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Short Communication

Sublingual microcirculation in patients with SARS-CoV-2 undergoing veno-venous extracorporeal membrane oxygenation

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ABSTRACT

Veno-Venous Extracorporeal Membrane Oxygenation (VV-ECMO) is a rescue treatment for severe acute respiratory failure refractory to conventional ventilation. We examined the alterations of sublingual microcirculation in patients with SARS-CoV-2 during VV-ECMO treatment and assessed the relationship between microvascular parameters and ventilation, hemodynamics, and laboratory tests.

Nine patients were included in the study and the following microcirculatory parameters were estimated: TVD 16.81 (14.46–18.6) mm/mm^2; PVD 15.3 (14.09–17.96) mm/mm^2; PPV 94.85% (93.82%–97.79%); MFI 2.5 (2.5–2.92); HI 0.4 (0.18–0.4). TVD and PVD were inversely related to D-dimer levels (rho = −0.667, p = 0.05 and rho = −0.733, p = 0.025 respectively), aspartate aminotransferase (AST) (rho = −0.886, p = 0.019 and rho = −0.886, p = 0.019 respectively) and alanine aminotransferase (ALT) (rho = −0.829, p = 0.042 and rho = −0.829, p = 0.042 respectively).

Our results showed an altered sublingual microcirculation in patients receiving VV-ECMO for severe SARS-CoV-2 and suggest a potential contribution of endothelia dysfunction to determine microvascular alteration.

1. Introduction

Veno-Venous Extracorporeal Membrane Oxygenation (VV-ECMO) is a rescue treatment for severe cases of acute respiratory failure refractory to conventional mechanical ventilation, neuromuscular blockade, and prone positioning (Sen et al., 2016). During the current pandemic outspread, many patients with severe acute respiratory syndrome due to novel Coronavirus (SARS-CoV-2), unresponsive to first line therapies, underwent VV-ECMO (Pravda et al., 2020). Multiple evidences suggest that the assessment of sublingual microcirculation may have a role to guide clinical decisions during ECMO treatment (Yeh et al., 2018). Monitoring of sublingual microcirculation provides clinically relevant information representative of microcirculatory alterations of other organ beds (Guven et al., 2020). We recently reported the presence of microcirculatory alterations in patients with SARS-CoV-2 (Damiani et al., 2020). Thus, the aim of this study was to describe the alterations of sublingual microcirculation in patients with SARS-CoV-2 treated with VV-ECMO and to assess relationship between microvascular parameters and ventilation, hemodynamics, and laboratory tests.

2. Materials and methods

A retrospective data collection has been performed including patients with SARS-CoV-2 admitted to Intensive Care Unit at Ospedali Riuniti of Ancona (Italy) between February 2020 and April 2020 receiving VV-ECMO support for severe respiratory failure unresponsive to conventional mechanical ventilation and pronation. The study has been approved by Ethical Committee of Regione Marche (record ID: 2020 121/6152).

We retrieved information of patients that received assessment of sublingual microcirculation as routine clinical practice. Sublingual microvascular videos were recorded using the Cytocam camera. The Cytocam is a third generation handheld videomicroscope that enables the non-invasive, real-time, *in vivo* visualization of the microcirculation. Three videos from different sublingual areas were recorded with

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Table 1
Clinical characteristics.

Male (n; %)	8 (89%)
Age (years)	51 (47–60)
BMI (kg/m^2)	31.14 (27.1–36.9)
Murray Score	3.5 (3.5–3.8)
Tidal volume (ml)	350 (200–400)
Pplat (cmH_2O)	26 (22–29)
ΔP (cmH_2O)	16 (12–19)
PEEP (cmH_2O)	10 (8–10)
RR (breath/min)	10 (10 − 13)
Cstat (ml/cmH_2O)	18 (13 − 30)
FIO_2	0.4 (0.4–0.55)
pH	7.45 (7.36–7.48)
PaO_2 (mmHg)	75 (59–85)
$PaCO_2$ (mmHg)	45 (41–53)
Lactate (mmol/l)	0.8 (0.7–0.95)
MAP (mmHg)	86 (68–98)
HR (beat/min)	93 (70–96)
AST (U/l)	54 (33.5–97.25)
ALT (U/l)	85.5 (38.75–172.75)
D-dimer (ng/ml)	1428 (628.25–5743.75)
aPTT (*sec*)	41.5 (35–45)

Data reported as median (interquartile range).
ALT: alanine aminotransferase; AST: aspartate aminotransferase; aPTT: activated partial thromboplastin time; BMI: body mass index; Cstat: static compliance ore respiratory system; HR: heart rate; FIO_2: fraction of inspired oxygen; MAP: mean arterial pressure; $PaCO_2$: arterial partial pressure of carbon dioxide; PaO_2: arterial partial pressure of oxygen; ΔP: driving pressure; PEEP: positive end expiratory pressure; Pplat: plateau pressure; RR: respiratory rate.

