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ПРОФЕССОРУ ДЖУРАБАЮ МАРИФБАЕВИЧУ САБИРОВУ 80 ЛЕТ

1 января 2026 г. исполнилось 80 лет со дня рождения Джурабая Марифбаевича Сабирова, доктора медицинских наук, почетного профессора кафедры анестезиологии и реаниматологии Центра развития профессиональной квалификации медицинских работников, председателя ассоциации Анестезиологов и реаниматологов Республики Узбекистан.

Джурабай Марифбаевич Сабиров родился в Ташкентской области Узбекской ССР.

В 1968 г. он успешно окончил Ташкентский государственный медицинский институт. После окончания института работал врачом-анестезиологом Каракалпакского Республиканского противотуберкулезного диспансера. С 1970 г. по 1973 г. — врачом–анестезиологом городской клинической больницы № 1 города Ташкента.

С сентября 1973 г. трудовая деятельность профессора Д. М. Сабирова связана с Ташкентским институтом усовершенствования врачей (ТашИУВ), где он уже более 40 лет органично совмещает врачебную, педагогическую и научную работу.

На кафедре анестезиологии и реаниматологии ТашИУВ в 1973–1975 гг. Джурабай Марифбетович прошел клиническую ординатуру под руководством профессора А. С. Зарзар. С 1975 г. по 1976 г. работал старшим лаборантом, а с 1976 г. по 1989 г. — ассистентом этой кафедры.

В 1983 г. Д. М. Сабиров защитил кандидатскую, а в 1990 г. — докторскую диссертацию по теме «Анестезия при оперативных вмешательствах у больных гипертонической болезнью, нефрогенной и эндокринной гипертензией». В 1991 г. ему было присвоено ученое звание «профессор».

В 1989 г. по инициативе Д. М. Сабирова в ТашИУВ была организована кафедра «Скорой и неотложной медицинской помощи». Создание специализированной кафедры, которую он возглавил в качестве заведующего, способствовало повышению квалификации врачей службы скорой помощи, что является существенным фактором успеха в дальнейшем лечении больных на госпитальном этапе.

Благодаря хорошо поставленной учебно-методической и научной работе, кафедра за короткий срок обрела широкую известность среди врачей скорой помощи не только в Республике Узбекистан, но и за ее пределами.

В 1992 г. произошло объединение кафедры анестезиологии-реаниматологии и кафедры скорой и неотложной медицинской помощи. Профессор Д. М. Сабиров стал заведующим кафедры анестезиологии и реаниматологии (1992–2025 гг.), созданной на основе этого объединения. В этом же году профессор Джурабай Марифбетович был назначен проректором по научной работе ТашИУВ, а с 1997 по 2017 гг. являлся ректором Центра развития профессиональной квалификации медицинских работников (ТашИУВ). На этих постах еще больше раскрылись организаторские способности профессора Д. М. Сабирова. Под его руководством продолжается учебно-методическая работа, осуществляется научный поиск решения проблем в таких областях, как анестезия при сопутствующих заболеваниях, интенсивная терапия острой дыхательной недостаточности, реанимация и интенсивная терапия при острых отравлениях.

Будучи заведующим кафедрой анестезиологии и реаниматологии на протяжении 33 лет, председателем Специализированного Совета по защите докторских диссертаций, членом редакционных коллегий и советов журналов «Вестник экстренной медицины», «Общая реаниматология», «Неврология», являясь педагогом и ученым, Джурабай Марифбетович всегда оставался блестящим врачом с широкой эрудицией, энциклопедическими знаниями и точным клиническим мышлением.

Коллектив редакции журнала «Общая реаниматология» присоединяется к поздравлениям профессора Джурабая Марифбетовича и желает юбиляру крепкого здоровья, долгих, плодотворных и счастливых лет жизни!

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The Effect of Preoperative Preparation with Helium-Oxygen Mixture on the Incidence of Pulmonary Complications in Patients with COPD and Lung Cancer

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Summary

Aim of the study. To study the effect of helium-oxygen mixture on predictors of postoperative pulmonary complications in cancer patients with chronic obstructive pulmonary disease (COPD).

Materials and methods. A single-center prospective clinical study with historical control included 208 patients, among them 104 patients received helium-oxygen mixture inhalations (70% helium and 30% oxygen) in the preoperative period (He group) and 104 patients were the historical control group (Ctrl group). Given the risk of bias associated with confounders, we conducted a one-to-one matching analysis based on pseudo-randomization to adjust for the unbalanced baseline characteristics of the groups. We used logistic regression to develop the pseudo-randomization estimates. We used the nearest neighbor matching 1:1 with a caliper of 0.1 to achieve better similarity among matched pairs. After pseudo-randomization, we included 87 patients in each group, ensuring adequate balance across all covariates. A multivariate logistic regression analysis was performed to identify factors associated with the risk of postoperative pulmonary complications.

Results. In the He group, there was a statistically significant improvement in a number of functional parameters compared to the Ctrl group. FEV_1, FVC, mod. Tiffeneau index values in the He group increased significantly (p=0.0009; p=0.0115; p=014, respectively), gas exchange parameters (PaO_2, $PaCO_2$, pH, SpO_2) improved (p=0.0006; p=0.004; p=0.0097; p=0.001, respectively). Hypoxia tolerance tests also showed significantly greater values in the He group (Stange test, p=0.016; Sabrazes (Hench) post-exhalation breath-holding test, p=0.024). Analysis of post-operative parameters showed significant advantage of the He group over the control group in terms of critically important clinical outcomes. At the final stage of stepwise selection, three independent predictors were included in the risk model for postoperative pulmonary complications: SpO_2, the breath-holding test, and the duration of post-operative mechanical ventilation. The quality of the model was high, with a correctly classified case rate of 92.2%, a Hosmer–Lemeshow goodness-of-fit statistic of p=0.933, and a total model significance of $p<0.000$.

