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Regional Cerebral Oxygenation in Patients with Severe COVID-19

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Регионарная церебральная оксигенация у пациентов с тяжелым течением COVID-19

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Summary

The aim of the study was to assess regional cerebral oxygenation ($rScO_2$) in patients with acute respiratory distress syndrome (ARDS) associated with COVID-19.

Material and methods. The cross-sectional study was conducted. Twenty-eight patients with severe COVID-19 who were admitted in the intensive care unit were enrolled. Regional cerebral oxygenation was assessed using near-infrared spectroscopy, laboratory markers of cerebral damage, clinical and laboratory characteristics.

Results. Median age of patients was 65 years, of whom 50% were men. Three (11%) patients had severe ARDS, 8 (29%) patients had moderate ARDS, and 17 (60%) patients had mild ARDS. Mechanical ventilation was performed in 20 (71%) patients, vasopressors were used in 14 (50%) patients. The median levels of cerebral saturation were normal and did not differ between the left ($rScO_{2l}$) and right ($rScO_{2r}$) hemispheres (68 (58–75) and 69 (59–76), respectively). The level of S-100 protein was increased (0.133 (0.061–0.318) μg/l) in contrast to the normal level of neuron-specific enolase (12.5 (8.0–16.5) μg/l). A correlation was found only between $rScO_2$ and hemoglobin level (rho=0.437, P=0.02) and between $rScO_2$ and lymphocyte count (rho=–0.449, P=0.016). An increase in S-100 negatively correlated with a decrease in Glasgow Coma Scale score (rho=–0.478, P=0.028).

Conclusion. Near-infrared spectroscopy did not reveal a decrease in $rScO_2$ among patients with ARDS associated with COVID-19. The S-100 protein is a useful marker for the assessment of impaired consciousness. Further study of the causes of cerebral dysfunction in patients with severe COVID-19 and methods for its early identification is warranted.

Keywords: cerebral oxygenation; neurological dysfunction; COVID-19; S-100 protein

Conflict of interest. Authors declare no conflict of interest.

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Introduction

The outbreak of the novel coronavirus infection (COVID-19) has swept over 140 countries in a short period of time and has become a global public health problem [1]. In addition to the high incidence of acute respiratory distress syndrome (ARDS) [2]

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and cardiovascular complications [3], neurological complications [4] have been considered common in patients with COVID-19, making their early rehabilitation very difficult.

Underlying diseases of the central nervous system, multiple organ failure, use of sedatives and muscle relaxants make early diagnosis of COVID-19-related brain dysfunction difficult [5]. We suggested that screening of regional cerebral oxygenation ($rScO_2$) using near-infrared spectroscopy in patients with severe COVID-19 would not only allow noninvasive assessment of cerebral perfusion in ARDS, but also reveal its relationship with prognostic markers of disease severity.

The aim of the study was to assess the regional cerebral oxygenation ($rScO_2$) in patients with acute respiratory distress syndrome (ARDS) associated with COVID-19.

Material and Methods

A cross-sectional study assessed the $rScO_2$ values of 28 randomly selected patients with severe COVID-19 who were hospitalized in the intensive care unit within one day. There were no exclusion criteria. Diagnosis of COVID-19, evaluation of disease severity, and treatment, including respiratory therapy for acute respiratory failure, were performed according to the temporary guidelines of the Ministry of Health of the Russian Federation on prevention, diagnosis and treatment of the novel coronavirus infection (COVID-19) [6]. Mechanical ventilation was performed using Hamilton G5 and Hamilton C2 (Hamilton Medical, Switzerland) devices. Bilateral $rScO_2$ monitoring was performed using INVOS® 5100C cerebral oxymeter (Somanetics, Troy, Michigan, USA) until stable cerebral oscillation values (difference between values less than 10%) were achieved within 30 min. During $rScO_2$ measurement, mean arterial pressure (MAP), gas exchange indices (SpO_2, PaO_2, PaO_2/FiO_2, $PaCO_2$) and blood count (hemoglobin (Hb), lymphocytes (LYM)) were taken in all patients, as well as the levels of inflammatory markers (procalcitonin (PCT), C-reactive protein (CRP), interleukin-6 (IL-6), D-dimer, and markers of neuronal damage (protein S-100 (S-100), neuron-specific enolase (NSE)). Patients who did not receive sedatives and muscle relaxants were additionally divided into subgroups with impaired consciousness (n=7) and with clear consciousness (n=14). The Richmond Agitation-Sedation Scale was used to assess the depth of hypnosis in patients who were ventilated. The Glasgow Coma Scale (GCS) was used in patients with impaired consciousness.

Quantitative data were presented as medians (*Me*) and quartiles (25%; 75%), categorical data as absolute numbers (n) and proportion (%). Mann–Whitney test was used to evaluate significance of differences in quantitative variables between subgroups. Spearman's correlation coefficient (ρ) was used to identify correlations. The missing data percentage did not exceed 10% for each parameter. When testing statistical hypotheses, differences were considered significant at P<0.05. The data were analyzed using the SPSS 28.0.0.0 software package (IBM SPSS Statistics, Chicago, IL, USA).