Table 2
Parameters of sublingual microcirculation for small vessels.

TVD (mm/mm^2)	16.81 (14.46–18.6)
PVD (mm/mm^2)	15.3 (14.09–17.96)
PPV (%)	94.85 (93.82–97.79)
MFI	2.5 (2.5–2.92)
HI	0.4 (0.18–0.4)

Data reported as median (interquartile range).
HI: heterogeneity index; MFI: microvascular flow index; PPV: proportion of perfused vessels; PVD: perfused vessel density; TVD: total vessel density.

adequate contrast and focus and without pressure artefacts. The videos were analyzed offline with dedicated software (Automated Vascular Analysis 3.2, Microvision Medical, Amsterdam, NL) to obtain parameters of vessel density (total vessel density [TVD], perfused vessel density [PVD]) and blood flow quality (microvascular flow index [MFI], percentage of perfused vessels [PPV], and flow heterogeneity index [HI]), as described elsewhere (Scorcella et al., 2018). Only vessels with a diameter less than 20 μm were considered.

Data distribution was assessed using the Kolmogorov-Smirnov test. Data were reported as mean and standard deviation (SD) or median and interquartile range (IQR) as appropriate. The Pearson or Spearman correlation has been used to assessed relationship between microvascular and other clinical parameters.

3. Results

Nine patients with severe SARS-CoV-2 received VV-ECMO support within the study period. The main clinical characteristics are presented in Table 1 and the parameters regarding sublingual microcirculation are summarized in Table 2. TVD and PVD were inversely related to D-dimer levels (rho = −0.667, p = 0.05 and rho = −0.733, p = 0.025 respectively), aspartate aminotransferase (AST) (rho = −0.886, p = 0.019 and rho = −0.886, p = 0.019 respectively) and alanine aminotransferase (ALT) (rho = −0.829, p = 0.042 and rho = −0.829, p = 0.042 respectively). No other correlation was found between microcirculation parameters and hemodynamics or other laboratory tests.

4. Discussion

VV-ECMO is an established technique to support lung function during severe respiratory failure refractory to conventional mechanical ventilation and prone position (Peek et al., 2009). However, its role in SARS-CoV-2 needs to be clarified.

Microvascular parameters of patients with SARS-CoV-2 supported with VV-ECMO reported in our report were worse than those recorded in a mixed population of critically ill patients (Scorcella et al., 2018) but comparable to our previous report including SARS-CoV-2 patients not supported by ECMO (Damiani et al., 2020). This is an indirect evidence that ECMO *per se* is not able to improve microvascular alterations. SARS-CoV-2 causes endothelial dysfunction (Jung et al., 2020) and the blood contact with ECMO circuit components may increase inflammatory state. Both previous conditions are likely to affect organ microcirculation and our findings showing impairment of both density and flow parameters suggest that monitoring sublingual microcirculation may provide clinically relevant information regarding the severity of the SARS-CoV-2. Moreover, we confirmed results from our previously report showing an inverse correlation between density parameters of microcirculation and D-dimer levels (Damiani et al., 2020). Interesting, this relation was confirmed in patients undergoing extracorporeal support with prolonged activated partial thromboplastin time (aPTT) due to heparin anticoagulation. Even if sepsis and SARS-CoV-2 may share common pathophysiological pathways like cytokine storm and endothelial dysfunction, the mechanisms of coagulopathy may be different (Iba et al., 2020). Anyhow, both diseases manifest themselves in a similar way at microvascular level, with reduced capillary density and altered flow. Although D-dimer was not previously related with capillary density in septic patients, it was associated with severity of illness (Angstwurm et al., 2004). Finally, the relationship between capillary density and liver enzymes may suggest that microvascular alteration may have a role in organ dysfunction. Unfortunately, the small number of patients considered in our analysis is the major limitation of the study and did not allow to demonstrate further relationship between microcirculation and other clinical parameters.

5. Conclusion

In our report considering patients with SARS-CoV-2 undergoing VV-ECMO, we found altered density and flow microvascular parameters and a relationship between capillary density and D-dimer level, suggesting a potential role of endothelial disfunction to determine microvascular alteration. Further studies are needed to clarify the relationship between microcirculation and other clinical parameters.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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