Phenotypes of COVID-19-Associated Dysautonomia in Patients Requiring Veno-Venous Extracorporeal Membrane Oxygenation

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Abstract

Background. *Patients with novel coronavirus infection (COVID-19) receiving veno-venous extracorporeal membrane oxygenation (VV-ECMO) are typically prone to hemodynamic disorders of various severity. Tachycardia, increased cardiac output, or arterial hypotension affect the effectiveness of VV-ECMO. One of the possible causes of hemodynamic disorders leading to ineffective VV-ECMO may be dysautonomia (DA), which refers to an imbalance of sympathetic and parasympathetic divisions of the autonomic nervous system (ANS). The development of DA in various critical conditions was described previously. Dysautonomia also develops in COVID-19 (COVID-19-associated DA), but it was studied only in stable non-ICU patients. The presented study focuses on COVID-19-associated DA in critical COVID-19 patients requiring VV-ECMO support.*
The study ***was aimed at*** *determining COVID-19-associated DA phenotypes, their impact on VV-ECMO effectiveness and disease outcomes.*
Materials and methods. *The study included 20 patients: 12 (60%) females, 8 (40%) males. The patients had an average age of 55 years. All the patients underwent 24-hour Holter monitoring with spectral analysis of heart rate variability (HRV) assessing low-frequency component of the spectrum (LF), the high-frequency component of the spectrum (HF), the LF/HF ratio on days 1, 3, and 5 of VV-ECMO. Diagnostic criteria for COVID-19-associated DA was a decrease in LF/HF < 2.28 or an increase in LF/HF > 6.94. The diagnostic criteria of predominant tone of sympathetic nervous system (sympathetic tone) was an increase in LF/HF > 6.94, while a decrease in LF/HF < 2.28 indicated predominant parasympathetic tone. Low sympathetic tone was determined by a decrease in LF < 15%, and an increase in LF > 40%. Low parasympathetic tone was determined by a decrease in HF < 15%, and an increase in HF > 25%. The criteria used were based on the results of previous studies.*
The following parameters were registered in the study population: VV-ECMO weaning, duration of respiratory and VV-ECMO support, length of stay in the intensive care unit (ICU) and in hospital, and disease outcomes.
Results. *COVID-19-associated DA was diagnosed in all the patients. LF/HF median value was 0.1. HRV spectrum parameters changed significantly over time: on day 5 of VV-ECMO support LF and HF values significantly decreased. The patients were divided into three groups according to the DA phenotype: group 1 (n = 4 [20%]) with normal sympathetic tone and high parasympathetic tone (nShP phenotype); group 2 (n = 14 [70%]) with low sympathetic tone and high parasympathetic tone (lShP phenotype); group 3 (n = 2 [10%]) with low sympathetic tone and normal parasympathetic tone (lSnP phenotype). The latter group was excluded from further statistical analysis due to the small sample size. In group 2, the mean HR was significantly higher compared with group 1. In group 1, VV-ECMO weaning was successful in 50% of cases, whereas in group 2 it was successful in 7.2% (p = 0.04).*
Conclusions. *To determine a dysautonomia phenotype, it is necessary to continuously monitor DA status in COVID-19 patients during VV-ECMO. Tachycardia in COVID-19 patients during VV-ECMO does not exclude the ANS imbalance with a significant predominance of parasympathetic tone over the sympathetic tone. It is this COVID-19-associated DA phenotype that is significantly associated with the unfavorable outcomes.*

Keywords: *COVID-19; novel coronavirus infection; dysautonomia; autonomic nervous system; extracorporeal membrane oxygenation*

Ethics approval. All patients provided their voluntary informed consent to participate in the study. The study was approved by the Ethics Committee of the Sklifosovsky Research Institute of Emergency Medicine (Protocol No. 11-22, dated 21 November 2022).

