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Impact of COVID-19-associated Dysautonomia Phenotypes on the Effectiveness of Venovenous Extracorporeal Membrane Oxygenation

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RELEVANCE It is known that patients with severe cases of the novel coronavirus infection (COVID-19) are characterized by the development of COVID-19-associated dysautonomia (COVID-19-DA). At the moment, there are no studies examining the impact of this phenomenon on the course and outcomes of the disease in the most severe cohort of patients with COVID-19, namely those requiring venovenous extracorporeal membrane oxygenation (VV ECMO). The purpose of the presented work is to study the effect of different COVID-19-DA phenotypes on the performance parameters and effectiveness of VV ECMO, gas exchange and hemodynamics in patients with COVID-19.

MATERIAL AND METHODS The study included 20 patients, 12 (60%) women, 8 (40%) men, with COVID-19 who underwent VV ECMO. Patients underwent 24-hour Holter monitoring with assessment of the spectral parameters of heart rate variability (HRV): the low-frequency component (LF), the high-frequency component (HF), the ratio of the low-frequency component to the high frequency component (LF / HF) on days 1, 3, 5 of the VV ECMO. Patients were divided into three groups based on the identified COVID-19-DA phenotypes. The groups were compared in terms of gas exchange, hemodynamics, and VV ECMO performance parameters.

RESULTS The level of partial pressure of carbon dioxide in arterial blood (paCO2) in the phenotype with low sympathetic tone and high tone of the parasympathetic division of the autonomic nervous system (ANS) (lShP) was significantly higher than in the phenotype with normal sympathetic tone and high tone of the parasympathetic division of the ANS (nShP) with equal VV ECMO performance parameters. The heart rate (HR) in the nShP phenotype was significantly lower than in the lShP phenotype. A significant increase in respiratory dysfunction was revealed over time in the lShP phenotype. Weaning from VV ECMO in the nShP phenotype was successful in 50%, whereas in the lShP phenotype, weaning from VV ECMO was observed in 7,2% of patients. No significant differences in the mortality rate were obtained. The most common cause of death in both groups was septic shock.

CONCLUSIONS The COVID-19-DA phenotype, manifested by decreased tone of the sympathetic division and increased tone of the parasympathetic division of the ANS, leads to low efficiency of VV ECMO, resulting in a statistically significantly less frequent ECMO discontinuation in those patients.

Keywords: COVID-19, novel coronavirus infection, dysautonomia, autonomic nervous system, extracorporeal membrane oxygenation
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ABS — acid-base state
AH — arterial hypertension
ANS — autonomic nervous system
CHF — chronic heart failure
CT — computed tomography
DA — dysautonomia
DM — diabetes mellitus
ECG — electrocardiography
Echo — CG - echocardiography
EDV — end diastolic volume
EF — ejection fraction
ESV — end systolic volume
HF — high frequency component of heart rate variability
HFOT — high-flow oxygen therapy
HR — heart rate
HRV — heart rate variability
ICU — intensive care unit
IVC — inferior vena cava
LF — low frequency component of heart rate variability
lShP — decreased tone of the sympathetic division and high tone of the parasympathetic division of the autonomic nervous system
MV — mechanical ventilation
MVC — minute volume of blood circulation
NA — the highest dosage of injected norepinephrine
nMV — non-invasive mechanical ventilation
nShP — normal tone of the sympathetic division and high tone of the parasympathetic division of the autonomic nervous system
P/f — the ratio of the partial pressure of oxygen in arterial blood to the concentration of oxygen in the inhaled gas mixture
RD — respiratory dysfunction
RDS — respiratory distress syndrome
SS — septic shock
SV — stroke volume
VV ECMO — venovenous extracorporeal membrane oxygenation

INTRODUCTION

In December 2019, an outbreak of the novel coronavirus disease (COVID-19) occurred in the city of Wuhan, People's Republic of China, which subsequently caused a worldwide pandemic. The most common and life-threatening complication of COVID-19 is respiratory distress syndrome (RDS) [1]. According to the recommendations of the World Health Organization, if a patient with COVID-19 develops RDS with refractory gas exchange disorders, it is necessary to consider the advisability of using venovenous extracorporeal membrane oxygenation (VV ECMO) [2].

Hemodynamic disturbances characteristic of such patients are of fundamental importance during VV ECMO, since they can become a direct cause of discrepancy between the patient's own and artificial minute volume of blood circulation (MVC), and lead to inadequate gas exchange during the procedure [3, 4]. One of the likely causes of hemodynamic disorders, in particular refractory tachycardia, may be an imbalance of the sympathetic and parasympathetic autonomic nervous system (ANS), or dysautonomia (DA) [5].