Conclusion. We performed the first clinical study that showed the importance of preoperative preparation using a helium-oxygen mixture in cancer patients with chronic obstructive pulmonary disease and identified predictors of pulmonary complications after thoracic surgery.

Keywords: predictors of pulmonary complications; helium-oxygen mixture; Heliox; chronic obstructive pulmonary disease; lung cancer

Conflict of interest. The authors declare no conflict of interest.

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Introduction

Lung cancer is one of the most common causes of cancer-related morbidity and mortality, representing a significant challenge within healthcare systems. Worldwide over 2 million cases of various malignant lung tissue neoplasms, such as adenocarcinoma, squamous cell carcinoma, neuroendocrine carcinoma, and carcinoid, are reported annually [1].

Lobectomy and pulmonectomy are the main surgical options for lung cancer. According to most authors, it is advisable to consider reducing the

scope of surgical intervention in patients with limited functional reserves, i.e., to reduce the volume of resected lung tissue and limit lymph node dissection. This approach is common in patients with metastatic lung disease, and also relevant in primary lung cancer, especially in patients with severe respiratory failure [2].

It's not uncommon that surgical access may require single-lung ventilation, which can increase dead space and intrapulmonary shunting, thereby causing hypoxemia in patients with low respiratory reserve. Traditional methods, including increasing PEEP, peak pressure, and plateau pressure, can worsen oxygenation and respiratory mechanics, especially in patients with COPD. In addition, thoracic surgeries are associated with postoperative complications such as alveolar-pleural fistula, pneumonia, and ARDS [3, 4]. According to some authors, the mortality rate after lung resection for cancer reaches 6% [5].

There are several factors that are directly and indirectly related to the risk of negative treatment outcomes. These include patient-related (ASA ⩾ III) and surgery-anesthesia related (ARISCAT ⩾ 26 scores) criteria. Quitting smoking provided a beneficial effect on patient's respiratory status during comprehensive preoperative preparation. According to the LAS VEGAS study, the number of pulmonary complications did not differ between smokers and non-smokers in the postoperative period, but the incidence of respiratory failure was statistically significantly higher in smokers (5.1% and 3.0%, respectively) [6].

Conventionally used predictors of postoperative pulmonary complications, such as age, volume of resected lung tissue, and baseline respiratory function, are well known. However, most existing models are static and do not take into account the potential for preoperative optimization of respiratory status. Berry et al. study has demonstrated that the predictive value of functional pulmonary tests in relation to postoperative pulmonary complications in patients with respiratory failure depends on the surgical access, as statistically significant correlation was found only in thoracotomy access, not in video-assisted thoracic surgery (VATS) [7]. D. Almqvist et al. have demonstrated in a recent study that FEV_1 and lung diffusion capacity did not have prognostic value in relation to survival rates in patients after surgical resection for early stage lung cancer. Meanwhile, the same functional tests significantly correlated with length of hospital stay [8].

The breath-holding test was introduced into practice in 1902 by Sabrazès Jean-Emile (1867–1943), who established that the normal duration of apnea is 20–25 seconds, and a reduction in time to 5–10 seconds is associated with various pathologies, such as mitral valve insufficiency. Later, V. A. Stange (1856–1918) recommended this test as «the best indicator of the patient's heart condition during operations under general anesthesia» [9].

Noble gases are a promising direction in therapy of critical conditions [10]. Xenon and argon possess organoprotective properties *in vitro* and *in vivo*, while studies of krypton are only at the beginning of the experimental path [11–13].

Helium is a monoatomic noble gas with a lower molecular mass compared to diatomic nitrogen (Mr He = 4.0 g/mol vs Mr N2 = 28.0 g/mol). Graham's law (Thomas Graham, 1805–1869), known as the law of relative rates of passage of substances through a membrane, states that the rate of gas flow is inversely proportional to the square root of its mass density [14]. Therefore, replacing nitrogen with helium in a breathing mixture will lead to a more active penetration of oxygen through the alveoli into the blood, which may be beneficial for patients with impaired gas exchange.

Heliox (a mixture of helium and oxygen) has been used for medical purposes since 1934, when Alvan Barach first described his own research on the use of the gas in patients with bronchial asthma and upper airway obstruction [15]. The dominant area of clinical application of Heliox is currently related to respiratory diseases, while its potential effects on other physiological systems (CNS, circulation, immunity) remain the subject of preclinical studies [15–21].

According to a systematic review and meta-analysis (Lakhin et al., 2022), adding of Heliox to conventional respiratory therapy for severe acute pneumonia improves oxygenation, reduces acute-phase proteins (APPs) levels, but does not reduce the length of ICU stay, rates of mechanically assisted ventilation, or in-hospital mortality rates [22].

Prevention of respiratory complications is a basic principle of perioperative management in thoracic anesthesiology. Finding the best strategy and tactics for managing patients can lead to a decrease in mortality, paving the way for a solution to this problem. To date, there are no studies on the impact of Heliox on the quality of prevention of pulmonary complications in the perioperative period.

The aim of the study is to investigate the effect of helium-oxygen mixture on predictors of postoperative pulmonary complications in cancer patients with chronic obstructive pulmonary disease.

Materials and Methods

A single-center prospective clinical study with historical control was conducted. The study protocol was approved by the local ethics committee of the Perm regional clinical hospital, No. 42 dated March 31, 2023.

The study analyzed two time-related cohorts. The retrospective part was formed from patients who met the

inclusion criteria and received treatment between 01.11.2022 and 31.10.2023. The prospective cohort was recruited between 15.01.2024 and 15.06.2025. A buffer interval (November–December 2023) was set to exclude temporal overlap and potential data mixing between cohorts.