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Фенотипы COVID-19-ассоциированной дисавтономии у пациентов, нуждающихся в проведении вено-венозной экстракорпоральной мембранной оксигенации

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Аннотация

Актуальность. *При проведении вено-венозной экстракорпоральной мембранной оксигенации (вв-ЭКМО) у пациентов с новой коронавирусной инфекцией (COVID-19) типичны гемодинамические нарушения разной степени тяжести. Тахикардия, увеличение сердечного выброса или артериальная гипотензия влияют на эффективность вв-ЭКМО. Одной из возможных причин нарушений гемодинамики, приводящих к неэффективности вв-ЭКМО, может стать дисавтономия (ДА) – дисбаланс симпатического и парасимпатического отделов вегетативной нервной системы (ВНС). Ранее описано развитие ДА при различных критических состояниях. При COVID-19 также развивается ДА (COVID-19-ДА), но объектом исследований, её изучавших, были исключительно стабильные, нереанимационные пациенты. Представленное исследование посвящено проблеме COVID-19-ДА у пациентов с COVID-19, находящихся в критическом состоянии, требующем проведения вв-ЭКМО.*

Цель *исследования – определение фенотипов COVID-19-ДА, их влияния на эффективность вв-ЭКМО и исходы заболевания.*

Материалы и методы. *В исследование вошли 20 пациентов: 12 (60%) женщин, 8 (40%) мужчин. Средний возраст – 55 лет. Пациентам проводили суточное холтеровское мониторирование с оценкой спектральных параметров вариабельности сердечного ритма: низкочастотного (LF) и высокочастотного (HF) компонентов записи, отношения LF/HF на 1, 3, 5-е сутки проведения вв-ЭКМО. Критерием COVID-19-ДА являлось снижение LF/HF менее 2,28 или повышение LF/HF более 6,94. Критерием преобладающего тонуса симпатического отдела ВНС являлось увеличение LF/HF более 6,94, парасимпатического – снижение LF/HF менее 2,28. Критерием пониженного тонуса симпатического отдела ВНС являлось снижение LF менее 15%, повышенного – увеличение LF более 40%. Критерием пониженного тонуса парасимпатического отдела ВНС являлось снижение HF менее 15%, повышенного – увеличение HF более 25%. Используемые критерии были основаны на результатах ранее проведённых работ.*

У пациентов фиксировали факт отлучения от вв-ЭКМО, длительность респираторной терапии и вв-ЭКМО, длительность пребывания в отделении реанимации и интенсивной терапии и срок госпитализации, исходы заболевания.

Результаты. *COVID-19-ДА была диагностирована во всех наблюдениях. Медиана LF/HF составила 0,1. Параметры вариабельности сердечного ритма достоверно изменялись в динамике: на 5-е сут вв-ЭКМО достоверно снижались параметры LF и HF. В зависимости от тонуса симпатического и парасимпатического отделов ВНС пациенты были разделены на три группы: 1-я (n = 4; 20%) – фенотип с нормальным тонусом симпатического отдела и высоким тонусом парасимпатического отдела ВНС; 2-я (n = 14; 70%) – фенотип с пониженным тонусом симпатического отдела и высоким тонусом парасимпатического отдела ВНС; 3-я (n = 2; 10%) – фенотип с пониженным тонусом симпатического отдела и нормальным тонусом парасимпатического отдела ВНС (эта группа была исключена из дальнейшей статистической обработки, поскольку являлась малочисленной). Во 2-й группе средняя частота сердечных сокращений была достоверно выше по сравнению с 1-й группой. В 1-й группе отлучение от вв-ЭКМО было успешно в 50% случаев, тогда как во 2-й – в 7,2% (p = 0,04).*

Выводы. *При проведении вв-ЭКМО у пациентов с COVID-19 необходим продлённый мониторинг ДА для определения её фенотипа. Наличие тахикардии у пациентов с COVID-19 при проведении вв-ЭКМО не исключает наличия дисбаланса ВНС с существенным преобладанием тонуса парасимпатического отдела ВНС над симпатическим. Именно такой фенотип COVID-19-ДА достоверно ассоциирован с развитием неблагоприятного исхода.*

