

DOI: 10.56871/RBR.2024.97.86.002

УДК 616-036.21+578.834.1+616.24-008.44+577.3

## ИЗМЕНЕНИЯ ГЕМОДИНАМИКИ ПРИ РАЗВИТИИ ДЫХАТЕЛЬНОЙ НЕДОСТАТОЧНОСТИ У ПАЦИЕНТОВ С ТЯЖЕЛЫМИ ФОРМАМИ COVID-19

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**Для цитирования:** Шилин Д.С., Кошовкина Н.Н., Шаповалов К.Г. Изменения гемодинамики при развитии дыхательной недостаточности у пациентов с тяжелыми формами COVID-19 // Российские биомедицинские исследования. 2024. Т. 9. № 1. С. 13–18.

DOI: <https://doi.org/10.56871/RBR.2024.97.86.002>

Поступила: 11.12.2023

Одобрена: 15.01.2024

Принята к печати: 04.03.2024

**Резюме. Актуальность.** Поиск эффективных предикторов тяжести течения COVID-19 является важной проблемой медицинской науки на современном этапе. В патогенезе тяжелого течения новой коронавирусной инфекции существенное значение имеют изменения состояния гемодинамики. **Цель исследования** — выявить изменения гемодинамики у пациентов с COVID-19 при прогрессирующей дыхательной недостаточности. **Материалы и методы.** Исследование выполнили у 100 пациентов обоего пола с внебольничной полисегментарной вирусно-бактериальной пневмонией на фоне COVID-19. Проспективно пациенты были разделены на 2 группы с учетом развития тяжелой дыхательной недостаточности. В 1-ю группу вошли 50 пациентов, которым не потребовалась механическая вентиляция, во 2-ю вошли пациенты, которым либо проводилась на момент исследования механическая вентиляция, либо потребуется в будущем. Наблюдение осуществляли с помощью комплекса аппаратно-программного неинвазивного исследования центральной гемодинамики методом объемной компрессионной осциллометрии. **Результаты.** У пациентов с прогрессированием дыхательной недостаточности на фоне новой коронавирусной инфекции COVID-19 меньше значение ударного объема и индекса в 1,27 и 1,16 раз соответственно до прон-позиции, а также в 1,3 и 1,23 раза после прон-позиции соответственно по сравнению с больными группы благоприятного течения. Помимо этого, во 2-й группе показатель объемной скорости выброса в положении на спине меньше в 1,26, на животе в 1,22 раза. Податливость сосудистой стенки и реакция прекапилляров у пациентов, которым потребовалась механическая вентиляция легких, ниже в 1,19 и 1,81 раз соответственно до прон-позиции, а также в 1,28 и 2,04 раза соответственно после прона. **Выводы.** У пациентов с прогрессированием тяжелой дыхательной недостаточности на фоне новой коронавирусной инфекции COVID-19 выявлены изменения ударного объема и индекса, объемной скорости выброса, податливости сосудистой стенки.

**Ключевые слова:** предикторы, дыхательная недостаточность, прон-позиция, COVID-19, гемодинамика

## CHANGES OF HEMODYNAMICS DURING THE DEVELOPMENT OF RESPIRATORY FAILURE IN PATIENTS WITH SEVERE FORMS OF COVID-19

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**For citation:** Shilin DS, Koshovkina NN, Shapovalov KG. Changes of hemodynamics during the development of respiratory failure in patients with severe forms of COVID-19. Russian Biomedical Research. 2024;9(1):13-18. DOI: <https://doi.org/10.56871/RBR.2024.97.86.002>