Despite a large number of works researching COVID-19-associated dysautonomia (COVID-19-DA), there have been currently no studies examining the impact of this phenomenon on the course and outcomes of the disease in the most severe cohort of patients with COVID-19, namely patients requiring VV ECMO. Our research is devoted to this problem.

MATERIAL AND METHODS

The aim of the study was to evaluate the impact of COVID-19-DA phenotypes on the performance parameters and effectiveness of VV ECMO, as well as on central hemodynamic parameters in patients with COVID-19.

The inclusion criteria for the study were as follows:

— patient age over 18 years;

— confirmed diagnosis of COVID-19;

— RDS with refractory gas exchange disorders;

— need for VV ECMO.

The exclusion criteria were as follows:

— depression of the level of wakefulness to atonic coma;

— presence of permanent or paroxysmal form of atrial fibrillation/flutter;

— presence of sinoatrial blockades, sick sinus syndrome, atrioventricular blockades;

— presence of high-grade ventricular extrasystole according to Lown classification (IVa, IVb, V);

— presence of an artificial pacemaker;

— presence of DA diagnosed before the development of COVID-19.

All the patients received the entire necessary range of medical care in accordance with the temporary guidelines of the Ministry of Health of the Russian Federation that were current at the time of treatment [6]. Indications for starting VV ECMO were the P/f ratio of less than 150 mmHg, or pH less than 7.20, and partial pressure of arterial carbon dioxide (paCO2) more than 80 mmHg for more than 6 hours [7].

Contraindications to the VV ECMO procedure were as follows [7]:

— patient's age of more than 70 years;

— duration of mechanical ventilation (MV) before the start of VV ECMO of more than 10 days;

— impossibility of cannulation of the central vein;

— contraindications to the use of anticoagulant therapy;

— concomitant incurable diseases in the terminal stage.

To perform VV ECMO, the internal jugular and femoral veins were cannulated with cannulas measuring 15–23 Fr and 21–25 Fr, respectively; the following devices were used: Stockert (Sorin, USA), Cardiohelp (Maquet, Germany), Rotaflow (Maquet, Germany), DeltaStream (Medos, Germany). The procedure was considered effective if normoxia, normal arterial blood saturation (SpO2), and normocapnia were achieved.

Upon admission, the patients underwent computed tomography (CT) of the lungs using an Aquilion Prime CT scanner (Toshiba, Japan). During the study, we recorded the parameters and total duration of respiratory support, which was provided to all the patients with respiratory dysfunction (RD) using SV300 devices (Mindray, China). All the patients underwent continuous monitoring of heart rate (HR), blood pressure, SpO2 by pulse oximetry using CARESCAPE B650 bedside monitors (GE, USA). The study of the acid-base state (ABS) of arterial blood was carried out using an ABL800 analyzer (RADIOMETER, Denmark). The worst ABS indicators were included in the study. All of the above parameters were recorded on the 1st, 3rd and 5th days of VV ECMO (I, II and III research points, respectively).

Myocardial contractility and volumetric status were assessed on the 1st day of VV ECMO using transthoracic echocardiography (Echo-CG) with a MyLab 70 device (Esaote, Italy). The criteria for hypovolemia were a decrease in left ventricular end-diastolic volume (EDV) of less than 56 ml, and a decrease in the diameter of the inferior vena cava (IVC) of less than 15 millimeters [8]. If the development of COVID-19-DA was suspected, the patients were treated with intravenous or oral beta-blockers, and a prolonged intravenous infusion of dexmedetomidine at a dose of 0.7–1.4 μg/kg/hour, according to the concept of "decatecholaminization" [9].

All developing complications, the fact of weaning from VV ECMO and its duration, length of stay in the intensive care unit (ICU) and the Institute, and disease outcomes were recorded. The diagnosis of "Sepsis" was established in the presence of a source of bacterial infection and progression of organ dysfunction with an increase in the SOFA score by 2 or more points [10]. The diagnosis of "Septic shock" (SS) was established when arterial hypotension developed against the background of sepsis with the need for the administration of vasopressors [10]. The diagnosis of "Hemorrhagic shock" was established when the patient developed unstable hemodynamics against the background of bleeding, requiring the administration of vasopressor drugs [11]. The diagnosis of "Cardiogenic shock" was established when the patient developed unstable hemodynamics against the background of left ventricular, right ventricular or biventricular hemodynamic instability, accompanied by a critical decrease in oxygen delivery to tissues and organs with the development of their hypoperfusion and the need to administer drugs with inotropic and vasopressor effects [12].

