) | OR 2.5 [0.2–144] <i>p</i> = 0.6 |
| VIS score | 80 [35–141] | 85 [40–135] | 100 [40–166] | 0.7 |
| Biological parameters at PICU admission | | | | |
| CRP (mg/L) | 27 [13–102] | 24 [14–126] | 44 [8–93] | 0.57 |
| Hemoglobin (g/dL) | 11 [10–14] | 11 [9.5–13.5] | 11 [10.3–15.3] | 0.39 |
| Leukocyte (G/L) | 13.9 [8.8–23.9] | 15.9 [11.3–31] | 14.6 [9.2–24] | 0.05 |
| Platelet (G/L) | 187 [135–297] | 173.5 [135.7–297] | 194 [158–261.5] | 1 |
| TP (%) | 64 [45.7–77.5] | 64 [45.7–77.5] | 61 [42–82] | 0.7 |
| Creatinine (μmol/L) | 41.5 [30–66] | 37 [30–60] | 64 [29–69] | 0.71 |
| PaCO ₂ mm Hg | 60 [47–73] | 65 [56–77] | 55 [38–63] | 0.09 |
| PaO ₂ mm Hg | 47 [37.5–68] | 49 [36–65] | 45 [40–67] | 0.96 |
| pH | 7.10 [7–7.28] | 7.1 [7–7.2] | 7.2 [7.1–7.26] | 0.7 |
| SpO ₂ /FiO ₂ | 85 [70–97] | 92 [77–100] | 73 [50–85] | 0.014* |
| Oxygenation index | 37 [31–47] | 37 [32–44] | 37 [31–47] | 0.34 |
| Duration ECMO treatment (d) | 8 [5–13] | 6 [4–15] | 10 [7.5–12] | 0.19 |
| ICU stay (d) | 18 [14.5–32.5] | 20 [14–41] | 20 [15–30] | 0.96 |
| Death <i>n</i> (%) | 6 (20%) | 3 (15%) | 3 (27%) | OR 1.7 [0.19–15] <i>p</i> = 0.65 |

Note: Continuous data are presented as median (Q1–Q3), categorical data as *n* (%).

Abbreviations: CRP, C-reactive protein; ECMO, extracorporeal membrane oxygenation; PaCO₂, CO₂ arterial pressure; PaO₂, O₂ arterial pressure; ELOD score, pediatric logistic organ dysfunction; SNAPPE II, score for neonatal acute physiology; Score TP, thrombin time; VIS, vasoactive-inotropic score.

*Statistically significant value.

3.1 | Microcirculatory parameters

We did not find any significant differences in macrocirculatory parameters between groups (Table 3). All children were assessed for microcirculation parameters during the weaning trial (Table 4). There was no significant difference in the De Backer score, TVD, and MFI. The MFI in both groups was high with a median of 2.3 in small vessels. The MFI was higher in the instability group than the stability group, but the difference was not significant (2.6 (2.4–2.7) versus 2.4 (2.3–2.7), *p* = 0.14).

Table 5 shows the microcirculatory parameters according to the ECMO modality, age, and survival. None of the microcirculatory parameters showed significant differences between groups.

4 | DISCUSSION

Our study evaluated the predictive value of sublingual microcirculation during ECMO weaning trials in neonates and infants for the first time. The MFIs acquired in the

weaning period did not predict hemodynamic stability after weaning off ECMO. Moreover, the microcirculation parameters did not correlate with the ECMO modalities (VA-ECMO and VV-ECMO), age, or mortality rate. We decided to include VV-ECMO because pulmonary arterial hypertension is common in neonates and is responsible

for right and left cardiac failure, which may even lead to refractory shock in the post-weaning phase.

The macrocirculatory parameters are key points during the weaning phase of ECMO. Vasopressors were not given to 70% of our patients during the weaning test. With improvement in the clinical status during the weaning phase, it is not surprising that the microcirculation demonstrated improvement but was not fully restored. This result is in accordance with the respiratory and macrocirculatory stability in children at the beginning of ECMO withdrawal. Our data do not suggest any predictive capability of microcirculation parameters in regard to ECMO mortality rate. The six deaths were related to palliative care due to significant neurologic injury but not related to major hemodynamic failures. All of these patients died during their stay in intensive care.

No previous study has explored the monitoring of microcirculation during weaning in a pediatric ECMO population. Top et al. have shown that the functional capillary density (FCD) increases after beginning ECMO in cases of severe neonatal respiratory disease.¹¹ However, a second study in 2012 did not validate this.¹³

Microcirculation data on ECMO are mainly collected from adult patients with cardiac failure on VA-ECMO and probably cannot be compared to our pediatric population. A recent study has shown that the microcirculation is very impaired before starting ECMO, but strong

TABLE 2 Hospitalization pattern.

| Primary indications for ECMO | Patients (n) |
|--------------------------------------|--------------|
| Infectious lung disease | 7 |
| ECPR | 6 |
| Septic shock | 4 |
| MAS | 3 |
| Lung development anomaly | 2 |
| Myocarditis | 1 |
| CDH | 2 |
| HUC (<i>Escherichia coli</i>) | 2 |
| PHT | 1 |
| Anoxic ischemic encephalopathy | 1 |
| Hemodynamic failure without etiology | 1 |

Abbreviations: CDH, congenital diaphragmatic hernia; ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; HUC, hemolytic uremic syndrome; MAS, meconium aspiration syndrome; PHT, pulmonary hypertension.