Ключевые слова: *COVID-19; новая коронавирусная инфекция; дисавтономия; вегетативная нервная система; экстракорпоральная мембранная оксигенация*

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Introduction

Viral pneumonia caused by a novel coronavirus infection (COVID-19) leads to the development of acute respiratory distress syndrome (ARDS) in 8–15% of patients [1]. According to the current clinical guidelines, a veno-venous extracorporeal membrane oxygenation (VV-ECMO) should be initiated when a COVID-19 patient develops ARDS causing progressive refractory gas exchange impairment despite the use of lung-protective mechanical ventilation, adequate sedation, myorelaxation, and prone positioning [2].

COVID-19 patients requiring VV-ECMO are prone to hemodynamic disorders of various severity degrees: hypo- and hypertension, refractory tachycardia, which can affect the VV-ECMO effectiveness, causing a mismatch in minute volume between intrinsic and artificial blood circulation [3, 4]. Hemodynamic disorders in such patients may be caused by DA due to imbalance of sympathetic and parasympathetic divisions in the autonomic nervous system (ANS) [5]. DA develops in patients with critical conditions caused by a wide range of diseases. DA has also been described in COVID-19 patients (COVID-19-associated DA) [6–8]. Previously published studies on COVID-19-associated DA are mostly based on the data obtained from stable non-ICU patients. We were unable to find studies on COVID-19-associated DA in critical ICU-patients requiring VV-ECMO in available literature. Our study focuses on this issue.

The study **was aimed at** determining COVID-19-associated DA phenotypes, their impact on VV-ECMO effectiveness and disease outcomes.

Materials and methods

Inclusion criteria:
- aged 18 years and older;
- confirmed COVID-19 diagnosis;
- ARDS with refractory gas exchange impairment;
- need for VV-ECMO support.

Exclusion criteria:
- atonic coma;
- persistent or paroxysmal atrial fibrillation;
- sinoatrial block, sick sinus syndrome; atrioventricular block;
- high-grade premature ventricular contractions (Lown grade IVa, IVb, V);
- artificial cardiac pacemaker;
- dysautonomia diagnosed prior to COVID-19.

All patients were provided with the full range of necessary medical care approved by the temporary guidelines of the Ministry of Health of the Russian Federation on prevention, diagnosis and treatment of COVID-19, valid in the period of the treatment [9].

On admission, patients underwent chest computed tomography (CT) using Aquilion Prime CT scanner (Toshiba) with subsequent assessment of lung injury severity. In case of respiratory dysfunction, the patients were provided with respiratory support using SV300 ventilator (Mindray), non-invasive ventilation (NIV) with high-flow oxygen and mask ventilation, and invasive mechanical ventilation. Sedation and myorelaxation as indicated to patients were performed by prolonged intravenous infusion of propofol at a dose of 4–12 mg/kg per hour and

rocuronium bromide at a dose of 0.3–0.6 mg/kg per hour. If COVID-19-associated DA was suspected, we initiated intravenous or enteral administration of β-blockers (esmolol, metoprolol at appropriate doses) and intravenous infusion of dexmedetomidine (DMM, central α-sympathomimetic) at a dose of 0.7–1.4 μg/kg per hour. This therapy strategy was proposed by A. Rudiger et al. for managing dysautonomia symptoms in sepsis and was called decatecholaminization [20]. Myocardial contractility and volemic status were evaluated on transthoracic echocardiogram (TTE) using MyLab 70 ultrasound system (Esaote).

Indications for VV-ECMO [10]:
- ratio of arterial oxygen partial pressure and fraction of oxygen in inspired air (PaO_2/FiO_2) < 150 mm Hg, or
- PaO_2/FiO_2 < 60 mm Hg > 6 hours, or
- PaO_2/FiO_2 < 50 mm Hg > 3 hours, or
- pH < 7.20 and arterial partial CO_2 pressure ($PaCO_2$) > 80 mm Hg > 6 hours, or
- $PaO_2/FiO_2 \geqslant$ 150 mm Hg with pH < 7.20 and $PaCO_2$ > 80 mm Hg > 6 hours.