Taking into account the risk of systematic error associated with confounding bias, characteristic of retrospective studies, we used a propensity score matching (PSM) — a one-to-one matching analysis based on pseudo-randomization to adjust for the unbalanced baseline characteristics of the groups. Logistic regression was used to develop estimates of pseudorandomization. We used the nearest neighbor matching 1:1 with a caliper of 0.1 to achieve better similarity among matched pairs. This value of the caliper allowed to achieve a satisfactory balance between the SMD $<$ 0.1 groups. Age, gender, Charlson comorbidity index, Stange post-inhalation breath-holding test, PaO_2, FEV_1, FVC, and COPD were included as covariates. The balance of covariates between groups was assessed by calculating and visualizing standardized mean differences (SMDs) using a love plot, using the threshold value of SMD $\leqslant$ 0.1 as a success criterion.

Criteria for the inclusion of patients in the study:

- verified diagnosis of lung cancer (non-small cell cancer);
- presence of chronic obstructive pulmonary disease (COPD stage I–III);
- age: 40–75 years old;
- elective surgery ((lobectomy, bilobectomy, pulmonectomy);
- consent to participate in the study.

Criteria for excluding patients from the study:

- severe concomitant somatic pathology (decompensated cardiovascular insufficiency, severe renal or hepatic dysfunction);
- acute infectious diseases in the preoperative period;
- absence of patient's informed consent;
- incomplete clinical and laboratory data that impede correct analysis (for example, absence of spirometry data (FEV_1, FVC), arterial blood gases, ABGs (PaO_2, $PaCO_2$, pH, SpO_2), breath holding tests — after deep inhalation and after full exhalation (Stange and Sabrazes (Hench) tests, respectively), or important demographic and clinical characteristics (age, COPD stage, Charlson comorbidity index, CCI) necessary for statistical analysis and comparison of the groups)

As part of the preoperative preparation, all patients underwent a comprehensive diagnostic examination. In cases of chronic respiratory failure, ventilation disorders were corrected under the dynamic supervision of a pulmonologist. During preparation for surgery, all patients were managed according to the current National clinical guidelines for patients with COPD and lung cancer that are prepared for thoracic surgery. The program included standard of care therapy (bronchodilators, inhaled glucocorticosteroids as indicated), breathing exercises, correction of nutritional status, and mastering coughing technique, if necessary.

Preoperative preparation in the He group. The breathing gas mixture of 70% helium and 30% oxygen «Heliox 70/30» was heated to 70°C and the inhalation procedure was performed for 10 minutes. After a short pause of 4 minutes, the procedure was repeated. After 6–8 hours, a second session of two inhalations was performed in the same mode. This inhalation regimen was carried out for 5–7 days during the preoperative period.

Preoperative preparation in the Ctrl group. Helium-oxygen mixture was not used in this group.

The results of preoperative preparation were assessed based on cardiovascular and respiratory system indicators, including ABGs analysis and spirometry, electrocardiography, and echocardiography data.

Criteria for the effectiveness of preoperative preparation:

- Improvement in the patient's well-being;
- Reduction in the severity of respiratory disorders (reduction in shortness of breath, dyspnea);
- Improvement in ABGs composition (increase in $pO_2 > 80$ mmHg, decrease in $pCO_2 < 45$ mmHg, P/F ratio > 300 mmHg);
- Improvement in spirometry indicators $FEV_1 > 70\%$, FVC, modif. Tiffeneau index;
- Improvement in functional test indicators (increase in Stange test > 30 sec, Sabarazes–Hench > 20 sec);

Patient's readiness for lung cancer surgery or the need for extended preoperative preparation was established by a consilium based on the dynamics in patient's condition evaluated by clinical data, results of laboratory and instrumental examinations.

All surgical interventions for lung cancer were performed under combined anesthesia: low-flow inhalation anesthesia based on desflurane and epidural anesthesia with ropivacaine [23, 24]. Ventilation with protective modes was performed using a Datex-Ohmeda Avance S/5 anesthesia and ventilation machine. Extended intraoperative monitoring included the following parameters: pulse, heart rate, noninvasive blood pressure, desflurane concentration, CO_2 and O_2 on inspiration and expiration, body temperature, depth of anesthesia (Conox, Fresenius Kabi). Before suturing the thoracotomy wound, anesthesia of the lung root and intercostal blockade were performed. Postoperative care was continued either in an intensive care or resuscitation unit, depending on patient's condition.

Statistical methods. The data were analyzed using Microsoft Office Excel 2019 spreadsheet software. Quantitative data were described as *Me* [*Q1; Q3*], where *Me* is the median value, *Q1* is the first quartile (25^{th} percentile), and *Q3* is the third quartile (75^{th} percentile). The Shapiro–Wilk test was used to assess the normality of the data. The distribution of most quantitative unrelated variables was significantly different from normal, therefore the nonparametric Mann–Whitney *U* test was used to assess intergroup differences. The Chi-square test or the Fisher's exact test was used to compare frequency of variables in unrelated groups (in cases where the frequency of the outcome was less than 10%).

To assess the degree of predictors' influence on the outcome of a particular event, the odds ratio (OR) was used. To assess the significance of predictors (of the development of a particular event, i. e., pneumonia, death), multivariate and univariate analyses based on logistic regression were used, as well as ROC analysis of the sensitivity and specificity of predictors. Multivariate analysis was performed using a stepwise method with inclusion criteria at $p < 0.05$ and exclusion criteria at $p > 0.1$. To determine the optimal cutoff point (related criterion) in ROC analysis, the Youden index was used. The critical two-tailed significance level p was set at 0.05. SPSS Statistics software (IBM SPSS Statistics for Windows, Version 27.0.1 Armonk, NY: IBM Corp) and MedCalc (MedCalc Software Ltd version 20.305, Ostend, Belgium; https://www.medcalc.org; 2023) were used for statistical data processing.