In order to diagnose COVID-19-DA and verify its phenotype, Holter ECG monitoring was performed using a CardioMem CM 3000 device (GE, USA) with assessment of the spectral parameters of heart rate variability (HRV): low-frequency component (LF), high-frequency component (HF), ratio of low-frequency component to high-frequency component (LF/HF) during 24 hours on the 1st day of the VV ECMO procedure (research point I). The criteria for COVID-19-DA were a decrease in LF/HF of less than 2.28 or an increase of more than 6.94. The criterion for the predominant tone of the sympathetic division of the ANS was an increase in LF/HF of over 6.94. The criterion for the predominant tone of the parasympathetic division of the ANS was a decrease in LF/HF of under 2.28. The criterion for decreased tone of the sympathetic division of the ANS was a decrease in LF by less than 15%, and for elevated one - an increase in LF by more than 40%. The criterion for decreased tone of the parasympathetic division of the ANS was a decrease in HF by less than 15%, and for elevated one - an increase in HF of more than 25%. The above reference values are based on the results of previous studies [13–15].

Statistical analysis of the data was carried out using Statistica 12 by StatSoft. Comparative analysis of the groups based on quantitative characteristics was carried out using the Mann–Whitney method. Comparison of qualitative characteristics between the groups was performed using Fisher's exact test, comparison of parameters within the groups (dependent parameters) – with the Wilcoxon signed-rank test. The result of the study was considered significant when it reached $p \leqslant 0.05$.

The study was carried out on the basis of the Infectious Diseases Hospital of the N.V. Sklifosovsky Research Institute for Emergency Medicine (the Institute). The study included 20 patients admitted to the Institute between September 2021 and February 2022 with the diagnosis of "COVID-19 complicated by acute respiratory distress syndrome". All the patients underwent VV ECMO. The average age of the patients was 55 (Q1; Q3: 38.25; 60.00) years. Of the 20 patients, there were 8 men (40%) and 12 women (60%). General characteristics of the patients are presented in Table 1.

RESULTS

COVID-19-DA was diagnosed in all the cases. The median LF/HF was 0.1 (Q1; Q3: 0.04; 0.23), which indicates a pronounced predominance of the parasympathetic division over the sympathetic division of the ANS in all presented observations. Depending on the tone of the sympathetic and parasympathetic divisions of the ANS, the patients were divided into three groups in accordance with the phenotypes of COVID-19-DA. Group I (nShP phenotype) – a phenotype with normal tone of the sympathetic division, high tone of the parasympathetic division of the ANS (n=4; 20%); Group II (lShP phenotype) - a phenotype with a decreased tone of the sympathetic division, high tone of the parasympathetic division of the ANS(n=14; 70%); Group III (lSnP phenotype) - a phenotype with reduced tone of the sympathetic division, normal

Table 1

General characteristics of patients upon admission to the intensive care unit, before the start of venovenous extracorporeal membrane oxygenation

Patient demographics	
Age, years*	55.00 (38.25; 60.00)
Gender	
Male, n (%)	8 (40)
Female, n (%)	12 (60)
Comorbidities	
AH, n (%)	13 (65)
DM, n (%)	3 (15)
CHF, n (%)	2 (10)
General information	
Days from onset of the disease to admission*	14.50 (11.00; 25.00)
Days from admission to the start of VV ECMO*	1.50 (1.00; 3.00)
Days from the onset of the disease to the start of VV ECMO*	17.50 (15.00; 28.75)
Respiratory support upon admission	
HFOT /nMV, n (%)	9 (45)
MV, n (%)	11 (55)
Gas exchange parameters upon admission (against the background of respiratory support)	
P/f*	92.00 (62.75; 110.00)
SpO2, %*	94.00 (89.25; 96.00)
The degree of lung damage according to CT data upon admission	
CT-3, n (%)	4 (20)
CT-4, n (%)	16 (80)
Complications before VV ECMO start	
Bacterial inflammation, n (%)	11 (55)
Sepsis, n (%)	3 (15)
SS, n (%)	1 (5)

Notes: * – data are presented as median, lower (1st) and upper (3rd) quartiles. AH – arterial hypertension; CT – computed tomography; CHF – chronic heart failure; DM – diabetes mellitus; ECMO – venovenous extracorporeal membrane oxygenation; MV – mechanical ventilation; nMV – non-invasive mechanical ventilation; P/f – the ratio of the partial pressure of oxygen in arterial blood to the oxygen concentration in the inhaled gas mixture; SpO_2 – arterial blood oxygen saturation according to pulse oximetry data; SS – septic shock; VV HFOT – high flow oxygen therapy

tone of the parasympathetic division of the ANS (n=2; 10%). Group III was excluded from further interpretation of the results due to its small size. Groups I and II did not differ significantly in age, gender, severity of condition upon admission and at the time of VV ECMO initiation, or the presence of concomitant pathology (Table 2). A comparative analysis of HRV parameters in patients of Groups I and II is presented in Table 3.