Contraindications for VV-ECMO [10]:
- patients over 70 years;
- duration of mechanical ventilation prior to VV-ECMO > 10 days;
- inability of cannulla placement;
- contraindications to anticoagulant therapy;
- concomitant incurable end-stage diseases.

DA was diagnosed by heart rate variability (HRV) parameters obtained during 24 h Holter monitoring using CardioMem CM 3000 Digital Recorder (GE). Holter monitoring allowed to assess heart rate (HR), low-frequency component of the HR variability spectrum associated with sympathetic tone (LF), high-frequency component associated predominantly with parasympathetic tone (HF), and LF/HF ratio.

Reference values for the monitored parameters [11–14, 28–31]:
1) average 24 h HR: 60–80 bpm;
2) LF percentage in total frequency spectrum: 15–40%;
3) HF percentage in total frequency spectrum: 15–25%;
4) LF/HF: 2.28–6.94.

Altered LF/HF ratio may indicate an ANS imbalance. HRV spectrum analysis allows to determine the dysautonomia phenotype based on the assessment of the sympathetic and parasympathetic tones. The LF/HF ratio below the reference values indicates the predominant parasympathetic tone [31], above the reference values – the predominant sympathetic tone [31].

Patients underwent 24 h Holter monitoring with the assessment of the above parameters on days 1, 3 and 5 of VV-ECMO. Data containing significant errors making more than 20% of the Holter recording and confounding HRV assessment were excluded from further analysis. The following parameters were registered in the study population: the results of the VV-ECMO weaning, duration of respiratory therapy and VV-ECMO, length of stay in the ICU and in hospital, and disease outcomes.

Statistical data were processed using Statistica 12 software (StatSoft). Data per group were compared using the Mann–Whitney method, qualitative inter-group variables were compared using Fisher's exact test, intra-group parameters (dependent variables) were assessed using Wilcoxon test.

Results

The study was conducted in the ICU of the infectious diseases department in Sklifosovsky Research Institute of Emergency Medicine, Moscow, Russia from September 2021 till February 2022. The study included 20 patients (12 (60%) females and 8 (40%) males) with COVID-19-associated ARDS requiring VV-ECMO. The average age of the patients was 55 years. Table 1 presents general characteristics of the patients included in the study at their ICU admission prior to VV-ECMO.

COVID-19-associated DA was diagnosed in all the patients. Table 2 presents HRV parameters reflecting the ANS balance.

The obtained data demonstrate significant changes of sympathetic and parasympathetic tones in COVID-19 patients. So, LF and HF values significantly decreased on day 5 of VV-ECMO. These data indicate the need to monitor HRV in COVID-19 patients during at least the whole period of VV-ECMO support.

Depending on COVID-19-associated DA phenotype, namely, on sympathetic and parasympathetic ANS activity, the patients were divided into three groups:
5) group 1, *n* = 4 (20%): normal sympathetic tone and high parasympathetic tone (nShP);
6) group 2, *n* = 14 (70%): low sympathetic tone and high parasympathetic tone (lShP);
7) group 3, *n* = 2 (10%): low sympathetic tone and normal parasympathetic tone (lSnP).

Since group 3 included only 2 patients, the analysis data would be considered not eligible for formal analysis. Therefore, data from group 3 were removed from further analysis and interpretation of its results. Only data from groups 1 and 2 were compared. These groups were statistically similar by age, gender, severity of condition at admission and at the time of VV-ECMO start, and concomitant diseases (Table 3).