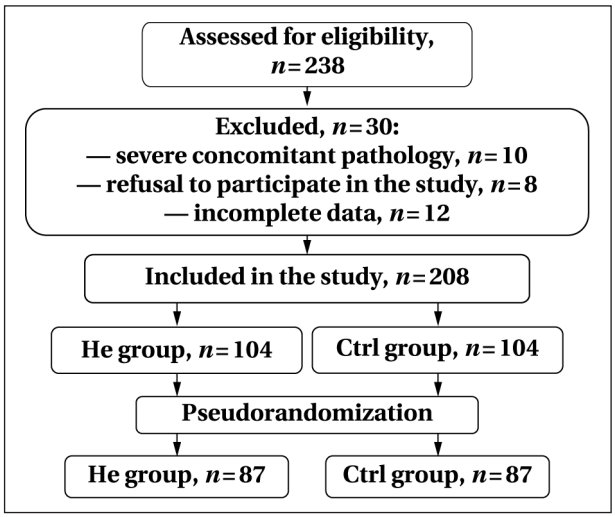

Fig. 1. Patient inclusion scheme.

Results

A total of 238 patients were evaluated. After screening for selection criteria, 30 patients were excluded from the study for the following reasons: presence of severe concomitant pathology ($n=10$), refusal to participate in the study ($n=8$) and incomplete data ($n=12$). As a result, 208 patients were included in the study, and divided into two groups: He group (receiving inhalations of a helium-oxygen mixture, $n=104$), and Ctrl group (historical control, $n=104$). After pseudo-randomization, 87 patients in each group with an adequate balance across all covariates were included in the final analysis (Fig. 1, Table 1).

After preoperative preparation, there was a statistically significant improvement of monitored functional parameters in He group compared with the Ctrl group (Table 2). FEV_1, FVC, and modified Tiffeneau index significantly improved in He group, as well as gas exchange parameters (PaO_2, $PaCO_2$, pH, SpO_2). Hypoxia tolerance tests values (Stange and Sabrazes (Hench) tests) also showed a statistically significant increase in He group.

Analysis of postoperative parameters demonstrated the advantage of the He group in terms of a number of critically important clinical outcomes (Table 3). In the He group, compared with the Ctrl group, the duration of mechanical ventilation was shorter: 4 [0–7] hours vs. 5 [0–9] hours ($p=0.032$); lactate 12 hours after surgery was lower: 1.9 [0.5–2.3] vs. 2.3 [0.5–3.1] mmol/L ($p=0.002$); the P/F ratio was higher at 6 hours (395 [395–395] vs. 373 [327–385] mmHg, $p<0.0001$) and at 12 hours (398 [398–400] vs. 381 [357–397] mmHg, $p<0.0001$), reflecting improved lung oxygenation. The ICU stay was shorter in the He group compared to the Ctrl group: 1 [0–2] vs. 2 [1–4] days ($p<0.0001$). The total length of hospital stay was also shorter in the He group than in the Ctrl group: 21 [18–25] vs. 23 [19–28] days ($p=0.006$). The incidence of pulmonary complica-

Table 1. Patient characteristics.

Parameters	Values in the groups		*p*
	He, $n=87$	Ctrl, $n=87$	
Age, years	56 [47–64]	56 [44.5–67.5]	0.720
Gender (male), %	90	90	NA
Body weight, kg	65 [62–71.5]	68 [63–73]	0.053
BMI	22 [21–23]	22 [20–23]	0.669
COPD stage I, %	32	29	0.674
COPD stage II, %	54	54	1.000
COPD stage III, %	14	17	0.592
Charlson Comorbidity Index, score	9 [6–10]	8 [6–10]	0.804
FEV_1, % of predicted	71 [27–82]	67 [30–83]	0.618
FVC, L	4.24 [3.46–4.66]	4.28 [3.65–4.68]	0.851
Mod Tiffeneau–Pinelli (Hensler) index	0.62 [0.58–0.71]	0.6 [0.57–0.71]	0.263
Stange test, sec	34 [25–45]	33 [25–45.5]	0.777
Sabrazes (Hench) test, sek	20 [13–24]	19 [12–25]	0.647
PaO_2, mmHg	78 [73.5–80]	77 [74–80]	0.655
$PaCO_2$, mmHg	43 [40–47]	44 [40–48]	0.434
pH	7.39 [7.38–7.41]	7.39 [7.37–7.41]	0.789
SpO_2, %	95 [93–96]	96 [93–96]	0.603

tions in the He group was significantly lower than in the Ctrl group: respiratory failure — 3 vs. 13 cases ($p=0.019$), atelectasis — 1 vs. 4 ($p=0.029$), total number of pulmonary complications — 9 vs. 23 ($p=0.006$). Extrapulmonary complications and mortality did not differ statistically significantly between the groups ($p>0.05$).

Next, we conducted a univariate analysis of risk factors for pulmonary complications using univariate logistic regression. We identified a number of statistically significant predictors (Table 4, white rows).

Thus, both preoperative (especially pulmonary function tests, gas exchange parameters, and oxygen saturation) and early postoperative parameters served as significant risk factors for the development of pulmonary complications.

Multivariate logistic regression analysis was performed to identify factors associated with an increased risk of postoperative pulmonary complications (Table 5).

At the final stage of stepwise selection, two preoperative prognostic parameters (SpO_2 and Sabrazes (Hench) test) and one early postoperative marker/risk factor (duration of mechanical ventilation) were included in the model:

- SpO_2 after preparation: increased blood oxygen saturation was associated with a reduced risk of complications (coefficient = –0,09; $p=0,0004$; OR = 0,41; 95% CI: 0,27–0,63);
- Sabrazes (Hench) test after preparation: a decrease in the duration of post-exhalation breath holding increased the risk of complications (coefficient = 0,2; $p=0,0001$; OR = 1,22; 95% CI: 1,09–1,36);

Table 2. Pulmonary function tests and gas exchange parameters after preoperative preparation of patients in the study groups.