Results

The median age of the patients was 65 years, half of them were male. Twenty (71%) patients were ventilated for 12 to 72 hours during $rScO_2$ measurement, with 50% of all patients sedated with dexmedetomidine until a target sedation level of –5 to 0 on the Richmond Excitation-Sedation Scale was achieved, depending on the clinical situation. After discontinuation of sedation, 7 (33%) patients were observed to have impaired consciousness (7 to 14 points on the Richmond Arousal-Sedation Scale). Neuroimaging (computed tomography or magnetic resonance imaging) revealed brain damage in only one of these patients, while in the remaining patients the changes were limited to the enlargement of the CSF spaces. In 7 patients, a reliable assessment of wakefulness level was impossible due to muscle relaxation and deep sedation. 50% of all patients received vasopressor support (norepinephrine) during $rScO_2$ measurement to maintain MAP ⩾60 mm Hg. Due to severe respiratory failure, 6 (21%) patients were in a prone position (Table 1).

Cerebral saturation values of the left ($rScO_{2l}$) and right ($rScO_{2r}$) hemispheres did not differ and averaged 68% and 69%, respectively, P=0.819. The $rScO_2$ values were generally normal (there were no episodes of $rScO_2$ falling below 45%), despite the fact that in 8 (29%) patients the PaO_2/FiO_2 ratio corresponded to moderate ARDS (according to the Berlin criteria for ARDS [7]), and in 3 (11%) patients, to severe. In subgroup comparisons, $rScO_{2l}$ (P=0.488) and $rScO_{2r}$ (P=0.322) scores did not differ between patients in full and impaired consciousness.

In the general patient cohort, we found a moderate increase in protein S-100 levels with normal NSE ones. When comparing subgroups, S-100 protein levels were higher in patients with impaired consciousness than in patients in full consciousness (0.154 (0.122–0.424) vs 0.095 (0.044–0.128), P=0.025, respectively), NSE level did not differ between subgroups (14.1 (9.9–42.2) vs 11.2 (6.0–15.4), P=0.11, respectively).

We found weak correlations of $rScO_2$ values: a direct one with hemoglobin level (rho=0.437, P=0.02) and an inverse one with lymphocyte count (rho=–0.449, P=0.016). S-100 level was negatively correlated with the GCS score (rho=–0.478, P=0.028), and NSE level had a significant positive moderate correlation with

General patient characteristics, *n*=28.

Parameter	Values
Age, years	65 (57–75)
Males, *n* (%)	14/28 (50%)
Mechanical ventilation	20/28 (71%)
On vasopressors	14/28 (50%)
Sedated	14/28 (50%)
Prone position	6/28 (21%)
GCS, points	15 (13–15)
Impaired consciousness	7/21 (33%)
MAP, mm Hg	88 (82–95)
SpO_2, %	96 (94–99)
PaO_2, mm Hg	90.8 (70.9–113)
$PaCO_2$, mm Hg	40.9 (35.7–46.2)
PaO_2/FiO_2	218 (155–269)
Hb, g/L	119 (91–136)
LYM, $\times 10^3/\mu L$	1.02 (0.66–1.46)
PCT, ng/mL	0.87 (0.32–2.10)
CRP, mg/mL	137 (53–209)
IL-6, pg/mL	111 (40–625)
D-dimer, μg/mL	1.46 (0.93–2.71)
S-100 protein, μg/mL	0.133 (0.061–0.318)
NSE, μg/mL	12.5 (8.0–16.5)
$rScO_{2l}$, %	68 (58–75)
$rScO_{2r}$, %	69 (59–76)

Note. GCS — Glasgow Coma Scale; MAP — mean arterial pressure; SpO_2 — arterial blood oxygen saturation according to pulse oximetry; PaO_2 — arterial blood oxygen pressure; $PaCO_2$ — arterial blood carbon dioxide pressure; FiO_2 — oxygen fraction in inhaled gas mixture; Hb — hemoglobin level; LYM — absolute number of lymphocytes; CRP — C-reactive protein; IL-6 — interleukin-6; NSE — neuron-specific enolase; $rScO_{2l}$ — regional cerebral oxygenation of the left cerebral hemisphere; $rScO_{2r}$ — regional cerebral oxygenation of the right cerebral hemisphere.

IL-6 level (rho=0.546, *P*=0.035). No relationship of $rScO_2$ with the severity of ARDS, frequency of vasopressor support and sedation was found.

Discussion

Currently, the putative mechanisms of neurological dysfunction in COVID-19 include hypercoagulation, vascular damage, hypoxia, immune dysregulation, electrolyte disturbances, and direct viral brain damage [8-11] and have been brought into focus. Laboratory markers of neurological dysfunction, such as lymphocytopenia, elevated concentrations of D-dimer, IL-6 and procalcitonin, also predict disease severity and adverse outcome [12–14], which may indicate the multifactorial nature of CNS damage in the context of COVID. The lack of correlation of $rScO_2$ with the levels of these laboratory markers in our study did not allow us to pinpoint the specific cause of cerebral dysfunction in COVID-19. The wide range of neuroimaging changes in the brain in severe disease and low detection rate of SARS-CoV-2 coronavirus in cerebrospinal fluid [11, 15, 16] make direct viral damage to the brain less likely to be the leading pathogenetic mechanism. Focusing on endothelial changes and consequences of abnormal immune response could help explain the mechanisms of CNS dysfunction in COVID-19.

The small sample size (which was not predetermined) and the lack of correlation of clinical results with the histological findings are the main limitations of our study. In addition, an assessment of changes in cerebral oxygenation and laboratory parameters at different stages of the disease is necessary.

Conclusion

Cerebral oxygenation parameters in patients with severe COVID-19 remained within the reference range despite hypoxemia. Increased S-100 in patients with severe COVID-19 has more diagnostic value than NSE and correlates with the depth of hypnosis. Cerebral dysfunction in COVID-19 is likely to be multifactorial and depends on the severity of cerebral damage requiring further scrutiny and investigation.

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