Received: 11.12.2023

Revised: 15.01.2024

Accepted: 04.03.2024

**Abstract. Background.** The search for effective predictors of the severity of COVID-19 is an important problem in medical science at the present stage. In the pathogenesis of the severe course of a new coronavirus infection, changes in the state of hemodynamics are essential. **Aim:** to identify hemodynamic predictors of decompensated respiratory failure in patients with COVID-19. **Materials and methods.** The study was carried out on 100 patients of both sexes with community-acquired polysegmental viral-bacterial pneumonia against the background of COVID-19. Next, the patients were divided into 2 groups based on the development of severe respiratory failure. The 1st group included 50 patients who did not require mechanical ventilation, the second included patients who were either undergoing mechanical ventilation at the time of the study or will be undergoing it in the future. The studies were carried out using a complex of hardware-software non-invasive study of central hemodynamics using volumetric compression oscillometry. **Results.** In patients with progression of respiratory failure against the background of the new coronavirus infection COVID-19, the value of stroke volume and index is 1.27 and 1.16 times less before the prone position, as well as 1.3 and 1.23 times after the prone position according to compared with patients in the favorable group. In addition, in group 2, the volumetric ejection velocity in the supine position was 1.26 times less, and in the stomach position it was 1.22 times less. The compliance of the vascular wall and the reaction of precapillaries in patients who required mechanical ventilation were lower by 1.19 and 1.81 times before proning, and by 1.28 and 2.04 times after proning. **Conclusions.** In patients with progression of severe respiratory failure against the background of the new coronavirus infection COVID-19, changes in stroke volume and index, volumetric ejection velocity, and vascular wall compliance were identified.

**Keywords:** predictors, respiratory failure, prone position, COVID-19, hemodynamics

## BACKGROUND

Coronavirus disease 2019 (COVID-19) is an extremely contagious disease produced in humans by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [15]. Due to mild symptoms and high contagiousness, the infection quickly spread throughout the world [14]. 81 percent of COVID-19 patients had cold-like symptoms and moderate pneumonia, 14 percent had severe respiratory syndrome, and 5 percent had critical respiratory failure, septic shock, and/or multiple organ dysfunction or failure; the overall fatality rate was 1%. [18]. Approximately 17 to 35% of hospitalized patients with COVID-19 are treated in the intensive care unit, most often due to hypoxemic respiratory failure and the development of ARDS, and between 29 and 91% of patients in intensive care units require invasive ventilation. [7]. More than 75% of patients hospitalized with COVID-19 require supplemental oxygen. [12, 17]. A number of risk factors for severe COVID-19 have been identified, among which the patient's age and comorbidity are of leading importance — factors that determine the prognosis of in-hospital mortality of hospitalized patients [2, 6]. Therefore, it is extremely important to research the pathophysiological features of patients, identify risk factors of disease progression, prognosticate severity for clinical diagnosis and early initiation of adequate treatment, which is crucial to improve the survival of critically ill patients.

## AIM OF THE STUDY

To identify changes in hemodynamics in patients with COVID-19 with progressive respiratory failure.

## MATERIALS AND METHODS

A prospective non-randomized study was performed in 100 patients. The study was performed in the City Clinical Hospital № 1 in Chita, Russian Federation. The investigation was carried out after approval by the local ethical committee of Chita State Medical Academy (protocol № 102 of 15.05.2020) according to the local treatment protocols.

The study was carried out in two stages. First, a hemodynamic study was performed in patients of both sexes with community-acquired polysegmental viral-bacterial pneumonia against the background of COVID-19, aged from 35 to 87 years, in intensive care units, with various types of respiratory support. The diagnosis was made according to the temporary methodological recommendations of the Provisional Guidelines of the Russian Ministry of Health on prevention, diagnosis, and treatment of novel coronavirus infection COVID-19. The patients were diagnosed with at least 50% viral-induced involvement of lungs using chest computed tomography. The patients were prescribed the standard treatment according to the current version of the Provisional Guidelines of the Russian Ministry of Health on prevention, diagnosis, and treatment of novel coronavirus infection COVID-19. During the study, patients at various stages of respiratory support were randomly recruited. Respiratory support through a face mask with a flow of 5–7 liters was provided for 40 patients, death was recorded in 8 of them. Non-invasive artificial pulmonary ventilation was performed in 41 patients, of which 23 died. Mechanical pulmonary ventilation was performed in 19 patients who subsequently died.

Next, the patients were divided into 2 groups based on the dynamics of respiratory failure (Table 1). The first group included

50 patients who did not require mechanical ventilation, the second group included patients who were either undergoing mechanical ventilation at the time of the study or would be undergoing it in the future. The need for mechanical ventilation during hospitalization was a sign of decompensation.

The non-inclusion criteria included neoplastic diseases, severe immunodeficiency, unstable hemodynamics, vasopressor infusion, signs of hypovolemia, uncontrolled hypertension (SBP above 200 mm Hg).