Parameters	Values in the groups				*p*
	He, *n* = 87		Ctrl, *n* = 87		
	Me [*Q1*; *Q3*]	95% CI	*Me* [*Q1*; *Q3*]	95% CI	
FEV_1, % of predicted	81 [33–89]	77–87	69 [30–85]	62–73	0.0009
FVC, L	4.65 [3.78–5]	4.55–4.72	4.34 [3.7–4]	4.08–4.50	0.0115
modified Tiffeneau index	0.67 [0.64–0]	0.65–0.68	0.63 [0.59–0]	0.61–0.64	0.014
Stange test, sek	40 [30–54.5]	35–45	35 [26–48]	33–38	0.016
Sabrazes (Hench) test, sek	24 [15–29]	19–24	19 [12.5–25]	16–22	0.024
PaO_2, mmHg	84 [80–84]	84–84	80 [80–84]	80–84	0.0006
$PaCO_2$, mmHg	40 [38–43]	39–41	42 [38–46]	40–43	0.004
pH	7.42 [7.41–7.44]	7.41–7.43	7.41 [7.39–7.43]	7.40–7.42	0.0097
SpO_2, %	97 [91–97]	97–97	96 [91–97]	95–97	0.001

Table 3. Postoperative parameters and complications in patients in the study groups.

Parameters	Values in the groups		*p*
	He	Ctrl	
Frequency of pneumonectomy	9%	8%	0.817
Frequency of bilobectomy	3%	4%	0.725
Frequency of lobectomy	37%	38%	0.894
Risk scale post-op RF	39 [22–39]	34 [22–39]	0.387
Duration of post-op mechanical ventilation	4 [0–7]	5 [0–9]	0.032
Lactate 6 hours post-op, mmol/L	2.5 [0.7–3.3]	2.7 [0.7–3.2]	0.871
Lactate 12 hours post-op, mmol/L	1.9 [0.5–2.3]	2.3 [0.5–3.1]	0.002
PaO_2/FiO_2 = P/F ratio, mmHg after 1 hour	330 [279–370]	331 [281–360]	0.508
P/F ratio (after 3 hours)	344 [321–380]	341 [315–361]	0.323
P/F ratio (after 6 hours)	395 [395–395]	373 [327–385]	< 0.0001
P/F ratio (after 12 hours)	398 [398–400]	381 [357–397]	< 0.0001
Length of stay in the ICU, days	1 [0–2]	2 [1–4]	< 0.0001
Length of hospital stay, days	21 [18–25]	23 [19–28]	0.006
Pneumonia, cases	1	3	0.060
Respiratory failure, sl.	3	13	0.019
Atelectasis, cases.	1	4	0.029
Bronchospasm, cases	1	0	0.500
ARDS, cases.	1	3	0.060
All pulmonary complications, cases	9	23	0.006
ACS, cases	1	2	0.123
PE, cases	1	2	0.123
Cerebral stroke, cases.	0	0	н/п
Severe arrhythmia, cases	4	6	0.001
Acute circulatory failure, cases.	1	2	0.123
All extrapulmonary complications, cases	7	12	0.226
In-hospital mortality, %	1.15	2.30	0.123

Table 4. Significance of risk factors for pulmonary complications.

Parameters	OR	95% CI	*p*
Baseline			
Age	0.98	0.94–1.23	0.320
Gender (male)	1.11	0.23–5.33	0.898
BMI	0.92	0.61–1.38	0.696
Charlson Comorbidity Index	0.98	0.78–1.38	0.681
FEV_1, % of predicted	0.95	0.92–0.98	0.0007
FVC, L	0.48	0.27–0.86	0.014
Stange test	0.95	0.91–0.99	0.029
Sabrazes (Hench) test	1.0	0.94–1.08	0.787
PaO_2	0.88	0.82–0.93	0.004
$PaCO_2$	1.19	1.08–1.33	0.0006
pH	1.38E-9	1.48E-14–0.0001	0.0016
SpO_2	0.65	0.52–0.82	0.0002
After preoperative preparation			
He group	2.74	0.92–8.17	0.058
FEV_1, % of predicted	0.93	0.91–0.97	0.0001
FVC, L	0.48	0.27–0.86	0.014
Modif Tiffeneau index	1.38E-9	1.48E-14–0.0001	< 0.0001
Stange test	0.95	0.91–0.99	0.02
Sabrazes (Hench) test	1.01	0.95–1.06	0.79
PaO_2	0.89	0.80–0.98	0.02
$PaCO_2$	1.24	1.12–1.38	0.0003
pH	1.38E-9	1.48E-14–0.0001	0.013
SpO_2	0.59	0.46–0.76	< 0.0001
Post-operative			
Pulmonectomy	2.0	0.59–6.74	0.28
Bilobectomy	4.82	1.30–17.82	0.03
Lobectomy	3.71	1.32–10.44	0.016
Risk scale post-op RF	1.07	0.99–1.16	0.054
Post-op mechanical ventilation	1.33	1.14–1.56	0.0001
Lactate 6 hours post-op	1.61	0.89–2.91	0.095
Lactate 12 hours post-op	2.55	1.35–4.82	0.002

• Duration of postoperative mechanical ventilation: prolongation of mechanical ventilation increased the likelihood of developing pulmonary complications (coefficient = 0,35; p = 0,0005; OR = 1,41; 95% CI: 1,16–1,72).

The quality of the final model was high: the percentage of correctly categorized cases was 92.2%, Hosmer–Lemeshow goodness-of-fit test was p = 0.933, and the overall significance of the model was $p < 0.0001$.

It should be noted that variables such as age, gender, type of surgery, Charlson comorbidity index, FEV_1, PaO_2, $PaCO_2$ after preparation, were not included in the final model, which confirms the independence of the identified factors from important clinical and demographic characteristics.

