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Impaired Microvascular Function in Patients With Critical COVID-19

OBJECTIVES: Severe coronavirus disease 2019 is characterized by infected microvascular endothelial cells. The primary aim of this study was to investigate microvascular function in patients with critical coronavirus disease 2019.

DESIGN: A prospective observational study was conducted in which patients with critical and severe COVID-19 were investigated during acute disease phase and at least 3 months after disease onset.

SETTING: Single-center study at Danderyd University Hospital.

PATIENTS: Twenty-three patients with critical coronavirus disease 2019 treated with noninvasive or invasive mechanical ventilation, seven patients with severe COVID-19 with dyspnea or need of oxygen supply up to 8 L/min, and 15 noncoronavirus disease controls.

INTERVENTIONS: None.

MEASUREMENTS: Skin perfusion was investigated through laser speckle contrast imaging before and after iontophoresis of acetylcholine and sodium nitroprusside for determination of the endothelial-dependent and the endothelial-independent vasodilation, respectively.

MAIN RESULTS: Patients with critical COVID-19 had higher basal skin perfusion during both the acute (34 ± 9 perfusion unit; $p = 0.0003$) and the postinfectious phase (29 ± 8 perfusion unit; $p = 0.04$), compared with noncoronavirus disease controls (23 ± 7 perfusion unit). In addition, endothelial-dependent and endothelial-independent vasodilation were reduced in patients with critical COVID-19 during the acute disease phase ($p < 0.001$ for both), whereas no significant differences between patients and controls were found during the postinfectious phase. In patients with severe COVID-19, basal skin perfusion and endothelial-dependent vasodilatation were not significantly changed, whereas endothelial-independent vasodilatation was reduced ($p = 0.02$) compared with controls.

CONCLUSIONS: Changes in skin microcirculation in patients with critical COVID-19 indicate that the infection induces a systemic microvascular impairment with persisting long-term effects on the microvascular function.

KEY WORDS: COVID-19; critical illness; endothelial dysfunction; microangiopathy; microcirculation; skin microvascular function

Severe COVID-19 is characterized by a massive inflammatory response mainly mediated by infected microvascular endothelial cells (1, 2). Increased biomarker levels of endothelial dysfunction have been shown in COVID-19 and seem to correlate to disease severity (3–6). Intravital microscopy has demonstrated that COVID-19 patients in need for mechanical ventilation have reduced sublingual microvascular blood flow compared with patients without mechanical ventilation (3). Although these studies indicate that severe COVID-19 is associated with a widespread endothelial cell damage of the microvasculature, the impact of the COVID-19-induced endothelitis on

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the microvascular capacity and responsiveness is less studied. In addition, possible long-term effects of critical COVID-19 on microvascular function have not been investigated.

In this study, we evaluated endothelial-dependent and endothelial-independent microvascular reactivity through bedside investigation of skin microcirculation in patients with critical COVID-19. We hypothesized that critical COVID-19 is associated with reduced endothelial-dependent skin microvascular reactivity compared with non-COVID control subjects (primary aim). The study also included a smaller group of patients with severe COVID-19. The initial examination was performed during the acute disease phase, whereas a second examination of survivors took place at least 3 months after disease onset in order to study possible long-term effects.

MATERIALS AND METHODS

Study Design

We investigated skin microvascular reactivity in hospitalized patients with COVID-19 during the acute disease phase and at least 3 months after disease onset in a single-center prospective study. A sample size calculation estimated the need of 22 patients for detection of a large effect size (Cohen's $d > 0.8$) in delta levels of acetylcholine-mediated vasodilatation between patients and controls in a two-tailed independent t test with a significance level 0.05 and power of 80%.

Subjects

The study included 23 patients with critical COVID-19 and seven patients with severe COVID-19. Patients eligible for the study were hospitalized adults at any age, with a confirmed COVID-19 infection and critical or severe respiratory failure according to the World Health Organization definitions (7). Critical COVID-19 was defined as respiratory failure with need for invasive or noninvasive ventilation or high-flow nasal oxygen, and severe COVID-19 was defined as respiratory rate greater than 30 breaths per minute and/or need for oxygen supply up to 8L/min at rest. Confirmed COVID-19 infection was defined by the detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in a respiratory specimen by a polymerase chain reaction assay. Patients were included by convenience sampling at Danderyd University Hospital between May 15, 2020, and December 18, 2020. The results from the 12

patients and controls included during the first wave of COVID-19 have been published as a pilot study (8). All surviving patients were scheduled for a follow-up visit at least 3 months after disease onset.