Hemodynamic studies of two groups of patients were performed using the integrated hard- and software system for non-invasive central hemodynamic study by volumetric compression oscillometry «KAP TsG Osm-Globus» (Russia).

The following sets of parameters were recorded: blood pressure, cardiac activity and vascular parameters. The first block included data on systolic (SBP), diastolic (DBP), mean (SBP), oscillometric 'true' systolic (OTSBP), pulse (pBP) and stroke (StBP) blood pressure, pulse blood pressure velocity (PBPV). The second set consisted of indicators of pulse, cardiac output (CO) and cardiac index (CI), stroke volume (SV) and stroke index (SI), volume ejection rate (VER), left ventricular contractile power (LVCP) and energy expenditure (EE) per 1 liter of cardiac output per minute. The third block was presented by the linear blood flow rate (LBFR) and pulse wave velocity (PWV), vascular compliance (VC), total peripheral resistance (TPR) and normalized peripheral resistance (NPR) as well as NPR actual/NPR estimated ratio (FS). All parameters were obtained from the software and hardware readings and calculated according to the instructions. The indicators recorded in patients in the laying position belong to the 1st group of parameters, the data recorded on the stomach belong to the 2nd group.

The authors followed the International Committee of Medical Journal Editors (IC MJE) guidelines and the Statistical Analysis and Methods in the Published Literature (SAMPL) guidelines when conducting statistical analyses. The normality of the distribution of characteristics was assessed using the Kolmogorov–Smirnov test. Taking into account the distribution of characteristics that differed from normal in all studied groups, the data obtained were presented as the median, first and third quartiles: Me (Q1; Q3). To compare two independent groups on one quantitative characteristic, the Mann–Whitney test (U) was used. Nominal data were described with absolute values and percentages. Comparisons of nominal study data were made using Pearson's  $\chi^2$  test. For small samples, preference was given to the Pearson chi-square test with likelihood adjustment. If the number of expected observations in at least one cell of the four-field table was less than 10, the chi-square test with Yates' correction for continuity was used to compare two independent groups of nominal data. If the number of expected observations in at least one of the cells of the four-field table was less than 5, Fisher's exact test is used to compare two independent groups of nominal data. The prognostic model was built using logistic regression [3]. To establish the diagnostic value of the prognostic model, ROC analysis was used. Statistical processing of the study results was carried out using

the IBM SPSS Statistics Version 25.0 software package (International Business Machines Corporation, license No. Z125-3301-14, USA).

## RESULTS

When comparing the indicators recorded before the prone position, it was found that in patients of the 1st group, systolic and pulse blood pressure was higher than in patients of the 2nd group by 1.04 times at  $p=0.05$ , 1.13 times at  $p=0.023$ . The values of stroke volume and stroke index are also higher in patients who did not require mechanical ventilation, 1.27 times at  $p<0.005$  and 1.16 times at  $p<0.005$  (Table 2 and 3).

The parameters of the volumetric cardiac output velocity and left ventricular power are greater in group 1 by 1.26 times at  $p<0.005$  and 1.23 times at  $p<0.005$  than in group 2. The compliance of the vascular wall and the FS coefficient in the group where respiratory failure did not progress were 1.19 times higher at  $p<0.005$  and 1.81 times higher at  $p<0.005$ , respectively.

When comparing the pulse rate measured before the prone position maneuver, the indicators were 1.2 times lower in patients of the 1st group than in the 2nd group with  $p<0.005$ .

Table 1

Characteristics of patient groups (M[25;75])

Parameter	Group 1, n =50	Group 2, n= 50	Statistical significance
Age, years	63,00 [58,19;62,70]	68,00 [64,05;67,46]	<b>p=0,049</b>
Height, m	1,67 [1,66;1,70]	1,67 [1,66;1,69]	<b>p=0,812</b>
Weight, kg	80,00 [82,26;88,84]	80,00 [79,19;85,46]	<b>p=0,364</b>
BMI, kg/m <sup>2</sup>	30,04 [29,25;30,97]	29,24 [28,38;30,33]	<b>p=0,266</b>
Hypertension	36/50 (72%)	36/50 (72%)	p=0,87
CHD	21/50 (42%)	33/50 (67,3%)	p=0,011
Chronic heart failure	16/50 (32,7%)	30/50 (61,2%)	p=0,005
Chronic obstructive pulmonary disease	6/50 (12%)	8/50 (16,3%)	p=0,742
Diabetes mellitus	8/50 (16%)	12/50 (24,5%)	p=0,423
Chronic kidney disease	4/50 (8%)	8/50 (16,3%)	p=0,336
Neurological diseases	6/50 (12%)	16/50 (33,3%)	p=0,011

p — statistical significance of indicators.