To assess the discriminatory ability of the factors, we performed ROC analysis of significant predictors of pulmonary complications (Table 6).

Factors with satisfactory and good model quality:

• FEV_1 after preparation: AUC = 0.813 (95% CI: 0.753–0.863), sensitivity 74.07%, specificity 77.35%%;

• SpO_2 after preparation: AUC = 0,814 (95% CI: 0,747–0,870), sensitivity 88,24%, specificity 68,00%;

• modified Tiffeneau index after preparation: AUC = 0,803; sensitivity 94,12%, specificity 59,33%;

• duration of post-op mechanical ventilation: AUC = 0,750; sensitivity 76,47%, specificity 83,33%.

Discussion

Reducing cardiorespiratory complications in patients with combined pathology (lung cancer and COPD) during surgery is an extremely pressing issue that requires development of appropriate treatment standards [25, 26]. Several factors contribute to the significant risks of postoperative respiratory failure, such as the duration of surgery exceeding 3 hours, urgency, tumor location in the chest, and trauma of major surgery (FAR guidelines, 2022). The negative effects of mechanical ventilation and intraoperative factors can lead to serious changes in respiratory biomechanics at all stages of anesthetic care [27].

Helium, due to its low density, reduces airway resistance, improving ventilation and gas exchange. A statistically significant improvement in functional parameters was reported in patients treated with helium-oxygen mixture: FEV_1 increased to 81% (versus 69% in the control group, p = 0.0009), SpO_2 reached 97% (p = 0.001), and the Tiffeneau index improved to 0.67 (p = 0.014). This confirms the effectiveness of using helium to optimize respiratory function in patients with obstructive pulmonary disease in the preoperative period. In our opinion, these indicators can be a useful tool in risk stratification.

The data obtained are comparable to the study by P. Jolliet et al., where a multicenter randomized controlled trial evaluating the effectiveness of Heliox in patients with COPD showed that the helium-

Table 5. Results of multivariate regression analysis.

Parameters	Coefficient	P	OR corr.	95% CI
SpO_2 after preparation	–0.09	0.0004	0.41	0.27–0.63
Sabrazes (Hench) test after preparation	0.2	0.0001	1.22	1.09–1.36
Duration of post-op mechanical ventilation	0.35	0.0005	1.41	1.16–1.72
Constant	75.06	0.0001		
Overall model quality assessment		<0.0001		
Percentage of correctly categorized cases 92.2%				
Hosmer–Lemeshow goodness-of-fit test, p = 0.933				

Note. Here and in the Table 6: AUC > 0.9 — excellent model quality; AUC > 0.8 — good model quality; AUC > 0.7 — satisfactory model quality.

Table 6. ROC analysis of significant predictors of pulmonary complications.

Parameters	AUC	95% CI	Related criterion	Sensitivity	95% CI	Specificity	95% CI
Baseline							
FEV_1, % of predicted	0.767	0.695–0.829	⩽47	47.06	23.0–72.2	92.00	86.4–95.8
FVC, L	0.677	0.600–0.747	⩽4.04	70.59	44.0–89.7	68.00	59.9–75.4
Stange test	0.649	0.572–0.722	⩽46	100.00	80.5–100.0	26.67	19.8–34.5
PaO_2	0.672	0.596–0.743	⩽72	47.06	23.0–72.2	85.33	78.6–90.6
$PaCO_2$	0.711	0.636–0.778	>46	58.82	32.9–81.6	74.00	66.2–80.8
pH	0.751	0.678–0.814	⩽7.38	76.47	50.1–93.2	64.67	56.5–72.3
SpO_2	0.767	0.696–0.829	⩽93	70.59	44.0–89.7	76.67	69.1–83.2
After preoperative preparation							
FEV_1, % of predicted	0.813	0.753–0.863	⩽61	70.59	44.0–89.7	78.00	70.5–84.3
FVC, L	0.680	0.603–0.750	⩽4.08	70.59	44.0–89.7	71.33	63.4–78.4
Mod Tiffeneau index	0.803	0.734–0.860	⩽0.64	94.12	71.3–99.9	59.33	51.0–67.3
Stange test	0.667	0.589–0.737	⩽36	76.47	50.1–93.2	54.67	46.3–62.8
PaO_2	0.627	0.549–0.701	⩽80	58.82	32.9–81.6	65.33	57.1–72.9
$PaCO_2$	0.715	0.640–0.782	>39	82.35	56.6–96.2	47.33	39.1–55.6
pH	0.701	0.626–0.770	⩽7.4	58.82	32.9–81.6	73.33	65.5–80.2
SpO_2	0.814	0.747–0.870	⩽95	88.24	63.6–98.5	68.00	59.9–75.4
Postoperative							
Duration of post-op mechanical ventilation	0.750	0.677–0.813	>8	76.47	50.1–93.2	83.33	76.4–88.9
Lactate 12 hours post-op	0.698	0.623–0.767	>2.3	52.94	27.8–77.0	70.67	62.7–77.8

oxygen mixture reduced respiratory acidosis, decreased shortness of breath, and reduced the severity of encephalopathy [28].

ABGs analysis remains the gold standard in assessing gas exchange in patients with COPD in the acute stage. The use of Helioxs led to an improvement in parameters such as PaO_2, $PaCO_2$, and pH, indicating a significant correction of ventilation-perfusion mismatch in the He group. Improved oxygenation and tissue perfusion parameters reduced the risk of multiple organ dysfunction and the frequency of pulmonary complications. This inevitably led to a reduction in duration of mechanical ventilation and ICU stay among patients in the He group. According to a study by L.V. Shogenova, the use of a helium-oxygen mixture in combination with nitric oxide and molecular hydrogen also led to a reduction in hypercapnia and hypoxemia, an increase in exercise tolerance, and an improvement in the clinical condition of patients with COPD [29].