Data on demographics, comorbidities, medical treatments, disease course, and hospital discharge were obtained from the patients and the electronic health records. Obesity was defined as body mass index (BMI) greater than or equal to 30.0 kg/m². Chronic kidney disease (CKD) was defined as CKD stage 3 or higher with reduced estimated glomerular filtration rate less than 60 mL/min/1.73 m². Patient treatment was in adherence to contemporary guidelines for COVID-19, including use of glucocorticoids, anticoagulants and the antiviral drug remdesivir to patients with severe respiratory distress. Among the 23 patients with critical COVID-19, 14 were treated with glucocorticoids and six with remdesivir. No chloroquine derivatives were used during the study period. All 23 patients with critical COVID-19 were treated with anticoagulants by either double prophylactic or by therapeutic doses of low molecular weight heparin or continuation of an ongoing oral anticoagulant therapy.

Fifteen control subjects without COVID-19 were also included. The control group consisted of adult healthy individuals or patients with common comorbidities recruited from an outpatient clinic at the hospital. We included control subjects matched against the patients with critical COVID-19 with regard to background factors including age, sex, BMI, and comorbidities. The only exclusion criterion for the control group was confirmed or suspected COVID-19 infection during 2020.

Skin Microvascular Reactivity

Skin microvascular reactivity was investigated through iontophoresis, a noninvasive method for drug application across the skin using a small electric current (8). Acetylcholine (ACh; Sigma-Aldrich AB, Stockholm, Sweden) and sodium nitroprusside (SNP; Hospira, Lake Forest, IL), diluted in sodium chloride solutions to final concentrations of 2%, were used to investigate the endothelium-dependent and the endothelium-independent microvascular reactivity, respectively. Two electrode chambers (LI611 Drug Delivery Electrode Imaging; Perimed, Järfälla, Sweden) were attached 5 cm apart to the volar side of the forearm and filled with ACh or SNP solutions. Iontophoresis of

ACh and SNP was performed simultaneously using a single current application of 0.02 mA for 200 seconds from a battery-powered iontophoresis controller (LI 760 PeriIont System; Perimed). Skin perfusion was recorded with one image per second before, during, and after iontophoresis by laser speckle contrast imaging (LSCI, PeriCam PSI NR; Perimed), and data were processed off-line through dedicated software (PIMSoft; Perimed). The entire electrode chamber (1.5 cm²) was examined as the region of interest. Time of interest, defined as the duration in seconds over which data are averaged, was set to 60 seconds for assessment of baseline values, 20 seconds for peak values, and 5 seconds for the other measurement points. The results are expressed in perfusion units (PUs).

Skin Temperature

Skin temperature of the volar side of the forearm, close to the site of skin perfusion examinations, was recorded with an electronic thermistor (Exacon, Copenhagen, Denmark).

Statistical Analysis

Categorical and continuous variables were presented as number of patients (*n*), means \pm SD, or medians with interquartile range (IQR). Independent *t* tests, Mann-Whitney *U* test, or Fisher exact test were used to evaluate differences between groups, as appropriate. *p* values less than 0.05 were considered statistically significant. All statistical analyses were performed with Statistica, TIBCO Software, Version 13 (TIBCO, Palo Alto, CA).

Ethical Consideration

The study protocol was approved by the Swedish Ethical Review Authority (approval number 2010-00533 for original application and 2020-02628 for amendment).

RESULTS

The characteristics of the study subjects are presented in **Table 1**. There were no significant differences in age, sex distribution, BMI, or comorbidities between patients with critical COVID-19 and controls. Among

TABLE 1.
Characteristics of Study Patients and Controls

Characteristics	Critical COVID (N = 23)	Severe COVID (N = 7)	Controls (N = 15)	<i>p</i> Critical vs Controls	<i>p</i> Severe vs Controls
Age (yr), mean \pm SD	63 \pm 13	54 \pm 6	62 \pm 8	0.69	0.03
Male sex, <i>n</i> (%)	20 (87)	6 (86)	10 (67)	0.22	0.62
Body mass index (kg/m ²), median (interquartile range)	27 (25–30)	28 (25–29)	25 (24–29)	0.43	0.72
Smokers, <i>n</i> (%)	0 (0)	0 (0)	0 (0)	N/A	N/A
Comorbidities, <i>n</i> (%)					
Obesity	8 (35)	1 (14)	2 (13)	0.26	1.00
Hypertension	12 (52)	2 (29)	7 (47)	1.00	0.65
Diabetes mellitus	6 (26)	3 (43)	1 (7)	0.20	0.08
Chronic kidney disease (stage 3B or higher)	0 (0)	0 (0)	0 (0)	N/A	N/A
Ischemic heart disease	2 (9)	0 (0)	1 (7)	1.00	1.00
Chronic heart disease	2 (9)	0 (0)	1 (8)	1.00	1.00
Chronic obstructive pulmonary disease	2 (9)	0 (0)	0 (0)	0.51	N/A
Active cancer	3 (13)	1 (14)	0 (0)	0.26	0.32
No comorbidities, <i>n</i> (%)	6 (26)	3 (43)	6 (40)	0.48	1.00

N/A = not applicable.

the patients with diabetes mellitus, none had any signs of diabetic microangiopathy. Most patients (18/23 patients with critical COVID-19 and all patients with severe COVID-19) were in good physical condition (regular sport activities and/or long daily walks) prior to disease onset, whereas five patients were less physically active (occasional walks).

