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Journal of Critical Care 61 (2021) 73–75

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Microcirculation alterations in severe COVID-19 pneumonia

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ARTICLE INFO

Keywords:
COVID-19
Pneumonia
Capillary refill time
Microcirculation

ABSTRACT

Purpose: To assess the presence of sublingual microcirculatory and skin perfusion alterations in COVID-19 pneumonia.
Materials and methods: This is a preliminary report of a prospective observational study performed in four teaching intensive care units. We studied 27 mechanically ventilated patients with acute respiratory distress syndrome secondary to COVID-19. Sublingual microcirculation was assessed by hand-held videomicroscopy. A software-assisted analysis of videos was performed. We also measured capillary refill time.
Results: Patients were hemodynamically stable with normal lactate (1.8 [1.6–2.5] mmol/L) and high D-dimer (1.30 [0.58–2.93] μg/mL). Capillary refill time was prolonged (3.5 [3.0–5.0] s). Compared to previously reported normal values, total and perfused vascular density (21.9 ± 3.9 and 21.0 ± 3.5 mm/mm^2) and heterogeneity flow index (0.91 ± 0.24) were high; and the proportion of perfused vessels (0.96 ± 0.03), microvascular flow index (2.79 ± 0.10), and red blood cell velocity (1124 ± 161 μm/s) were reduced. The proportion of perfused vessels was inversely correlated with total vascular density (Pearson $r = -0.41$, $P = 0.03$).
Conclusions: COVID-19 patients showed an altered tissue perfusion. Sublingual microcirculation was characterized by decreases in the proportion of perfused vessel and flow velocity along with high vascular densities. This last finding might be related to enhanced angiogenesis or hypoxia-induced capillary recruitment.

1. Introduction

Microvascular thrombosis has recently been diagnosed in patients with COVID-19, and it has been proposed to mediate the pathogenesis of organ injury in this disease [1]. While widespread pulmonary microvascular thrombosis was demonstrated [2], reports about the compromise of extrapulmonary microvessels are inconsistent. Some anatomopathological reports found extrapulmonary microvascular thrombosis, but others failed to show such alterations [3,4]. Recently, sublingual microcirculatory abnormalities were shown in 12 patients with COVID-19 pneumonia [5]. Since microvascular densities were inversely correlated with D-dimer levels, these abnormalities might have resulted from microthrombosis.

A growing body of evidence suggests that the microvascular disorder plays a role in the pathogenesis of septic shock and is related to outcome [6]. Thus, our goal was to assess the characteristics of sublingual microcirculation and skin perfusion in patients with acute respiratory distress syndrome (ARDS) secondary to COVID-19. In this report, we show the preliminary results of a prospective multicenter study.

2. Materials and methods

We included 27 patients with diagnosis of ARDS secondary to COVID-19 (positive result by polymerase chain reaction testing of nasopharyngeal or tracheal samples), from 4 intensive care units (ICU) in Argentina. All patients were intubated and mechanically ventilated, received infusions of midazolam, fentanyl and atracurium, and anticoagulant prophylaxis from their hospital admission. No patient had superinfections at the moment of the study. Blood pressure, heart rate and norepinephrine infusion remained unchanged for 3-h before the measurements. Sublingual microcirculation was assessed by means of hand-held videomicroscopy, within the first 3 days of ICU admission.

Abbreviations: COVID-19, coronavirus disease 2019; ARDS, acute respiratory distress syndrome (ARDS).

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https://doi.org/10.1016/j.jcrc.2020.10.002
0883-9441/

Relevant aspects of video acquisition and software-assisted analysis are described elsewhere [6]. Several videos were taken in each patient. Based on the total microcirculation image quality score, the best three videos were selected for analysis [7]. Analysis was focused on small microvessels (diameter < 20 μm) whereas large microvessels were only considered for ruling out compression artifacts. For the calculation of proportion of perfused vessels and perfused vascular density, we took into account microvessels with continuous and sluggish flow. Capillary refill time was measured by applying firm pressure to the ventral surface of the right index finger distal phalanx with a glass microscope slide. The pressure was increased until the skin was blank and maintained for 10 s. The time for return of the normal skin color was registered with a chronometer, and a refill time greater than 3 s was defined as abnormal.

The respective institutional review boards approved this study and waived patient informed consent.

We present continuous variables as median (interquartile range [IQR]) or mean ± SD, and categorical variables as numbers and percentages. Values of COVID-19 patients were compared with those of healthy volunteers from a previous study.by unpaired *t*-test [6]. Analyses were performed using Stata version 15 (StataCorp).

3. Results

Main clinical and laboratory characteristics of the patients are shown in Table 1. Norepinephrine (0.03 [0.01–0.17] μg/kg/min) was required in 12 patients (44%). The fluid balance in the previous 24-h was 600 [100–1490] mL. D-dimer and ferritin levels were elevated (Table 1). Median plasma lactate was normal (1.8 [1.6–2.5] mmol/L). Capillary refill time was prolonged (3.5 [3.0–5.0] s).