Table 2

General characteristics of patients in Groups I and II

Parameters	Patient groups		*p*
	I (nShP phenotype, n=4)	II (lShP phenotype, n=14)	
Patient demographics			
Age, years*	46.50 (37.50; 58.50)	57.50 (40.20; 62.00)	0.3
Gender			
Male, n (%)	1 (25)	6 (42.8)	0.7
Female, n (%)	3 (75)	8 (57.2)	0.7
Days from the onset of the disease to the start of VV ECMO, days*	14.00 (7.75; 21.00)	19.00 (15.00; 33.25)	0.2
Comorbidities			
Arterial hypertension, n (%)	3 (75)	10 (71.4)	0.1
Diabetes, n (%)	1 (25)	2 (14.2)	0.5
CHF, n (%)	0	2 (14.2)	0.6
Respiratory support upon admission			
HFOT /nMV, n (%)	2 (50)	6 (42.8)	0.3
MV, n (%)	2 (50)	8 (57.2)	0.3
Respiratory support at the time of VV ECMO initiation			
HFOT /nMV, n (%)	0	2 (14.2)	0.4
MV, n (%)	4 (100)	12 (85.7)	0.4
Gas exchange parameters upon admission (against the background of respiratory support)			
P/f	97.00 (52.75; 256.75)	92.00 (68.25; 110.25)	0.9
SpO_2, %	95.00 (76.75; 96.75)	94.00 (88.75; 96.50)	0.9
The degree of lung damage according to computed tomography			
CT-3, n (%)	2 (50)	1 (7.1)	0.08
CT-4, n (%)	2 (50)	13 (92.9)	0.08
Complications before VV ECMO start			
Bacterial inflammation, n (%)	2 (50)	3 (21.4)	0.2
Sepsis, n (%)	2 (50)	3 (21.4)	0.2
Septic shock, n (%)	1 (25)	3 (21.4)	0.8

Notes: * – data are presented as median, lower (1st) and upper (3rd) quartiles. CHF – chronic heart failure; CT – computed tomography; HFOT – high flow oxygen therapy; LFOT – low flow oxygen therapy; lShP – decreased tone of the sympathetic division and high tone of the parasympathetic division of the autonomic nervous system; MV – mechanical ventilation; nMV – non-invasive mechanical ventilation; nShP — normal tone of the sympathetic division and high tone of the parasympathetic division of the autonomic nervous system; VV ECMO – venovenous extracorporeal membrane oxygenation

Table 3

Comparative analysis of heart rate variability parameters in Groups I and II

Parameters	Patient groups		*p*
	I (nShP phenotype, n=4)	II (lShP phenotype, n=14)	
LF, %	24.67 (17.55; 31.24)	5.30 (2.06; 7.52)	**0.001**
HF, %	54.42 (36.54; 57.14)	56.00 (41.96; 74.20)	0.6
LF/HF	0.47 (0.43; 0.58)	0.09 (0.03; 0.12)	**0.001**

Notes: * – data are presented as median, lower (1st) and upper (3rd) quartiles. HF—high-frequency component of the recording (15–25%); LF—low-frequency component of the recording (15–40%); LF/HF – ratio of the low-frequency component of the recording to the high-frequency one (2.28–6.94); lShP — decreased tone of the sympathetic division and high tone of the parasympathetic division of the autonomic nervous system; nShP — normal tone of the sympathetic division and high tone of the parasympathetic division of the autonomic nervous system

The results of intergroup differences in the frequency of using beta-blockers and the combination of beta-blockers with dexmedetomidine are shown in Table 4.

Table 4

Use of beta blockers, and the combination of beta blockers and dexmedetomidine

Parameters	Patient groups		*p*
	I (nShP phenotype, n=4)	II (lShP phenotype, n=14)	
Beta blocker use, n (%)	2 (50)	8 (57.1)	0.8
Use of beta blockers and dexmedetomidine, n (%)	2 (50)	5 (35.7)	0.6

Notes: lShP — decreased tone of the sympathetic division and high tone of the parasympathetic division of the autonomic nervous system; nShP — normal tone of the sympathetic division and high tone of the parasympathetic division of the autonomic nervous system

As can be seen from the table, the groups did not differ statistically significantly in the frequency of use of the above drugs. This indicates that these drugs did not affect the COVID-19-DA phenotype and, therefore, the validity of dividing the patients into groups.

The influence of COVID-19-DA phenotypes on gas exchange and hemodynamics during VV ECMO, as well as on its performance parameters, was assessed (Table 5).