Brief clinical status of the patients with critical and severe COVID-19 on the days of examination is presented in **Table 2**. At the time of inclusion (day of examination during acute disease phase), 21 of the 23 patients with critical COVID-19 were treated with noninvasive ventilation or high-flow nasal oxygen, whereas two patients were treated with invasive ventilation. During the disease course, 11 of the 23 patients with critical COVID-19 were treated with invasive ventilation. In total, the patients were treated with noninvasive or invasive ventilation for a median of 9 days (IQR, 5–18 d). SARS-CoV-2 was detected in serum samples of 19 patients (83%) with critical COVID-19 and two patients (29%) with severe COVID-19. Six patients with critical COVID-19 had positive blood cultures during hospitalization, of which one patient (survivor) developed septic shock while in the ICU.

Seven patients, all with critical COVID-19, died during hospitalization. Six of these fatal cases were due to progression of respiratory failure, whereas one patient died from cardiac arrest. There were no significant differences in age, sex, BMI, or comorbidities between survivors and nonsurvivors.

Microcirculation analyses were performed in 20 of the 23 surviving patients during the post COVID phase. Two patients (one with critical COVID-19 and one with severe COVID-19) declined the follow-up visit, and one patient (severe COVID-19) could not be reached. Median time from disease onset until time of follow-up was 114 days (range, 96–144 d). At follow-up, all surviving patients had been discharged to their homes without oxygen supply. Twelve patients (60%) experienced a slightly or markedly reduced physical condition compared with their physical status prior to COVID-19, whereas eight patients (40%) reported restored activity levels. All patients had completed the COVID-related treatments including anticoagulants and glucocorticoids, and no additional treatments had been initiated.

Figure 1 shows microvascular reactivity before, during, and after iontophoresis of ACh and SNP in patients

TABLE 2.
Clinical Status of Patients During Examination of Skin Microvascular Function

Clinical Variables	Critical COVID		Severe COVID	
	Acute Phase	Post COVID	Acute Phase	Post COVID
Respiratory status				
Respiratory rate (rate/min), mean \pm SD	29 \pm 7	ND	19 \pm 3	ND
Arterial saturation (%), mean \pm SD	91 \pm 2	ND	96 \pm 2	ND
O ₂ supply (n)	23	0	3	0
Noninvasive ventilation (n)	21	0	0	0
Invasive ventilation (n)	2	0	0	0
Circulatory status				
Systolic blood pressure (mm Hg), mean \pm SD	122 \pm 17	127 \pm 19	118 \pm 15	128 \pm 13
Diastolic blood pressure (mm Hg), mean \pm SD	67 \pm 12	81 \pm 10	71 \pm 9	79 \pm 7
Heart rate (beats/min), mean \pm SD	80 \pm 15	72 \pm 14	70 \pm 14	70 \pm 22
IV vasoactive drugs (n)	2	0	0	0
Body temperature (°C), mean \pm SD	37.1 \pm 1.1	ND	36.8 \pm 0.3	ND
C-reactive protein level (mg/L), median (interquartile range)	150 (111–292)	ND	86 (40–88)	ND

ND = nondetermined.