Table 1. General characteristics of patients included in the study at their ICU admission prior to VV-ECMO

Parameter	Value
Age, years, Me (Q_1; Q_3)	55.00 (38.25; 60.00)
Gender, *n* (%)	
males	8 (40)
females	12 (60)
Concomitant diseases, *n* (%)	
arterial hypertension	13 (65)
diabetes mellitus	3 (15)
chronic heart failure	2 (10)
General data, Me (Q_1; Q_3)	
time from disease onset to admission, days	14.50 (11.00; 25.00)
time from admission to VV-ECMO start, days	1.50 (1.00; 3.00)
time from disease onset to VV-ECMO start	17.50 (15.00; 28.75)
Respiratory support, *n* (%)	
NIV	9 (45)
invasive mechanical ventilation	11 (55)
Gas exchange parameters (with respiratory support), Me (Q_1; Q_3)	
P/f	94.00 (89.25; 96.00)
SpO_2, %	92.00 (62.75; 110.00)
Lung injury CT score, *n* (%)	
CT-3	4 (20)
CT-4	16 (80)
Complications, *n* (%)	
bacterial inflammation	11 (55)
sepsis	3 (15)
septic shock	1 (5)

Note. Me — median; Q_1 — lower quartile; Q_3 — upper quartile.

Table 2. Changes in HR and HRV parameters, Me (Q_1; Q_3)

Parameter	VV-ECMO duration, days		
	1	3	5
n	20	20	19
24 h HR, bpm	84.50 (77.50; 97.75)	83.50 (75.00; 98.75)	84.00 (65.00; 101.00)
LF, %	5.60 (2.02; 9.22)	8.99 (2.92; 12.75)	2.98* (1.13; 6.48)
HF, %	53.50 (31.13; 70.57)	53.30 (45.88; 61.60)	29.95* (15.18; 43.23)
LF/HF	0.1 (0.04; 0.23)	0.12 (0.05; 0.3)	0.11 (0.03; 0.18)

Note. *$p < 0.05$ compared with day 3 of VV-ECMO.

Table 3. General characteristics of patients in group 1 and group 2

Parameter	Group	
	1	2
n	4	14
Age. years. Me (Q_1; Q_3)	46.50 (37.50; 58.50)	57.50 (40.20; 62.00)
Gender. *n* (%)		
males	1 (25)	6 (42.8)
females	3 (75)	8 (57.2)
Concomitant disease. *n* (%)		
arterial hypertension	3 (75)	10 (71.4)
diabetes mellitus	1 (25)	2 (14.2)
chronic heart failure	0	2 (14.2)
Respiratory support at admission. *n* (%)		
NIV	2 (50)	6 (42.8)
invasive mechanical ventilation	2 (50)	8 (57.2)
Respiratory support at VV-ECMO start, *n* (%)		
NIV	0	2 (14.2)
invasive mechanical ventilation	4 (100)	12 (85.7)
Lung injury CT score. *n* (%)		
CT-3	2 (50)	1 (7.1)
CT-4	2 (50)	13 (92.9)

Table 4. Comparative HR and HRV analysis in group 1 and group 2 on day 1 of VV-ECMO, Me (Q_1; Q_3)

Parameter	Group	
	1	2
n	4	14
24 h HR, bpm	74.00 (65.00; 82.25)	86.50* (79.75; 97.25)
LF, %	24.67 (17.55; 31.24)	5.30** (2.06; 7.52)
HF, %	54.42 (36.54; 57.14)	56.00 (41.96; 74.20)
LF/HF	0.47 (0.43; 0.58)	0.09** (0.03; 0.12)

Note. *$p < 0.05$; **$p < 0.001$ compared with group 1.

Results of comparative HR and HRV analysis in group 1 and group 2 on day 1 of VV-ECMO are presented in Table 4.

According to the presented data, HR in group 2 was significantly higher compared with group 1. Considering lower sympathetic tone in group 2 patients, such HR values make a data paradox.

The groups were statistically similar by the duration of VV-ECMO, mechanical ventilation, length of ICU and hospital stay, and the frequency of outcomes, except for the frequency of weaning patients from VV-ECMO (Table 5). In group 1 VV-ECMO weaning was successful in 50% patients, while in group 2 — in 7.2% patients ($p = 0.04$). From all the patients included in the study, a patient from group 2 was the only survivor. This fact suggests an importance of the said inter-group difference. However, statistical analysis revealed no significant difference in mortality between the groups.