Table 5

Comparison of the groups according to hemodynamic status, effectiveness and performance of venovenous extracorporeal membrane oxygenation

Parameters	Patient groups		*p*
	I (nShP phenotype, n=4)	II (lShP phenotype, n=14)	
Research point I (1st day of ECMO, n=18)			
Gas exchange parameters			
paO_2, mmHg	87.00 (65.50; 92.00)	72.50 (65.50; 83.00)	0.3
$paCO_2$, mmHg	34.50 (31.37; 50.00)	37.90 (35.00; 42.25)	0.3
SpO_2, %	96.50 (91.50; 97.00)	94.00 (92.25; 96.00)	0.2
P/f	151.50 (89.25; 203.25)	111.50 (94.50; 139.00)	0.3
FiO_2, %	57.50 (45.00; 77.50)	65.00 (55.00; 80.00)	0.3
VV ECMO parameters			
O_2 flow into the VV ECMO oxygenator, l/min	4.00 (3.00; 6.50)	5.00 (3.00; 7.25)	0.7
VV ECMO performance, ml/kg/min	32.19 (22.16; 45.74)	30.89 (26.58; 39.34)	0.9
Hemodynamic parameters			
Heart rate, beats/min	74.00 (65.00; 82.25)	86.50 (79.75; 97.25)	0.04
MAP, mmHg	97.50 (85.13; 134.63)	93.25 (87.38; 103.63)	0.5
NA, ng/kg/min	235.00 (117.50; 322.50)	225.00 (137.50; 400.00)	0.6
Research point II (3rd day of ECMO, n=18)			
Gas exchange parameters			
PaO_2, mmHg	71.50 (64.25; 92.25)	71.50 (61.50; 77.75)	0.7
$PaCO_2$, mmHg	34.25 (31.00; 34.87)	37.50 (35.00; 44.00)	0.01
SpO_2, %	94.00 (93.00; 97.25)	94.00 (88.50; 95.25)	0.4
P/f	151.50 (116.50; 171.50)	111.00 (78.00; 168.75)	0.3
FiO_2, %	50.00 (45.00; 62.50)	60.00 (48.75; 82.50)	0.3
VV ECMO parameters			
O_2 flow into the VV ECMO oxygenator, l/min	5.00 (3.00; 7.00)	5.00 (3.75; 7.00)	0.8
VV ECMO performance, ml/kg/min	32.19 (22.16; 45.74)	31.77 (26.14; 44.30)	0.8
Hemodynamic parameters			
Heart rate, beats/min	75.00 (64.50; 82.25)	85.00 (75.00; 96.25)	0.1
MAP, mmHg	100.00 (93.13; 125.63)	100.50 (88.13; 109.75)	0.8
NA, ng/kg/min	285.00 (117.50; 400.00)	330.00 (225.00; 650.00)	0.4

Research point III (5th day of ECMO, n=18)			
Gas exchange parameters			
PaO_2, mmHg	71.50 (53.00; 80.25)	59.50 (53.75; 75.50)	0.5
$PaCO_2$, mmHg	34.50 (34.00; 38.00)	38.50 (32.50; 41.25)	0.4
SpO_2, %	93.00 (84.25; 95.75)	89.50 (86.50; 95.00)	0.5
P/f	120.00 (77.75; 178.00)	78.00 (63.50; 146.25)	0.2
FiO_2, %	60.00 (45.00; 67.50)	77.50 (50.00; 86.25)	0.1
VV ECMO parameters			
O_2 flow into the VV ECMO oxygenator, l/min	4.00 (1.50; 6.50)	7.00 (3.75; 12.00)	0.1
VV ECMO performance, ml/kg/min	34.85 (22.16; 39.57)	35.05 (29.95; 57.72)	0.5
Hemodynamic parameters			
Heart rate, beats/min	63.50 (54.50; 86.00)	84.50 (68.00; 102.25)	0.06
MAP, mmHg	104.00 (91.63; 125.75)	94.00 (83.25; 108.75)	0.3
NA, ng/kg/min	400.00 (400.00; 400.00)	350.00 (237.50; 1075.00)	0.9

Notes: * – data are presented as median, lower (1st) and upper (3rd) quartiles. FiO_2 – concentration of oxygen in the inhaled gas mixture; lShP — decreased tone of the sympathetic division and high tone of the parasympathetic division of the autonomic nervous system; MAP – the lowest mean arterial pressure during the day; NA — the highest dosage of norepinephrine administered; nShP — normal tone of the sympathetic division and high tone of the parasympathetic division of the autonomic nervous system; O_2 – oxygen; $PaCO_2$ – partial pressure of carbon dioxide in arterial blood; PaO_2 — partial pressure of oxygen in arterial blood; P/f – the ratio of the partial pressure of oxygen in arterial blood to the concentration of oxygen in the inhaled gas mixture; SpO_2 – arterial blood oxygen saturation according to pulse oximetry data; VV ECMO – venovenous extracorporeal membrane oxygenation;

As can be seen from the table 5, heart rate at research point I (86.50 (Q1; Q3: 79.75; 97.25), and 74.00 (Q1; Q3: 65.00; 82.25), p=0.04), and paCO2 at research point II (37.50 (Q1; Q3: 35.00; 44.00), and 34.25 (Q1; Q3: 31.00; 34.87), p=0.01) were statistically significantly higher in the lShP phenotype than in the nShP phenotype. It is also noteworthy that heart rate at points II and III was higher in the lShP phenotype, but these differences did not reach the level of statistical significance. At the same time, as stated above, the frequency of beta-blocker use was not statistically significantly different among the patients of both groups, indicating that these drugs did not influence the difference in heart rate. The differences between the values of other studied parameters were not statistically significant either.