Table 2

**Comparison of vascular and cardiac performance indicators in patients with critical respiratory failure**

Parameter	Group 1, n=50	Group 2, n=50	p
Systolic blood pressure, mm Hg. Art.	128,00 [126,35;131,73]	123,00 [117,54;123,73]	<b>p=0,050</b>
Pulse blood pressure-1, mm Hg. Art.	52,00 [51,49;56,59]	46,00 [44,20;48,90]	<b>p=0,023</b>
Pulse-1, beats/min	69,00 [68,70; 73,83]	84,00 [84,73;91,44]	<b>p &lt;0,005</b>
Pulse-2, beats/min	73,00 [73,70;78,26]	88,00 [86,57;94,20]	<b>p=0,001</b>
Stroke volume-1, ml	89,00 [85,43;93,10]	70,00 [64,67;71,00]	<b>p &lt;0,005</b>
Stroke volume-2, ml	86,00 [78,07;84,66]	66,00 [65,83;74,70]	<b>p=0,007</b>
Stroke index-1, ml/m <sup>2</sup>	44,00 [44,67;48,96]	38,00 [34,81;38,13]	<b>p &lt;0,005</b>
Stroke index-2, ml/m <sup>2</sup>	43,00 [40,72;44,22]	35,00 [35,14;40,00]	<b>p=0,022</b>

p — statistical significance of indicators.

Table 3

**Comparison of vascular and cardiac activity parameters in patients with critical respiratory failure**

Parameter	Group 1, n=50	Group 2, n=50	p
Volumetric ejection velocity — 1, ml/s	272,00 [277,56;309,86]	215,00 [203,44;221,13]	<b>p &lt;0,005</b>
Volumetric ejection velocity — 2, ml/s	244,00 [243,81;267,70]	200,00 [207,31;232,89]	<b>p=0,016</b>
Left ventricular contraction power — 1, W	3,20 [3,38;3,86]	2,60 [2,36;2,64]	<b>p &lt;0,005</b>
Compliance of the vascular wall — 1. ml/mm Hg. Art.	1,52 [1,51;1,63]	1,28 [1,24;1,36]	<b>p &lt;0,005</b>
Compliance of the vascular wall — 2. ml/mm Hg. Art.	1,47 [1,42;1,53]	1,15 [1,19;1,32]	<b>p &lt;0,005</b>
FS - 1	0,58 [0,51;0,60]	0,32 [0,21;0,32]	<b>p &lt;0,005</b>
FS - 2	0,55 [0,45;0,53]	0,27 [0,17;0,30]	<b>p &lt;0,005</b>

p — statistical significance of indicators.

When comparing the group of indicators recorded after the prone position maneuver, stroke volume and stroke index were higher in patients of the 1st group by 1.30 times at  $p=0.007$  and 1.23 times at  $p=0.022$  than in the 2nd group.

The value of the volumetric cardiac output rate and vascular wall compliance was greater in the group where respiratory failure did not progress, by 1.22 times at  $p=0.016$  and 1.28 times at  $p <0.005$ . We also found that in patients where mechanical ventilation was not required, the FS coefficient was 2.04 times higher with  $p <0.005$ .

When comparing the pulse rate measured after the prone position maneuver, the indicators were lower in patients of the 1st group than in the 2nd group by 1.21 times with  $p <0.005$ .

When comparing the group of indicators recorded after the prone position maneuver, stroke volume and stroke index were higher in patients of the 1st group by 1.30 times at  $p=0.007$  and 1.23 times at  $p=0.022$  than in the 2nd group.