There were no significant differences across the groups in myocardial contractility and volemic status based on TTE results (see Table 6). Importantly, the TTE results in both groups were within normal range.

Taking into account the data on the β-blockers and DMM effectiveness in the managing DA symptoms using decatecholaminization strategy, as well as the potential influence of sedatives and myorelaxants on the ANS balance, we performed a comparative analysis between the groups by the frequency of using these agents by all study time points (Table 7).

Table 5. Comparison of groups by outcomes

Parameter		Group 1	Group 2
n		4	14
Mechanical ventilation duration, days	Me (Q_1; Q_3)	20.50 (6.00; 35.00)	11.00 (6.75; 13.25)
VV-ECMO duration, days	Me (Q_1; Q_3)	6.00 (6.00; 7.50)	8.50 (5.00; 12.25)
Length of ICU stay, days	Me (Q_1; Q_3)	16.50 (8.00; 32.50)	12.00 (7.75; 16.50)
Length of hospital stay, days	Me (Q_1; Q_3)	21.50 (8.00; 35.00)	12.00 (7.75; 16.50)
VV-ECMO-weaning	*n* (%)	2 (50)	1* (7.2)
Survived	*n* (%)	0	1 (7.2)
Deceased	*n* (%)	4 (100)	13 (92.8)

Note. *$p < 0.05$ compared with group 1.

Table 6. Comparison of the groups by TTE parameters

Parameter		Normal	Group 1	Group 2
n			4	14
Left ventricular ejection fraction, %	Me (Q_1; Q_3)	55–65	58.50 (52.75; 68.75)	62.50 (53.00; 66.25)
Left ventricular end-diastolic volume, ml	Me (Q_1; Q_3)	55–149	109.50 (100.75; 149.00)	104.50 (95.50; 112.50)
Left ventricular end-systolic volume, ml	Me (Q_1; Q_3)	18–40	44.50 (32.75; 66.00)	39.00 (33.50; 48.50)
Left ventricular stroke volume, ml	Me (Q_1; Q_3)	50–70	74.00 (57.25; 84.75)	68.00 (60.75; 73.50)
Inferior vena cava collapsibility > 50%	*n* (%)		1 (25)	6 (42.8)

Table 7. Comparison of groups by frequency of using sedatives, myorelaxants, and β-blockers, *n* (%)

Indicated agent	VV-ECMO duration, days 1		3		5	
	group 1	group 2	group 1	group 2	group 1	group 2
n	4	14	4	14	4	14
β-Blockers	2 (50)	8 (57.2)	2 (50)	8 (57.2)	2 (50)	6 (42.8)
β-Blockers and DMM	1 (25)	3 (21.4)	2 (50)	5 (35.7)	2 (50)	7 (50)
Propofol	3 (75)	11 (78.5)	0	8* (57.2)	1 (25)	9 (64.2)
Myorelaxants	3 (75)	9 (64.2)	0	7 (50)	1 (25)	7 (50)

Note. *$p < 0.05$ compared with group 1.

The presented data indicate that group 2 patients significantly more often received intravenous propofol infusion only on day 3 of VV-ECMO (p = 0.04). The frequency of using β-blockers, DMM, myorelaxants, and propofol on day 1 and day 3 of VV-ECMO in both groups is statistically similar. Moreover, DA phenotype was determined on day 1 of VV-ECMO, when the frequency of using agents that might affect the ANS was similar in both groups.

Discussion

The main objective of the presented study is to define the problem of dysautonomia in ICU patients in general and in COVID-19 patients requiring VV-ECMO as one of the most demanding ICU patient populations in particular. Based on the data obtained, we could emphasize two basic points. First, dysautonomia was present in all the patients with severe COVID-19, advanced ARDS, and the need for VV-ECMO. Second, based on the tone of the sympathetic and parasympathetic divisions of the ANS, we distinguished three COVID-19-associated DA phenotypes: nShP; lShP and lSnP. In our opinion, such a methodological approach to the DA issue in critically ill patients is innovative and extremely practical. It may lead to conceptual changes in the management of patients with critical conditions. It clarifies the necessity to monitor the ANS status, to prevent the development of hemodynamic disorders, and to apply targeted management taking into account the personal phenotype of DA.