Table 6 shows a comparative intergroup analysis of indicators of myocardial contractility and volumetric status at research point I.

Table 6

Comparison of the groups by echocardiography parameters

Parameters	Patient groups		*p*
	I (nShP phenotype, n=4)	II (lShP phenotype, n=14)	
LVEF*, %	58.50 (52.75; 68.75)	62.50 (53.00; 66.25)	0.5
LV EDV*, ml	109.50 (100.75; 149.00)	104.50 (95.50; 112.50)	0.5
LV ESV*, ml	44.50 (32.75; 66.00)	39.00 (33.50; 48.50)	0.6
LV SV*, ml	74.00 (57.25; 84.75)	68.00 (60.75; 73.50)	0.2
IVC diameter less than 15 mm, n (%)	1 (25)	6 (42.8)	0.5

Notes: * – data are presented as median, lower (1st) and upper (3rd) quartiles. EDV – left ventricular end-diastolic volume (55–149 ml); EF – left ventricular ejection fraction (55–65%); ESV — left ventricular end-systolic volume (18–40 ml); IVC — inferior vena cava; lShP — decreased tone of the sympathetic division and high tone of the parasympathetic division of the autonomic nervous system; nShP — normal tone of the sympathetic division and high tone of the parasympathetic division of the autonomic nervous system; SV – left ventricular stroke volume (50–70 ml)

As can be seen from the table 6, the groups did not differ statistically significantly in terms of Echo-CG and volumetric status parameters.

The comparative analysis showed that in the patients of Group I, the indicators of gas exchange, VV ECMO performance and hemodynamics did not change statistically significantly in dynamics. Table 7 shows the dynamics of statistically significantly different indicators of gas exchange and performance of VV ECMO in Group II.

As can be seen from the table 7, in lShP phenotype, RD progression was revealed in the form of a statistically significant decrease in P/f (111.00 (Q1; Q3: 78.00; 168.75), and 78.00 (Q1; Q3: 63.50; 146.25); p=0.02), increase in FiO2 (60.00 (Q1 ; Q3: 48.75; 82.50), and 77.50 (Q1; Q3: 50.00; 86.25); p=0.04), and oxygen flow into the ECMO circuit (5.00 (Q1; Q3: 3.75; 7.00), and 7.00 (Q1; Q3: 3.75; 12.00); p=0.05) to the research point III. There were no statistically significant intragroup differences in hemodynamic parameters in Group II.

Table 8 provides data on the duration of respiratory support and VV ECMO, as well as the structure of complications during VV ECMO and outcomes.

Table 7

Dynamics of gas exchange and VV ECMO performance parameters in Group II (lShP phenotype)

Parameters	Research stages			Statistical significance of differences	
	I point (n=14)	II point (n=14)	III point (n=14)	p_1	p_2
Gas exchange parameters					
P/f	111.50 (94.50; 139.00)	111.00 (78.00; 168.75)	78.00 (63.50; 146.25)	0.5	0.02
FiO_2, %	65.00 (55.00; 80.00)	60.00 (48.75; 82.50)	77.50 (50.00; 86.25)	0.07	0.04
VV ECMO parameters					
O_2 flow into the VV ECMO oxygenator, l/min	5.00 (3.00; 7.25)	5.00 (3.75; 7.00)	7.00 (3.75; 12.00)	0.2	0.05

Notes: * – performance. Data are presented as median, lower (1st) and upper (3rd) quartiles. FiO_2 – concentration of oxygen in the inhaled gas mixture; lShP — decreased tone of the sympathetic devision and high tone of the parasympathetic division of the autonomic nervous system; NA — the highest dosage of norepinephrine administered; O_2 – oxygen; p_1 – intragroup statistical significance of differences in indicators at research points I and II; p_2 – intragroup statistical significance of differences in indicators at research points II and III; P/f – the ratio of the partial pressure of oxygen in arterial blood to the concentration of oxygen in the inhaled gas mixture; VV ECMO – venovenous extracorporeal membrane oxygenation

As can be seen from the table 8, the incidence of complications, as well as the duration of mechanical ventilation, VV ECMO, stay in the ICU and in the hospital as a whole did not differ statistically significantly. Statistically significant differences were obtained when comparing the outcomes of the VV ECMO procedure. In the nShP phenotype, weaning from VV ECMO was successful in 50% of cases, whereas in the lShP phenotype this was observed in only 7.2% of patients (p=0.04). There were no statistically significant differences in the mortality rate (p=0.5). The most common cause of death in patients of both groups was SS (75% vs. 71.4%; p=0.9).