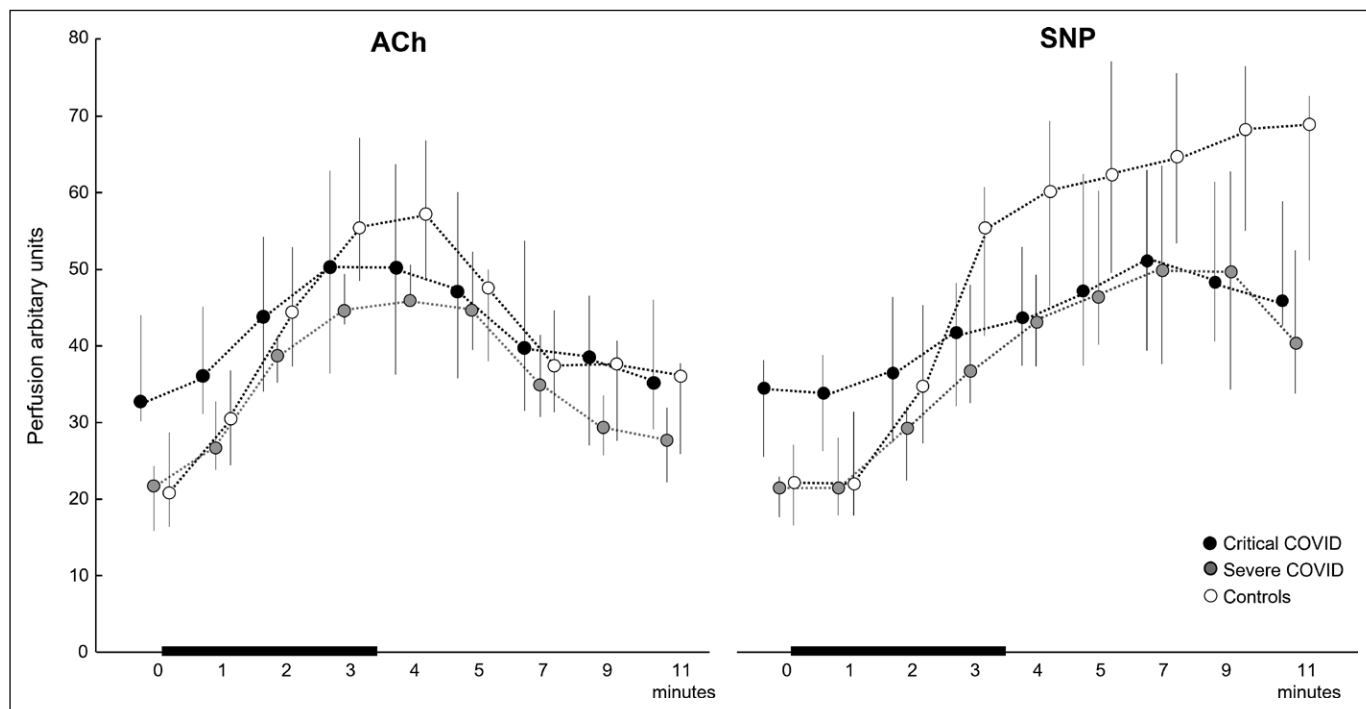


Figure 1. Skin microvascular reactivity in response to acetylcholine (ACh) and sodium nitroprusside (SNP) in patients with critical and severe COVID-19. Median and interquartile range of forearm skin perfusion before, during and after ACh and SNP iontophoresis in patients with critical (*black*, $n = 23$) and severe (*gray*, $n = 7$) COVID-19, and controls without COVID-19 (*white*, $n = 15$). Patients with critical COVID-19 have higher basal skin perfusion and reduced vasodilatory capacity compared with controls.

with critical and severe COVID-19 during their acute disease phase. Skin perfusion at rest and following ACh or SNP iontophoresis was not correlated to core body temperature and did not differ between patients with and without fever (data not shown). Patients with critical COVID-19 had higher forearm skin temperature ($31.6^{\circ}\text{C} \pm 1.6^{\circ}\text{C}$) compared with controls ($30.0^{\circ}\text{C} \pm 1.2^{\circ}\text{C}$; $p = 0.006$), but skin temperature was not correlated to basal skin perfusion among the patients ($r = 0.09$; $p = 0.70$). Core to skin temperature gradient was 1.18 ± 0.06 in patients with critical COVID-19 and 1.15 ± 0.04 in patients with severe COVID-19. The examination room temperature during acute disease phase did not differ between controls ($21.9^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$) and patients with critical ($22.3^{\circ}\text{C} \pm 0.7^{\circ}\text{C}$; $p = 0.27$) and severe ($22.3^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$; $p = 0.20$) COVID-19, respectively. ACh- and SNP-mediated vasodilation was not correlated to mean arterial blood pressure or to the ratio of arterial oxygen saturation/ FIO_2 (data not shown).

Basal skin perfusion levels in patients and controls are presented in **Figure 2A**. Patients with critical COVID-19 had a significantly higher basal skin perfusion during both the acute disease phase (34 ± 9 PU; $p = 0.0003$) and the post-COVID phase (29 ± 8 PU;

$p = 0.04$), compared with controls (23 ± 7 PU). These differences remained significant after removal of the two sedated patients treated with mechanical ventilation (data not shown). Basal skin perfusion in patients with severe COVID-19 during the acute disease phase (21 ± 5 PU) and the post-COVID phase (17 ± 6 PU) was not significantly different compared with controls. Patients with critical COVID-19 had significantly higher basal skin perfusion compared with patients with severe COVID-19, both during the acute ($p = 0.0009$) and the postinfectious ($p = 0.02$) phases. Differences in basal skin perfusion between the patients and controls are illustrated by color-coded images from the LSCI analyses in two patients with critical COVID-19 (a survivor and a nonsurvivor), one patient with severe COVID-19, and one control subject (**Fig. 2B**).