The total microcirculation image quality score was 1 [0–2] [7]. Compared to reported normal values [6], total and perfused vascular density and heterogeneity flow index were high; and the proportion of perfused vessels, microvascular flow index, and red blood cell velocity were reduced (Table 2). The proportion of perfused vessels was inversely correlated with total vascular density (Pearson $r = -0.41$, $P = 0.03$). D-dimer levels were not correlated with either total or perfused vascular density (Pearson $r = -0.12$, $P = 0.59$ and Pearson r = −0.12, $P = 0.57$, respectively). Total and perfused vascular density were correlated with capillary refill time (Pearson $r = -0.43$, $P = 0.02$ for both).

Table 1
Clinical and laboratory characteristics of the patients.

Characteristic	Value
Age, y	60 [51–63]
Female gender, No. (%)	7 (26)
APACHE II score	12 [9–17]
SOFA score	6 [3–8]
Dead, No. (%)	9 (33)
Discharged alive, No. (%)	3 (11)
Remained in hospital, No. (%)	15 (56)
Mean arterial pressure, mm Hg	76 ± 9
Heart rate, beats/min	86 ± 26
Positive end-expiratory pressure, cm H_2O	11 ± 2
Arterial pH	7.31 ± 0.05
Arterial PCO_2, mmHg	45 ± 8
Arterial PO_2, mmHg	90 ± 27
Hemoglobin, g/dL	11.7 ± 2.1
PaO_2:FiO_2 ratio (normal values > 400)	122 ± 43
White blood cell count, $\times 10^9$/L (reference range = 3.8–10.5 × 10^9/L)	11.0 ± 4.6
Lymphocyte blood cell count, $\times 10^9$/L (reference range = 1.0–3.3 × 10^9/L)	0.80 ± 0.04
International normalized ratio (reference range = 0.8–1.2)	1.1 ± 0.1
Activated partial thromboplastin time, s (reference range = 23–36 s)	369
Platelet count, $\times 10^3$/μL (reference range = 150–450)	235 ± 111
D-dimer, μg/mL (reference range < 0.50 μg/mL)	1.30 [0.58–2.93]
Ferritin, ng/mL (reference range = 15–400 ng/mL)	593 [454–1162]

Data are shown as number (%), median [IQR] or mean ± SD.
Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment.

Table 2
Sublingual microcirculatory variables.

Variable	Value	Normal values	*P*-value
Total vascular density (mm/mm^2)	21.9 ± 3.9	16.7 ± 1.6	<0.0001
Perfused vascular density (mm/mm^2)	21.0 ± 3.5	16.6 ± 1.6	<0.0001
Proportion of perfused vessels	0.96 ± 0.03	1.00 ± 0.00	<0.0001
Microvascular flow index	2.79 ± 0.10	2.97 ± 0.03	<0.0001
Red blood cell velocity (μm/s)	1124 ± 161	1331 ± 190	<0.0001
Heterogeneity flow index	0.91 ± 0.24	0.04 ± 0.03	<0.0001

4. Discussion

This is one of the few characterizations of sublingual microcirculation in patients with COVID-19 pneumonia. Our patients had moderate-to-severe ARDS and high levels of D-dimer, as biochemical evidence of intravascular coagulation and increased fibrinolysis. Although most of them were hemodynamically stable, they had alterations in sublingual microvascular flow and capillary refill time. Microcirculatory abnormalities consisted in an increased number of small vessels with stopped, intermittent or slow flow. These changes seem minor, compared to those described in septic shock [6]. The proportion of unperfused vessels, however, represented a several times increase from normal values. Microvascular heterogeneity was greatly augmented, while perfusion velocity was decreased. These abnormalities might contribute to the development of multiple organ failure. Interestingly, decreases in vascular densities were correlated with increases in the capillary refill time, which is now considered a valuable goal of resuscitation in septic shock [8].

Our most striking finding was the increase in vascular density, which was correlated with the proportion of unperfused microvessels. Different mechanisms might underlie these findings. Patients severely affected with COVID-19 develop fever and hypoxemia. Therefore, hypoxia-induced capillary recruitment could be an explanation for the increased vascular density observed [9,10]. Besides, high metabolic activity and tissue hypoxia are recognized stimuli for vascular growth [11]. Another well-known trigger for angiogenesis is microthrombosis [12]. The association of pulmonary microthrombosis, angiogenesis and capillary proliferation has been described in patients with severe COVID-19 [2,13]. Our results suggest that this association is not only restricted to the lung but might also be a systemic phenomenon.