THE DISCUSSION OF THE RESULTS

In the presented work, of 20 patients with COVID-19 who needed VV ECMO, death occurred in 19 patients. The mortality rate was 95%. This is an extremely important indicator that requires discussion and interpretation. During the pandemic, the Institute was entrusted with the functions of an expert ECMO center, where patients were routed from other infectious diseases hospitals specifically for ECMO. This means that the Institute received

Table 8

Mechanical ventilation and VV ECMO duration, structure of complications, VV ECMO and disease outcomes

Parameters	Patient groups		*p*
	I (nShP phenotype, n=4)	II (lShP phenotype, n=14)	
Complications			
Bacterial infection, n (%)	4 (100)	13 (92.8)	0.5
Sepsis, n (%)	3 (75)	11 (78.5)	0.8
Septic shock, n (%)	3 (75)	11 (78.5)	0.8
Hemorrhagic complications, n (%)	1 (25)	7 (50)	0.3
Thrombotic complications, n (%)	1 (25)	2 (14.2)	0.6
Outcomes			
Duration of mechanical ventilation, days*	20.50 (6.00; 35.00)	11.00 (6.75; 13.25)	0.7
Duration of VV ECMO, days*	6.00 (6.00; 7.50)	8.50 (5.00; 12.25)	0.2
Stay in ICU, days*	16.50 (8.00; 32.50)	12.00 (7.75; 16.50)	0.6
Hospital stay, days*	21.50 (8.00; 35.00)	12.00 (7.75; 16.50)	0.5
Weaning from VV ECMO, n (%)	2 (50)	1 (7.2)	0.04
Survived, n (%)	0	1 (7.2)	0.5
Died, n (%)	4 (100)	13 (92.8)	0.5
Causes of death			
Septic shock, n (%)	3 (75)	10 (71.4)	0.9
Hemorrhagic shock, n (%)	1 (25)	2 (14.2)	0.6
Cardiogenic shock, n (%)	0	1 (7.2)	0.5

Notes: * – data are presented as median, lower (1st) and upper (3rd) quartiles. ICU – Department of Resuscitation and Intensive Care; lShP — decreased tone of the sympathetic division and high tone of the parasympathetic division of the autonomic nervous system; MV – mechanical ventilation; nShP — normal tone of the sympathetic division and high tone of the parasympathetic division of the autonomic nervous system; the Institute – N.V. Sklifosovsky Research Institute for Emergency Medicine; VV ECMO – venovenous extracorporeal membrane oxygenation

patients who were in an extremely serious and decompensated condition, which partly explains such a high mortality rate. At the same time, literature data indicate that mortality during VV ECMO in patients with COVID-19-associated RDS is significantly higher compared to the outcomes of VV ECMO performed in patients with RDS of other etiologies [16].

According to the literature, VV ECMO for COVID-19-associated RDS is distinguished by two features: (1) low efficiency of VV ECMO, manifested by hypoxemia against the background of adequate performance of VV ECMO; (2) duration of VV ECMO, which is significantly longer than the duration of VV ECMO for ARDS of other etiologies [16]. Moreover, during the VV ECMO procedure, complications leading to death develop, while their early prevention and timely elimination can hypothetically lead to a decrease in mortality in this category of patients.

The presented research is devoted to studying the effect of ANS imbalance, that is, COVID-19-DA, on the VV ECMO outcomes in patients with COVID-19. The study revealed that patients with COVID-19 and the need for VV ECMO are characterized by COVID-19-DA with a predominant tone of the parasympathetic division of the ANS, which develops in 100% of cases. At the same time, COVID-19-DA is characterized by three phenotypes that differ in the tone of different parts of the ANS.

The study revealed that the nShP phenotype did not affect either the effectiveness or performance of VV ECMO. However, the lShP phenotype led to RD progression by the 5th day of the procedure. The low effectiveness of VV ECMO was not due to a decrease in its own performance, since it did not change statistically significantly throughout the study. Hypoxemia during VV ECMO in the lShP phenotype led to a statistically significantly lower rate of discontinuation and, consequently, a more frequent need to continue the ECMO procedure compared to the nShP phenotype. It was found that patients with the lShP phenotype, in contrast to patients with the nShP phenotype, are characterized by tachycardia, but the frequency of use of rhythm-slowing therapy and Echo-CG indicators reflecting the volume status were not statistically significantly different in the two groups.