Delta values in ACh-mediated (endothelial dependent) vasodilation were significantly reduced in the patients with critical COVID-19 during the acute disease phase (15 ± 11 PU) compared with controls (37 ± 14 PU; $p < 0.0001$) (**Fig. 3**). During the postinfectious phase, delta ACh-mediated response had increased to 31 ± 17 PU in patients with critical COVID-19 and was no longer significantly different

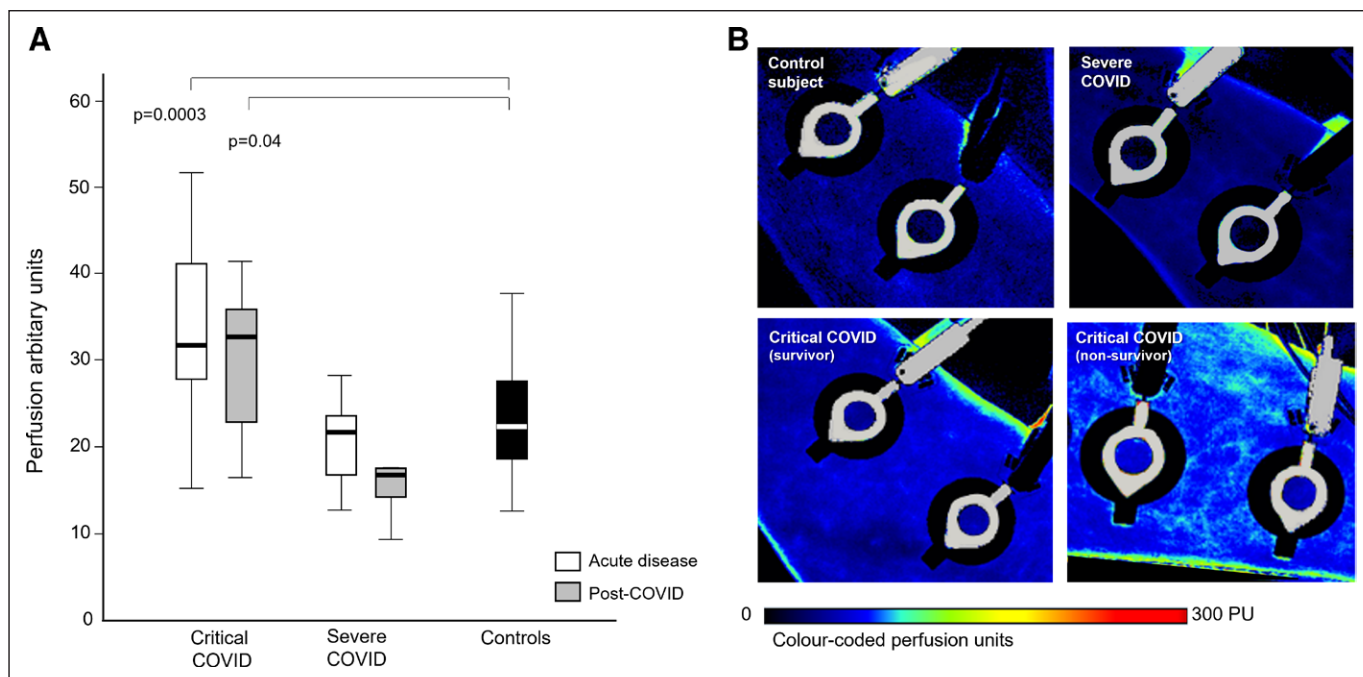


Figure 2. Basal skin perfusion in patients with critical/severe COVID-19. **A**, Presents forearm skin perfusion (medians, interquartiles, and nonoutlier ranges) in patients with critical and severe COVID-19 during acute disease and postinfectious phase and in non-COVID controls. **B**, Demonstrates color-coded images from laser speckle contrast imaging during measurement of basal skin perfusion in one control subject (72-yr-old male with hypertension), one patient with severe COVID-19, and two patients with critical COVID-19 (one survivor and one nonsurvivor). Average basal skin perfusion was 28 perfusion unit (PU) in the control subject, 22 PU in the patients with severe COVID-19, 41 PU in the survivor with critical COVID-19, and 52 PU in the nonsurvivor with critical COVID-19.