Contrary to our results, the previous report found decreases in vascular density [5]. Since hypoxemia produces both capillary recruitment and angiogenesis, differences might be related to the higher compromise of pulmonary oxygenation in our patients (PaO_2/FiO_2, 122 ± 43 vs. 207 ± 88 mmHg).

Our results showed that the diffusional determinants of microcirculatory oxygen availability–vascular densities–are increased whereas the convective components–microvascular flow index, proportion of perfused vessel and red blood cell velocity–are decreased. Besides, the presence of increased heterogeneity was a further challenge to tissue oxygenation. Since we only assessed microvascular perfusion, it is difficult to assert what the final impact on tissue oxygenation was.

Main limitations of this study are the small sample size and the assessment of tissue perfusion on sublingual mucosa and skin only. Measurements were taken at a single time point, which does not rule out different findings in other stages of the illness. As the study was merely descriptive, the underlying mechanisms of the microvascular disorder are only speculative. Finally, we did not include a control

group and microvascular variables were compared with referenced normal values.

5. Conclusions

Even though the microvascular disorder did not reach the characteristics of the widespread thrombotic microangiopathy described in the pulmonary bed, patients with severe COVID-19 pneumonia showed subtle but consistent alterations in sublingual microcirculation and skin perfusion.

Authors' contributions

AD had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Concept and design:* VSKE, JFGE, GF, AD. *Acquisition, analysis, or interpretation of data:* VSKE, JFGE, GF, EE, AD. *Drafting of the manuscript:* EE, AD. *Critical revision of the manuscript for important intellectual content:* VSKE, JFGE, GF, EE, AD. *Statistical analysis:* EE, AD.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and materials

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The respective institutional review boards approved this study and waived patient informed consent.

Consent for publication

Not applicable.

Data are shown as mean ± SD. Normal values are related to reference 6.

Declaration of Competing Interest

The authors declare that they have no competing interests.

References

[1] Bray MA, Sartain SA, Gollamudi J, Rumbaut RE. Microvascular thrombosis: experimental and clinical implications. Transl Res 2020;225:105–30.
[2] Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. N Engl J Med 2020;383(2):120–8.
[3] Nunes Duarte-Neto A, de Almeida Monteiro RA, da Silva LFF, et al. Pulmonary and systemic involvement of COVID-19 assessed by ultrasound-guided minimally invasive autopsy. Histopathology 2020;77:186–97.
[4] Schaller T, Hirschbühl K, Burkhardt K, Braun G, Trepel M, Märkl B, et al. Postmortem examination of patients with COVID-19. JAMA 2020;323(24):2518–20.
[5] Damiani E, Carsetti A, Casarotta E, Scorcella C, Domizi R, Adrario E, et al. Microvascular alterations in patients with SARS-COV-2 severe pneumonia. Ann Intensive Care 2020;10(60).
[6] Edul VS, Enrico C, Laviolle B, Vazquez AR, Ince C, Dubin A. Quantitative assessment of the microcirculation in healthy volunteers and in patients with septic shock. Crit Care Med 2012;40:1443–8.
[7] Massey MJ, Larochelle E, Najarro G, Karmacharla A, Arnold R, Trzeciak S, et al. The microcirculation image quality score: development and preliminary evaluation of a proposed approach to grading quality of image acquisition for bedside videomicroscopy. J Crit Care 2013;28(6):913–7.
[8] Hernández G, Ospina-Tascón GA, Damiani LP, Estenssoro E, Dubin A, Hurtado J, et al. Effect of a Resuscitation Strategy Targeting Peripheral Perfusion Status vs Serum Lactate Levels on 28-Day Mortality Among Patients With Septic Shock: The ANDROMEDA-SHOCK Randomized Clinical Trial. AJMA 2019;321(7):654–64.
[9] Hilty MP, Merz TM, Hefti U, Ince C, Maggiorini M, Pichler Hefti J. Recruitment of non-perfused sublingual capillaries increases microcirculatory oxygen extraction capacity throughout ascent to 7126 m. J Physiol 2019;597:2623–38.
[10] Parthasarathi K, Lipowsky HH. Capillary recruitment in response to tissue hypoxia and its dependence on red blood cell deformability. Am J Physiol 1999;277: H2145–57.
[11] Adair TH, Montani JP. Angiogenesis. San Rafael (CA): Morgan & Claypool. Life Sci; 2010; 19–27.
[12] Smadja DM, Guerin CL, Chocron R, Yatim N, Boussier J, Gendron N, et al. Angiopoietin-2 as a marker of endothelial activation is a good predictor factor for intensive care unit admission of COVID-19 patients. Angiogenesis 2020;23(4):611–20.
[13] Carsana L, Sonzogni A, Nasr A, Rossi RS, Pellegrinelli A, Zerbi P, et al. Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study. Lancet Infect Dis 2020;20(10):1135–40.