The likely reason for the low effectiveness of VV ECMO in the lShP phenotype is the lack of application point for beta blockers and dexmedetomidine. The target of the pharmacological action of these drugs is precisely the sympathetic division of the ANS, which is suppressed in the lShP phenotype [17, 18]. In this case, it is impossible to achieve a heart rate fall and, accordingly, a balance between the artificial and patient's own MVC, which leads to increasing hypoxemia [19]. It is the "vegetative paradox", characteristic of the very specific phenotype of COVID-19-DA, manifested by tachycardia against the background of reduced tone of the sympathetic division of the ANS, that can lead to low effectiveness of VV ECMO in patients with COVID-19.

The study revealed that in the group of patients with the lShP phenotype, one patient survived, while in the group of patients with the nShP phenotype there were no survivors. Statistical analysis did not reveal statistically significant differences in the mortality rate between the groups. It is likely that future studies with a larger sample of patients can provide clarity to the understanding of the impact of COVID-19-DA phenotypes on mortality among patients treated with VV ECMO. At the moment, given the lack of statistical significance, we can state that COVID-19-DA phenotypes do not affect mortality during VV ECMO.

The work of Rudiger and co-authors demonstrated the beneficial effects of the concept of "decatecholaminization" in patients with bacterial sepsis, which is characterized by a predominance of the tone of the sympathetic division of the ANS [9]. However, the literature describes the following relationship between the balance of the ANS and the severity of the critical condition: the more severe the patient's condition, the more predominant is the tone of the parasympathetic division of the ANS, including in SS [20, 21]. This contains possible limitations in the effectiveness of decatecholaminization, including in patients with COVID-19 and VV ECMO performance, since such therapy is aimed at correcting the predominant tone of the sympathetic division of the ANS. Probably, one of the promising methods for correcting COVID-19-DA, especially in patients with "vegetative paradox," may be controlled normo- or hypothermia. In this case, a decrease in the patient's MVC can be achieved as a result of a decrease in metabolic needs, without direct involvement of adrenergic receptors, and an even greater imbalance of the ANS. Of course, further research is needed to prove this point.

The presented study has a number of limitations. First, the study is a single-center one. Secondly, it included only 20 patients, which, from a formal point of view, is a small number. The limitations listed above necessitate further research on the problem of DA in intensive care patients requiring VV ECMO.

CONCLUSIONS

1. Patients with COVID-19 and the need for venovenous extracorporeal membrane oxygenation are characterized by COVID-19 dysautonomia with three phenotypes, which develops in 100% of cases. The phenotype of low sympathetic tone and high parasympathetic tone of the autonomic nervous system leads to low efficiency of venovenous extracorporeal membrane oxygenation.

2. The phenotype of reduced tone of the sympathetic division and high tone of the parasympathetic division of the autonomic nervous system, in contrast to the phenotype of normal tone of the sympathetic division and high tone of the parasympathetic division of the autonomic nervous system, is manifested by tachycardia on the 1st day of venovenous extracorporeal membrane oxygenation (86.50 (Q1; Q3: 79.75; 97.25), and 74.00 (Q1; Q3: 65.00; 82.25), p =0.04), and higher paCO2 on the 2nd day of the procedure (37.50 (Q1; Q3: 35.00; 44.00), and 34.25 (Q1; Q3: 31.00; 34.87), p=0.01).

3. Low efficiency of venovenous extracorporeal membrane oxygenation in case of the phenotype of low tone of the sympathetic division and high tone of the parasympathetic part of the autonomic nervous system is manifested by the progression of respiratory dysfunction by the 5th day of the procedure, accompanied by a decrease in P/f (111.00 (Q1; Q3: 78 .00; 168.75), and 78.00 (Q1; Q3: 63.50; 146.25); p=0.02), an increase in FiO2 (60.00 (Q1; Q3: 48.75; 82.50), and 77.50 (Q1; Q3: 50.00; 86.25); p=0.04), and an increase in O2 flow into the circuit of the extracorporeal membrane oxygenation apparatus (5.00 (Q1; Q3: 3.75; 7. 00), and 7.00 (Q1; Q3: 3.75; 12.00); p=0.05).

4. The result of the low effectiveness of venovenous extracorporeal membrane oxygenation in patients with the phenotype of low tone of the sympathetic division and high tone of the parasympathetic part of the autonomic nervous system is a statistically significantly less frequent weaning from venovenous extracorporeal membrane oxygenation compared to patients with the phenotype of normal tone of the sympathetic division and high tone of the parasympathetic division of the autonomic nervous system (7.2% and 50%, p = 0.04).

5. COVID-19-DA phenotypes do not affect mortality during venovenous extracorporeal membrane oxygenation (p=0.5). The most common cause of death in both groups was septic shock (75% vs 71.4%; p=0.9).

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