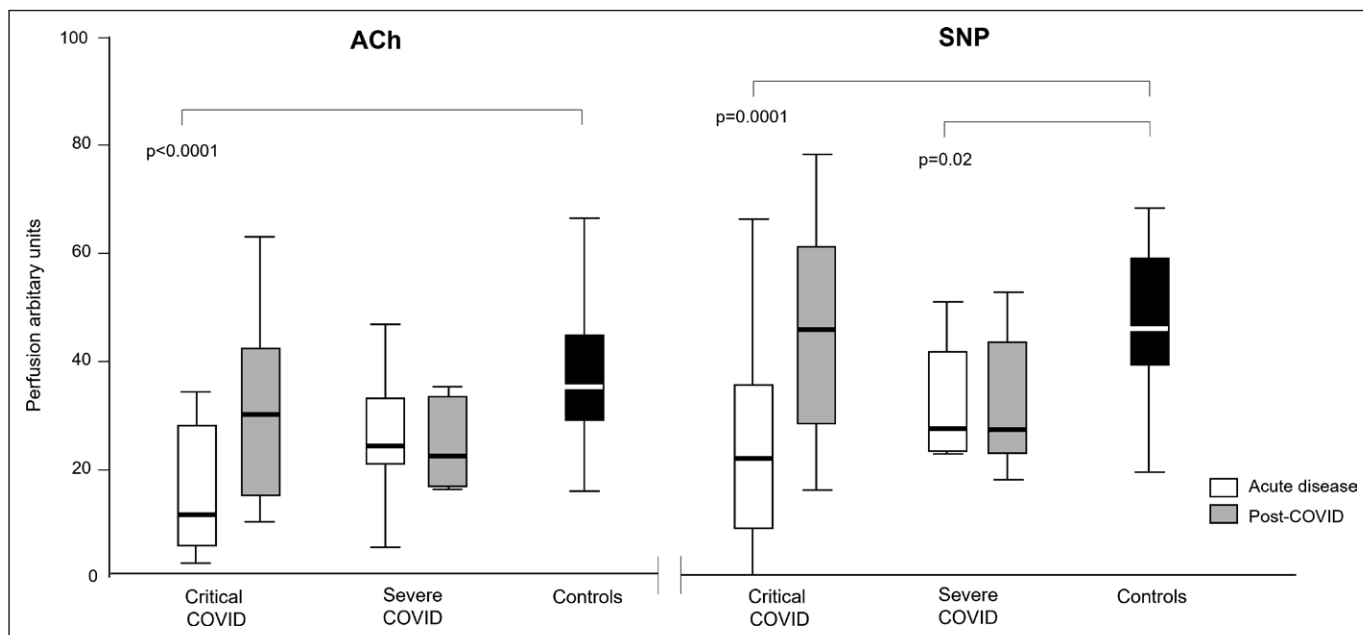


Figure 3. Endothelial-dependent (acetylcholine [ACh] mediated) and endothelial-independent (sodium nitroprusside [SNP] mediated) vasodilation in patients with critical and severe COVID-19 during acute and postinfectious phases, and in subjects without COVID-19. Data shows forearm skin perfusion (in medians, interquartiles, and nonoutlier ranges).

compared with controls ($p = 0.25$). Corresponding values in patients with severe COVID-19 were not significantly different compared with controls. We found no significant differences in delta values of ACh-induced vasodilatation between patients with critical and severe COVID-19.

Similarly, delta values in SNP-mediated (endothelial-independent) vasodilatation were significantly reduced in the patients with critical COVID-19 during the acute disease phase (23 ± 17 PU) compared with controls (47 ± 13 PU, $p = 0.0001$) (Fig. 3). During the postinfectious phase, delta SNP-mediated responses had improved to 43 ± 21 PU in patients with critical COVID-19 and did not differ compared with controls ($p = 0.53$). Patients with severe COVID-19 also had significantly reduced SNP-mediated vasodilatation compared with controls during the acute disease phase (median 27 PU [IQR, 23–41 PU] vs 45 PU [38–58 PU]; $p = 0.02$) (Fig. 3), whereas no differences were found during post-COVID phase. Delta SNP-induced vasodilatation was not significantly different between patients with critical and severe COVID-19. The ACh/SNP delta ratios were not significantly different between patients with critical/severe COVID-19 and controls, respectively (data not shown).

DISCUSSION

We have examined microvascular function in 23 patients with critically ill COVID-19 through bedside assessment of skin perfusion and microvascular reactivity in response to vasoactive drugs. We found that patients with critical COVID-19 had significantly higher basal skin perfusion and reduced responses to both endothelial-dependent and endothelial-independent vasodilatory drugs compared with non-COVID controls matched for age, sex, BMI, and comorbidities. During the postinfectious phase, at least 3 months after disease onset, basal skin perfusion was still significantly higher in surviving patients compared with controls, indicating that critical COVID-19 is associated with long-term microvascular dysregulation.