According to a study by P. Singh et al., preoperative assessment of the risk of respiratory disorders can be performed using the Sabrazes (Hench) test. This method allowed predicting the likelihood of hypoxia in the early postoperative period in patients after surgery on the paranasal sinuses [30]. Multivariate analysis demonstrated a statistically significant correlation between shortened Sabrazes (Hench) breath-holding test and an increased risk of pulmonary complications.

Therefore, SpO_2 value and the Sabrazes (Hench) test are clinically significant parameters for preoperative prediction. The duration of mechanical ventilation is an important postoperative risk factor and essential target indicator for the prevention of secondary complications during treatment.

It should be emphasized that inclusion of helium-oxygen therapy in comprehensive preoperative preparation led to an improvement in functional parameters and laboratory indicators, contributing to a reduction in postoperative respiratory risks in cancer patients.

Conclusion

The use of a helium-oxygen mixture as part of preoperative preparation in cancer patients with COPD undergoing lung resection leads to a statistically significant improvement in functional respiratory parameters and a reduction in the incidence of postoperative pulmonary complications. Low saturation after preoperative preparation may be associated with an increased risk of complications, confirming the importance of oxygenation in prevention of respiratory dysfunction. In our opinion, the results of Sabrazes (Hench) breath-holding test correlates with the risk of complications, which may imply a decrease in breathing reserve (BR). An increase in the duration of mechanical ventilation is associated with an increased likelihood of complications, which is explained by the risk of barotrauma, atelectasis, and ventilator-associated lung injury.

The study confirms that preoperative optimization of respiratory function reduces the incidence of postoperative pulmonary complications in patients with COPD. The identified predictors can be used for individual risk prediction and the development of personalized management protocols.

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Polymorphism of *OLR1* Gene Encoding Oxidized LDL Receptor LOX-1 Modifies the Course of Necrotizing Pulmonary Infection

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Summary

Necrotizing pulmonary infections (NPI) emerge as severe complications of community-acquired pneumonia (CAP), and immune system cells are involved in their pathogenesis. Highly informative biomarkers are required to determine high-risk patients to prevent life-threatening complications of NPI. Previously, we have shown that variations in immune cell numbers can be employed as prognostic biomarkers in NPI. We proposed that genetic variants encoding receptors detected on the surface of neutrophils, monocytes, and macrophages migrating to lung tissues during inflammation may predict the unfavorable course of NPI. One of these candidate genes could be the *OLR1* gene, which encodes LOX-1 receptors that bind oxidized low-density lipoproteins oxLDL on the surface of immune and other cells.

The aim of the study. To find out the *OLR1* gene single nucleotide polymorphism contribution to the clinical course of NPIs (pleural empyema) and variability in the number of immune cells in patients with post-CAP NPI.

Materials and methods. The study included patients of the Moscow City Hospital (aged 18–87 years, $n=216$) with NPIs developed after CAP. Categorical data were described by indicating absolute values, which were compared using four-field contingency tables and the χ^2 test with Yates' correction for sample continuity and Fisher's exact test (FET).

Results. NPIs were the most common complication of CAP. In patients with NPI and the minor allele G *OLR1* rs11053646, which encodes the LOX-1 167N variant, the course of the disease was less likely to be complicated by a fistula ($p=0.0015$; exact Fisher test (EFT); OR = 3.55, 95% CI: 1.55–8.13; RR = 2.37, 95% CI: 1.24–4.50; $n=216$). However, the significance of this association was influenced by previous COVID-19 documented in patient's medical history based on PCR test results. For patients who had been infected with COVID-19, this association persisted ($p=0.0058$; EFT; OR = 7.27, 95% CI: 1.54–34.3; RR = 4.28, 95% CI:1.31–16.23; $n=81$), whereas in patients with no PCR test confirmed COVID-19, this association was not statistically significant ($p=0.1065$, EFT, $n=135$). Thus, only post-COVID-19 carriers of the minor allele G *OLR1* rs11053646 were protected from a severe course of NPIs complicated with fistula development. A study in a limited subgroup of patients showed a trend for a fistula development to associate with increased OxLDL plasma concentration of more than 100 ng/ml ($p=0.045$; $n=19$).

Conclusion. Post-COVID-19 carriers of major *OLR1* rs11053646 CC genotype exhibit increased risk for the unfavorable course of NPI (pleural empyema) complicated with fistula. The presence of alternative G allele of *OLR1* rs11053646 in patient genotype associates with favorable course of NPIs.

Keywords: necrotizing pulmonary infections; OLR1 genetic polymorphism; LOX-1 receptor; oxidized low-density lipoproteins; OxLDL; community-acquired pneumonia; COVID-19; lung abscess; lung gangrene; pleural empyema

Conflict of interest. The authors declare that there is no conflict of interest.

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Introduction

Necrotizng pulmonary infections (NPIs) are severe pathological conditions characterized by inflammatory infiltration and subsequent destruction of lung tissue as a result of exposure to infectious agents [1]. Currently, there is a trend toward an increase in the incidence of NPIs. Despite improvements in treatment methods, mortality remains high, ranging from 5% to 30% and reaching 70% in cases of lung gangrene [2, 3]. Up to 15% of such patients seeking medical care require support for vital body functions [4]. At the same time age, nutritional status, concomitant diseases, the state of the immune system, and the timeliness of targeted antibacterial

and supportive therapy are essential for patient's condition [5].

Pleural empyema (PlE) is one of the most common entity among NPIs manifesting as accumulation of pus or fluid in the pleural cavity with biological signs of infection, involving the parietal and visceral pleura in the inflammatory process and causing secondary compression of the lung tissue. About 60% of PlE cases are associated with some primary pulmonary process emerging as an outcome of community-acquired pneumonia (CAP). Parapneumonic effusion and purulent- destructive processes complicating CAP are the main causes of pleural empyema. In some patients parapneumonic effusion results in PlE without fistula, while in others the outcome is less favorable and complicated by fistula formation, which worsens the course of the disease and prognosis [1, 6].