The DA issue is not new for intensive care practice. Dysautonomia is a frequent and typical manifestation of CNS failure in neurological ICU patients. HRV analysis data in patients with traumatic brain injury indicate DA development with predominant sympathetic tone in 8–20% cases [15]. HRV analysis in patients with aneurysmal subarachnoid hemorrhage demonstrates a pronounced increase in sympathetic tone [16]. High sympathetic tone is also typical for acute stroke patients [17]. In patients with combined trauma and sepsis, sympathetic tone also predominates significantly more often [18, 19].

Based on the results of these studies, the concept of decatecholaminization was developed, which subsequently successfully proved its effectiveness in ICU patients [20]. This concept is based on the combined use of DMM and esmolol. Combination of these agents inhibits the sympathoadrenal response developing in critical conditions. Septic shock treatment with DMM allows to reduce plasma concentrations of adrenaline by 40% [21]. Esmolol reduces mortality almost 2-fold (from 80.5% to 49.4%) in patients with septic shock and the need for high-dose vasopressor support.[22] All the decatecholaminization studies indicate that the combination of DMM and esmolol is effective in patients with DA associated with high sympathetic tone.

Subsequent studies have shown the heterogeneity of DA manifestations in ICU patients. For example, the predominance of sympathetic tone in sepsis, reflecting the activation of compensatory mechanisms to maintain homeostasis at the onset of bacterial inflammation, is subsequently replaced by the predominant parasympathetic tone. In this case, the severity of septic shock correlates with an increase in parasympathetic tone [23]. HRV analysis in stable non-ICU COVID-19 patients indicates predominance of parasympathetic tone [24]. Our study also demonstrated a significant and substantial predominance of parasympathetic tone over sympathetic tone in critical COVID-19 patients requiring VV-ECMO.

COVID-19 is known to cause both morphologic and functional damage to the central nervous system, where the ANS regulatory centers (paraventricular structures, the olfactory tract, the hippocampus) have been damaged earlier and more severely than the others [25]. It is the ANS regulation centers failure, as well as involvement of the vagus nerve in the COVID-19 pathogenesis, that might be the reason for the COVID-19-associated DA and, consequently, the predominance of parasympathetic tone.

The outcomes of VV-ECMO in COVID-19 patients are significantly and substantially worse compared to other ICU patients [26]. We believe that it is COVID-19-associated DA that plays an important, if not leading, role in those pathologic processes that trigger unfavorable disease outcomes in extremely severe COVID-19 patients. However, it remains unknown whether it is COVID-19-associated DA that causes severe disease course or it is an epiphenomenon.

Our study identified three COVID-19-associated DA phenotypes, which is a unique interpretation of the DA issue in the ICU patients. The most common lShP phenotype is significantly associated with failure to successfully complete VV-ECMO. On the contrary, successful VV-ECMO weaning was significantly more frequent in patients with nShP phenotype. Failure to wean the patient from VV-ECMO means inability to compensate for gas exchange impairment as a result of persisting hypoxemia, which eventually leads to the development of multi-organ dysfunction and lethal outcomes. In this regard, matching in minute volume between intrinsic and artificial blood circulation is one of the goals of intensive therapy, which allows to achieve adequate parameters of gas exchange and to avoid the development of multi-organ dysfunction and, consequently, an unfavorable outcome.