TABLE 3 Macrocirculatory parameters after 1 h of a weaning test.

| Patient's parameters | "Stability after weaning" | "Instability after weaning" | p value |
|--------------------------------------|---------------------------|-----------------------------|-----------|
| | N = 19 | N = 11 | |
| Vasoactive support (%) | 6 (30%) | 4 (35%) | |
| Heart rate (beat/min) | 125 [112–137] | 130 [123–136] | 0.3 |
| Systolic blood pressure (mm Hg) | 87 [81–98] | 77 [75–89] | 0.24 |
| Diastolic blood pressure (mm Hg) | 54 [43–58] | 52 [46–62] | 0.8 |
| Mean arterial blood pressure (mm Hg) | 65 [56–72] | 65 [55–70] | 0.6 |
| SpO ₂ (%) | 99 [96–100] | 99 [94–100] | 0.63 |
| Lactate (mmol/L) | 1.3 [1–1.5] | 1.5 [1.1–1.8] | 0.35 |
| NIRS right/left | 74 [68–81]/79 [72–79] | 70 [69–71]/71 [66–73] | 0.28/0.12 |
| ScVO ₂ (%) | 78.5 [75–81] | 78 [74–79] | 0.55 |
| Hemoglobin (g/dL) | 9.7 [8.7–10.7] | 9.6 [8.6–10.3] | 0.49 |
| pH | 7.4 [7.4–7.45] | 7.4 [7.34–7.44] | 0.7 |
| pCO ₂ (mm Hg) | 47 [43–57] | 46 [43–57] | 0.98 |
| PO ₂ (mm Hg) | 41 [36–45] | 35 [34–40] | 0.08 |
| VTI | 14 [11–18] | 13.4 [11–15] | 0.8 |
| LVEF | 70 [60–75] | 65 [52–77] | 0.65 |

Note: Continuous data are presented as median [Q1–Q3]. Univariate analysis was done to compare the "easy weaning group" and the "difficult weaning group" using the Mann–Whitney Wilcoxon test for quantitative variables.

Abbreviations: LVEF, left ventricular ejection fraction; NIRS, near-infrared spectroscopy; SpO₂, blood oxygen saturation; ScVO₂, venous oxygen saturation; VTI, aortic velocity-time integral.

TABLE 4 Microcirculatory parameters after 1 h of weaning test.

| Patient's parameters | "Stability after weaning" | "Instability after weaning" | p value |
|--|---------------------------|-----------------------------|---------|
| | N = 19 | N = 11 | |
| Detected vessel length (DVL, mm) | 5.5 [4.5–6] | 5.8 [5.2–6.4] | 0.4 |
| Vessel density (VD, mm/m ²) | 12.9 [10.8–14.8] | 13.3 [12.5–14.7] | 0.54 |
| Vessel surface (VS, mm/m ²) | 12.4 [10.5–14] | 13.1 [11.8–14] | 0.42 |
| Grid crossing | 30.9 [25.7–32] | 31 [28–34] | 0.38 |
| Grid length (mm) | 3.9 [3.9–3.9] | 3.9 [3.8–3.89] | 0.29 |
| De Backer score (1/mm ³) | 8 [6.6–8.3] | 8.1 [7.2–8.9] | 0.41 |
| Total vessel density (TVD, mm/m ²) | | | |
| Small | 11.2 [9.3–13.6] | 12.1 [11.2–13.9] | 0.25 |
| Other | 1.4 [0.8–1.95] | 1.3 [1–1.6] | 0.89 |
| All | 12.9 [10.8–14.8] | 13.9 [12.5–15.4] | 0.41 |
| Microvascular flow index (MFI) | | | |
| Small | 2.3 [1.8–2.4] | 2.3 [2.3–2.6] | 0.24 |
| Other | 2.7 [3.3–3.8] | 2.7 [2.5–2.8] | 0.86 |
| All | 2.4 [2.3–2.7] | 2.6 [2.4–2.7] | 0.14 |

macrocirculatory and microcirculatory improvements occur after cannulation. The study did not find a significant difference in MFI, but they did find differences in some parameters related to perfusion (perfused small vessel density, proportion of perfused vessels) between those on ECMO who had successful withdrawal and those who did not survive.¹² These parameters could be more relevant for further study.