Beside evaluation of microvascular function in critically ill patients with COVID-19 has been performed in a few observational studies investigating sublingual microcirculation (3, 9, 10). Although these studies have demonstrated disturbances in overall microvascular function, the results have been contradictory, showing

both increased and reduced microvessel density compared with healthy controls or to reference values (3, 9). In a German multi-center study, reduced vascular density and capillary blood flow in sublingual microcirculation were shown in COVID-19 patients in need for mechanical ventilation compared with patients without mechanical ventilation, indicating that microvascular dysfunction correlates with disease severity (3). Assessment of the sublingual microcirculation has the benefit of investigating a centrally located microvascular bed that is not affected by external factors such as room temperature. However, this method is limited to visualizing microvascular blood flow and vessel density under basal conditions, and this approach cannot assess the dynamics in the microcirculation. Since continuous modulation of microvascular blood flow in order to regulate tissue perfusion is an important function of the microcirculation, evaluation of microvascular dynamics and flow reserve is needed. For this purpose, we investigated the skin microvascular reactivity in patients with critical COVID-19.

Normally, at rest and during normothermic conditions, the skin microcirculation is mainly influenced by sympathetic vasoconstrictors and the skin blood flow is low. The markedly increased basal skin perfusion in the patients with critical COVID-19 during acute disease phase may indicate an altered sympathetic vasomotion and/or release of vasodilatory factors from inflamed endothelial or smooth muscle cells in the microvasculature. Since our method is based on a technique that detects overall RBC movement in superficial skin, we cannot evaluate if the increased basal skin perfusion in critical COVID-19 is caused by increased blood flow and/or increased vessel density in the skin microcirculation. In the smaller group of patients with severe COVID-19, we found no differences in basal skin perfusion between patients and controls, suggesting that increased basal microcirculation is a distinguished feature of critical COVID-19. However, due to the small number of patients in this group, data must be interpreted with caution. Nevertheless, these results agree with a study by Sabioni et al (4) which demonstrated increased basal skin perfusion in critically ill COVID-19 patients, but not in patients with mild to moderate COVID-19, compared with controls. This small study, though, assessed skin microcirculation through single-point laser Doppler flowmetry, which has a poorer spatial

reproducibility than the LSCI used in our study (11), and the control group consisted of healthy subjects without comorbidities seen among the patients. We now confirm these findings in a larger group of patients with critical COVID-19 and matched control subjects, which verifies that there are true differences in basal skin microcirculation between the patients and controls. However, whether the observed increased basal skin perfusion in patients with critical COVID-19 represents a generalized systemic vasodilatation in the microvasculature, as seen in patients with sepsis and septic shock, or is a manifestation specific to the skin microcirculation, remains to be elucidated. A widespread generalized systemic vasodilatation during critical COVID-19 should cause a distributive hypotension and hemodynamic instability, which was not found in our study, and has not been described as a common feature of patients with critical COVID-19. Thus, it seems that the distribution and manner of microvascular deterioration associated with critical COVID-19 differ from that in sepsis and septic shock, as also suggested by other research groups (12, 13). In addition, COVID-induced microangiopathy may be especially pronounced in the skin compared with many other organs, as histological findings have shown that the skin and the lungs are the organs with the highest expression of the SARS-CoV-2 entry receptor angiotensin-converting enzyme 2 receptors per unit area on endothelial cells in the microvasculature (14). Indeed, pronounced cutaneous microvascular inflammation has been demonstrated in histological specimen of grossly normal skin of deceased patients with COVID-19 (14). This suggests that the skin may be a promising organ to study in order to gain a better understanding of critical COVID-19 pathophysiology.

Measuring skin perfusion in response to ACh and SNP iontophoresis investigates different pathways for vasodilatation initiated by the vascular endothelium and smooth muscle cells, respectively. ACh binds to receptors on the endothelial cells and activates intracellular pathways leading to release of vasoactive chemicals such as nitric oxide (NO), prostaglandins, and endothelium-dependent hyperpolarization factor, which in turn stimulate smooth muscle cell relaxation through paracrine signaling. SNP, on the other hand, is a NO donor that causes a direct smooth muscle cell relaxation by activating the intracellular NO-sensitive guanylyl cyclase. A reduced response to ACh with no