According to the data obtained, there were no significant inter-group differences in the frequency of using β-blockers and DMM for decatecholaminization. It is the concept of decatecholaminization proposed as an effective management strategy for DA with high sympathetic tone that is hypothetically promising for matching in minute

volume between intrinsic and artificial blood circulation due to reduction of a patient's cardiac output. However, our study showed that patients with COVID-19-associated DA and the need for VV-ECMO predominantly develop a DA phenotype with a depressed sympathetic tone, while the parasympathetic tone is dramatically elevated. At the same time, there is a lack of application of the decatecholaminization strategy for COVID-19-associated DA management. This also explains why the course of the disease associated with high parasympathetic tone is more severe, outcomes are unfavorable, and management methods are lacking.

An interesting result of the study is that patients with lShP phenotype significantly more often received prolonged intravenous propofol infusion on day 3 of VV-ECMO. A more pronounced ANS imbalance and worse outcomes in this group suggest that the use of propofol for pharmacological sedation should be avoided in this cohort of patients. Propofol is likely to adversely affect the ANS balance, thereby intensifying DA and worsening the disease outcomes. However, the lack of significant difference between these two groups on day 1 of VV-ECMO in the frequency of the propofol use (and the use of other agents theoretically affecting the ANS) suggests that the COVID-19-associated DA phenotype is independent of propofol.

Another unique finding of the presented study is a significantly higher HR in the lShP group compared with the nShP group. In our opinion, this phenomenon is worthy of a separate description and further study. To define this phenomenon, we propose a term 'the ANS paradox' referring to a condition in which patients with lShP phenotype develop persistent tachycardia or an overt tendency to tachycardia. The main issue of the 'ANS paradox' is that tachycardia leads to obvious complications (such as persistent hypoxemia in patients with VV-ECMO support), while pharmacological heart rate lowering with β-adrenoblockers and central α-adrenomimetics leads to even greater ANS imbalance and, consequently, to more severe DA. It is noteworthy that statistical analysis of TTE parameters in patients of both groups revealed no significant differences. Normal TTE values indicate that tachycardia is not associated with hypovolemia or a hyperdynamic circulation.

A major issue to be addressed in future studies is the choice of optimal therapy for DA with an lShP phenotype. Controlled hypothermia could become such a therapy option. It is well known that moderate hypothermia reduces a patient's cardiac output by developing bradycardia and depressing metabolism. This leads to matching in minute volume between intrinsic and artificial blood circulation under VV-ECMO without affecting adrenoreceptors and, consequently, without worsening of the already distorted ANS imbalance [27].

The presented study has a number of limitations. First, it is a monocenter study. Second, the study included only 20 patients. From a formal point of view, this is a small sample size. However, given the unique study population and the phenomenon under investigation – COVID-19-associated DA in VV-ECMO – the volume of clinical material is perceived as sufficient and unparalleled in world practice. Third, the main method of DA diagnostics is the analysis of Holter ECG monitoring. Critically ill patients received a large number of drugs that influenced the ANS tone: sedatives and narcotic drugs, β-blockers and central α-sympathomimetics. Although for most of these drugs (with the exception of propofol) the frequency and duration of use in the groups were similar, we still suspect that the use of these drugs may have influenced our findings. Because of the above limitations, further studies are needed to address the issue of DA in the ICU patients requiring VV-ECMO.

Conclusion

1. COVID-19-associated DA is observed in all COVID-19 patients receiving VV-ECMO support, making prolonged monitoring of ANS status with HRV analysis mandatory.

2. COVID-19-associated DA has three phenotypes: phenotype with normal sympathetic tone and high parasympathetic tone (nShP); phenotype with low sympathetic tone and high parasympathetic tone (lShP); phenotype with low sympathetic tone and normal parasympathetic tone (lSnP). In terms of VV-ECMO effectiveness and the possibility of weaning, the lShP phenotype is the worst.

3. COVID-19-associated DA is characterized by the 'ANS paradox': tachycardia associated with lShP phenotype. The use of decatecholaminization strategy (DMM and esmolol), widespread in modern intensive care, in patients with this DA phenotype is pathophysiologically incorrect. In this regard, further studies are needed to manage the ANS tone in patients with the 'ANS paradox' and the DA phenotype with predominant parasympathetic tone. Controlled hypothermia may become such a method of intensive therapy.

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