In the present study, a single operator recorded the microcirculation videos, and a different operator was blinded and analyzed them. There were four patients who had to be excluded for the poor quality of the videos, which could have led to recruitment bias. The two main markers of microcirculation studies were the MFI and the De Backer score. The MFI is based on a subjective analysis of the microvascular flow, so it can be difficult to reproduce from one operator to another. According to De Backer et al.,¹⁴ an optimal analysis of microcirculation should include a density parameter and a perfusion parameter, as well as a marker of heterogeneity of the flow. Even though there may be a bias in the analysis of the data, the parameters studied seem to give a reliable representation of microcirculation. Due to the software, microcirculation parameters were limited, but including other parameters such as the functional capillary density and heterogeneity index could refine the index.²

Our cohort is balanced in terms of age and ECMO modalities, but the number of patients was limited, and we were unable to perform subgroup analyses. Only 20% of all ECMO patients seen during the study period were included due to technical difficulties, which limits the extension of the results. During this period, 97 weaning

trials were performed for ECMO patients, and only 33% of them met all of the weaning criteria. At the end, all of the included patients were weaned from ECMO, which is considered a likely source of hazard bias in the inclusion of patients and is partly explained by the small size of the cohort.

Another issue is that our weaning protocol is based on adult recommendations,^{15,16} and it is possible that the criteria used are not sufficiently discriminating for children. The weaning tests may have been carried out on very stable children at a time that was probably too late. We hypothesize that microcirculation has already been restored at the time of weaning. It would be interesting to study a specific protocol for pediatric weaning from ECMO. Finally, this study raises questions about the timing of ECMO weaning in pediatric populations. If the alteration of the microcirculation in the acute phase of ECMO treatment is found in several studies, a post clamping microcirculation analysis could be useful for the hemodynamic evaluation of patients.

5 | CONCLUSION

Our study is the first pediatric study to present microcirculation data from the ECMO weaning period. We found no predictive factor for the failure of ECMO withdrawal among microcirculations indices. Further studies will be needed, especially analyses of the microcirculation indices of patients who experience failure of ECMO weaning and the microcirculation kinetics after stopping ECMO.

TABLE 5 Microcirculatory parameters depending on age, ECMO type and survival.

| Patient's parameters | ECMO VA | ECMO VV | Children | Newborn | Survivor | Death | p-value |
|--|------------------|------------------|------------------|------------------|------------------|-----------------|---------|
| | N = 18 | N = 12 | N = 17 | N = 13 | N = 24 | N = 6 | |
| De backer score (1/mm ³) | 8 [7.1-8.3] | 8.1 [6.8-8.9] | 8 [6.4-8.4] | 8.2 [7.2-9] | 8 [6.9-8.9] | 7.5 [6.5-8.3] | 0.36 |
| Total vessel density (TVD, mm/m ²) | | | | | | | |
| Small | 11.4 [11-13.9] | 12.3 [9.4-14.1] | 11 [9.1-13.4] | 13.3 [11.2-14.4] | 11.8 [10.2-14.1] | 10.5 [8.1-12.4] | 0.14 |
| Other | 1.4 [0.9-1.7] | 1.4 [0.8-1.9] | 1.7 [0.8-1.9] | 1.2 [0.8-1.6] | 1.3 [0.8-1.7] | 1.5 [0.8-2.9] | 0.39 |
| All | 12.9 [12.3-14.6] | 13.3 [11.1-15.3] | 12.8 [10.8-14.8] | 13.6 [12.3-15.7] | 13.3 [11.4-15.5] | 12.6 [10.5-14] | 0.29 |
| Microvascular flow index (MFI) | | | | | | | |
| Small | 2.3 [2.2-2.4] | 2.3 [1.7-2.5] | 2.4 [2-2.6] | 2.3 [2.1-2.4] | 2.3 [2.1-2.5] | 2.2 [1.9-2.5] | 0.69 |
| Other | 2.7 [2.5-2.8] | 2.7 [2.5-2.9] | 2.7 [2.4-2.9] | 2.7 [2.4-2.8] | 2.7 [2.6-2.9] | 2.5 [1.9-2.7] | 0.07 |
| All | 2.5 [2.3-2.7] | 2.5 [2.3-2.7] | 2.5 [2.3-2.7] | 2.5 [2.3-2.7] | 2.5 [2.3-2.7] | 2.4 [2-2.6] | 0.43 |

Abbreviation: ECMO, extracorporeal membrane oxygenation.

AUTHOR CONTRIBUTIONS

Violette Suc did the data curation, formal analysis, and writing the original draft. Pierre-Louis Léger did the project administration, the investigation and supervision. Pierre-Louis Léger and Jerome Rambaud did the review.

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CONFLICT OF INTEREST STATEMENT

The authors have disclosed that they do not have any potential conflicts of interest.

ORCID

Violette Suc  <https://orcid.org/0009-0005-8261-8895>

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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