concurrent reduction in the SNP-mediated response would thus indicate endothelial cell dysfunction. Our results, however, showed that critical COVID-19 was associated with significantly reduced responses to both ACh and SNP with no differences in the ACh/SNP ratios between patients and controls. This indicates that the smooth muscle cell function is impaired. Whether or not the endothelial cells also are malfunctioning cannot be concluded from our results, as the vasodilatation is ultimately carried out by the smooth muscle cells. Nevertheless, in the light of previous studies, demonstrating the involvement of vascular endothelial cells in the pathophysiology of severe COVID-19 through histological specimens and plasma biomarkers (1–6), we believe that the pathophysiology behind microvascular impairment during critical COVID-19 most likely involves both vascular endothelium and smooth muscle. Similarly, experimental models of sepsis have shown that microvascular impairment in sepsis and septic shock include abnormalities within the vascular endothelial and smooth muscle cells and the interaction between these cells (15). The mechanisms behind vascular smooth muscle cell dysfunction during critical COVID-19 are yet unclear but may be explained by the massive inflammatory response in the microvasculature. Increased oxidative stress may attenuate the NO-sensitive signaling cascade within the vascular smooth muscle cells and/or reduce NO bioavailability, as superoxide anions combine with NO. In addition, it has been shown that the vascular smooth muscle cells, like the endothelial cells, express ACE2 receptors and could therefore be directly infected by the SARS-CoV-2 (16).

During the follow-up, several months after disease onset, the survivors of critical COVID-19 still had a higher basal skin perfusion compared with controls, indicating long-term effects on microvascular regulation. This could be one of the contributing factors behind persisting symptoms following a severe COVID-19 infection and deserve further investigations in a larger patient group.

The main limitation of this study is the small number of patients, especially for the patient group with severe COVID-19. However, our primary aim was to investigate skin microvascular function in patients with critical COVID-19 during the acute disease phase, and the group of 23 critically ill patients were in line with our power calculations. Although no conclusions from the

small group of patients with severe COVID-19 can be drawn, the variability of the data in that group was low, suggesting valid results.

CONCLUSIONS

In conclusion, our results indicate that critical COVID-19 induces a systemic microvascular impairment that in part persists during recovery, as significant changes in skin microcirculation were detected both during the acute and postinfectious phase. During the acute disease phase, the reactivity of skin microcirculation is markedly reduced by mechanisms that involve vascular smooth muscle cell function. Our study supports skin microcirculation as suitable for bedside investigation of COVID-induced microvascular dysfunction in critically ill patients.

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REFERENCES

- Varga Z, Flammer AJ, Steiger P, et al: Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020; 395:1417–1418
- Nagashima S, Mendes MC, Camargo Martins AP, et al: Endothelial dysfunction and thrombosis in patients with COVID-19—brief report. *Arterioscler Thromb Vasc Biol* 2020; 40:2404–2407
- Rovas A, Osiaevi I, Buscher K, et al: Microvascular dysfunction in COVID-19: The MYSTIC study. *Angiogenesis* 2020; 14:1–13.
- Sabioni L, De Lorenzo A, Lamas C, et al: Systemic microvascular endothelial dysfunction and disease severity in COVID-19 patients: Evaluation by laser Doppler perfusion monitoring and cytokine/chemokine analysis. *Microvasc Res* 2021; 134:104119
- Vassiliou AG, Keskinidou C, Jahaj E, et al: ICU admission levels of endothelial biomarkers as predictors of mortality in critically ill COVID-19 patients. *Cells* 2021; 10:186
- Vieceli Dalla Sega F, Fortini F, Spadaro S, et al: Time course of endothelial dysfunction markers and mortality in COVID-19 patients: A pilot study. *Clin Transl Med* 2021; 11:e283
- World Health Organization: Clinical Management of COVID-19: Interim Guidance. Geneva, Switzerland, World Health Organization. Available at: <https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-2>. Accessed March 20, 2021
- Tehrani S, Gille-Johnson P: Microvascular dysfunction in patients with critical COVID-19, a pilot study. *Shock* 2021; 56:964–968
- Edul VSK, Eguillor JFC, Ferrara G, et al: Microcirculation alterations in severe COVID-19 pneumonia. *J Crit Care* 2021; 61:73–75
- Damiani E, Carsetti A, Casarotta E, et al: Microvascular alterations in patients with SARS-COV-2 severe pneumonia. *Ann Intensive Care* 2020; 10:60
- Deegan AJ, Wang RK. Microvascular imaging of the skin. *Phys Med Biol* 2019; 64: 07TR01
- Hutchings SD, Watchorn J, Trovato F, et al: Microcirculatory, endothelial, and inflammatory responses in critically ill patients with COVID-19 are distinct from those seen in septic shock: A case control study. *Shock* 2021; 55:752–758
- Kubli S, Boëgli Y, Ave AD, et al: Endothelium-dependent vasodilation in the skin microcirculation of patients with septic shock. *Shock* 2003; 19:274–280
- Magro CM, Mulvey J, Kubiak J, et al: Severe COVID-19: A multifaceted viral vasculopathy syndrome. *Ann Diagn Pathol* 2021; 50:151645
- Hollenberg SM, Cunnion RE: Endothelial and vascular smooth muscle function in sepsis. *J Crit Care* 1994; 9:262–280
- Hamming I, Timens W, Bulthuis ML, et al: Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol* 2004; 203:631–637