The value of volumetric cardiac output velocity and vascular wall compliance was greater in the group where respiratory failure did not progress by 1.22 times at  $p=0.016$  and 1.28 times at  $p <0.005$ . It was also found that in patients where mechanical ventilation was not required, the FS coefficient was 2.04 times higher at  $p <0.005$ .

When comparing the pulse rate measured after the prone position maneuver, the indicators were lower in patients of the 1st group than in the 2nd group by 1.21 times with  $p <0.005$ .

**DISCUSSIONS OF THE RESULTS**

Previous studies have placed [8] importance on identifying and confirming factors that predict COVID-19 progression. Factors including age, comorbidities, immune response, radiographic data, laboratory markers, and indices of organ dysfunction may individually or collectively predict worse outcomes. Not all facts studied are conclusive evidence predicting severe disease, some are presumptive, and others are still preliminary and need further study. However, the difficulty of predicting the severity of COVID-19 disease is underscored by the fact that SARS-CoV-2 appears to have tropism for several tissues, including primarily the respiratory tract [9]. SARS-CoV-2 affects multiple organ systems, including the respiratory, cardiovascular and urinary systems, causing pneumonia and respiratory failure in patients [9, 11, 16].

Considering the fact that the treatment of respiratory failure is closely related to the use of prone position, we decided to study the hemodynamic state before and after proning of patients. Any change in the position of a patient in critical condition can cause different responses, which indicate a breakdown of adaptive mechanisms.

Patients whose respiratory failure did not progress had lower systolic blood pressure, pulse blood pressure, and pulse. This is probably due to changes in the block of cardiovascular parameters. Placing patients in a prone position caused an increase in intrathoracic and intra-abdominal pressure, which interferes with venous return and likely reduces ejection volume flow (EVF) [5].

Changes in stroke volume and index, the volumetric velocity of ejection, were observed both before and after the prone position. Probably, a significant decrease in the indicators of this block is due to the fact that patients in group 2 had more significant changes in the lungs (Tables 2 and 3). Extensive pneumonia caused by the new coronavirus infection COVID-19 led to damage to many alveolar units and disturbances in micro- and macrocirculation. A common complication in such patients is the development of pulmonary embolism [10, 13]. Often against this background, indicators of pulmonary hypertension increased [4], which in turn affected the speed and indicators of stroke volume. Also, against the background of a new coronavirus infection, ischemic and inflammatory processes occurred in the myocardium, which could also affect the indicators of cardiac block.

Compliance decreased statistically significantly both before and after the prone position. SARS-CoV-2 has a destructive effect on the cardiovascular system, which can be explained by both a direct cytotoxic effect on the endothelium and immune-mediated damage to endothelial cells. Angiotensin-converting enzyme 2, expressed on the endothelium, serves as a receptor for viral entry into the cell. The result of this interaction is an imbalance in the functioning of the renin-angiotensin system, which disrupts the regulation of vascular tone, stimulates proliferation and has a pro-inflammatory effect. Interleukin 6, which plays a key role in the development of cytokine storm, mediates a wide range of inflammatory changes that cause disturbances in the structural and functional organization of blood vessels [1]. An indirect sign of changes in hemodynamics in group 2 is reflected by the FS coefficient; it indicates the reaction of precapillaries to changes in cardiac output.

## CONCLUSIONS

1. In patients with progression of respiratory failure against the background of the new coronavirus infection COVID-19, the value of stroke volume and index is 1.27 and 1.16 times less before the prone position, as well as 1.3 and 1.23 times after the prone position according to compared with patients in the favorable group.

2. In addition, in group 2, the volumetric ejection velocity in the supine position was 1.26 times less, and in the stomach position it was 1.22 times less.

3. The compliance of the vascular wall and the reaction of precapillaries in patients who required mechanical ventilation were lower by 1.19 and 1.81 times before proning, and by 1.28 and 2.04 times after proning.

## ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

**Вклад авторов.** Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

**Конфликт интересов.** Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

**Источник финансирования.** Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

**Информированное согласие на публикацию.** Авторы получили письменное согласие пациентов на публикацию медицинских данных.

## ADDITIONAL INFORMATION

**Author contribution.** Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

**Competing interests.** The authors declare that they have no competing interests.

**Funding source.** This study was not supported by any external sources of funding.

**Consent for publication.** Written consent was obtained from the patient for publication of relevant medical information within the manuscript.

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