Early prediction of complicated NPI and its outcome is hampered by the lack of reliable and highly informative biomarkers that are pathogenetically substantive for the development of complications and are associated with immune disorders. Immune system cells are widely represented in the respiratory tract, and their migration and accumulation in the lungs significantly depends on receptor expression and chemokinesis. LOX-1 receptors, known as class E scavenger receptors, are common on the surface of neutrophils, monocytes, and macrophages [7], and their ligands are oxidized low-density lipoprotein molecules (OxLDL). Expression of these scavenger receptors on the cell surface increases when the *OLR1* receptor gene is activated in response to pro- inflammatory or proatherogenic factors [8]. The gene products — LOX-1 molecules, are involved in the pathogenesis of arterial hypertension, diabetes mellitus, hyperlipidemia, and ischemia/reperfusion [7, 9, 10, 11]. There is evidence of LOX-1 accumulation in the lungs of patients with acute respiratory distress syndrome and in mice with pneumonia [12]. LOX-1 contributes to the control of inflammatory responses in a wide range of ways: from stimulating the activity of innate immune cells [13] to activating myeloid-derived suppressor cells (MDSC) [14,15].

It is now known that ORL1 gene translation leads to expression of a wide range of protein isoforms, the composition and quantitative representation of which depends on alternative splicing and single nucleotide polymorphisms (SNPs) [16].

Alternative splicing of ORL1 results in three variants of LOX-1 mRNA: transcript 1 (ORL1 NM 002543), transcript 2 (ORL1D4 NM 001172632), and transcript 3 (LOXIN NM 001172633) [16]. Transcript variant 1 contains all 6 exons and leads to the transcription of a full-length LOX-1 with full binding activity to OxLDL. Transcript 2 lacks exon 4, so the encoded protein is shorter [17]. In transcript variant 3, the absence of exon 5 as a result of splicing leads to formation of the LOXIN protein, which lacks two-thirds of the LOX-1 lectin-like domain, a region important for OxLDL binding. The latter isoform plays a protective role in cardiovascular diseases associated with increased LOX-1 expression [16].

Another source of quantitative and structural diversity of *OLR1* gene products is single nucleotide polymorphism. Mutant variants of the *OLR1* gene are associated with the risk of acute myocardial infarction [18], carotid artery atherosclerosis [19, 20], ischemic stroke [21, 22], atherosclerotic lesions of the femoral and popliteal arteries [23], arterial hypertension [24], and vascular complications of diabetes mellitus [11].

The most studied are the associative links between various polymorphic variants of the *OLR1* gene and the development of cardiovascular diseases [8, 9, 17, 18]. One of the transversions, c.501 G > C (rs11053646) in exon 4, leads to the amino acid substitution of lysine for asparagine at 167 (p.K167N) position. The presence of this *OLR1* rs11053646 allele was shown to alter the binding and utilization of OxLDL, which increases the risk of acute myocardial infarction, ischemic stroke, and hypertension in its carriers [25, 21, 26, 27].

The significance of *OLR1* polymorphism in lung diseases, including NPIs, has not been studied, although the pathogenetic link between NPI, inflammation and immune system cells suggests the likelihood of such a connection [28]. Nowdays, the search for molecular predictors of the course and outcome of life-threatening lung conditions remains a challenge in critical care medicine [29, 28, 30. The results of our study show the potential contribution of the *OLR1* gene single nucleotide polymorphism to clinical course of NPIs that presumably may affect variations in innate and acquired immunity cells activity/counts in post-community-acquired pneumonia patients.

Materials and Methods

Study characteristics. A prospective observational study was conducted at the Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology (FRCC ICMR). Data collection was carried out at the I. V. Davydovsky City clinical hospital from July 2022 to August 2023 in the departments of thoracic surgery, pulmonology, resuscitation and intensive care, and the department of anesthesiology and resuscitation.

The study was approved by the Ethics Committee of the FRCC ICMR (protocol No. 2/22/1 dated July 26, 2022).

Development of fistula was the primary endpoint of the study.

An increase in immune cells counts was the secondary endpoint.

Characteristics of the study population.

- Criteria for inclusion of patients in the study:

— presence of CAP or NPI (lung abscess without sequestration, lung abscess with sequestration, lung gangrene, pleural empyema without fistula/fenestration, pleural empyema with fistula/fenestration) in a patient who had had a community-acquired bacterial infection in the previous 30 days;

— age 18 years or older;

— written informed consent to participate in the study;

— patient's ability to adequately cooperate in the clinical study for an extended period of time.

• Criteria for exclusion of patients from the study:

— patients' and/or their legal representatives' refusal to continue treatment;

— establishing the diagnosis of cancer or tuberculosis.

According to our preliminary data, the mortality rate for NPI averaged around 16%; taking this into account, we calculated the sample size [28]. Using the formula for calculating the sample size $n = (t^2 \times P \times Q) / \triangle^2$, where t is the critical value of Student's t-test (at a significance level of 0.05, it is 1.96); $\triangle$ is the maximum permissible error (5%); P is the proportion of cases in which the studied feature occurs (84%); Q is the proportion of cases in which the studied feature does not occur (16%); the resulting n was 206. To obtain statistically significant differences, the calculated sample size was increased by 5% to 216 patients.

The study included 216 patients with NPIs developed after CAP within the previous 30 days. The NPI cohort included patients from two groups: NPIs as the outcome of parapneumonic effusion not complicated by fistula (NPInF, $n=127$) and NPI complicated by fistula (NPIwF, $n=89$) as the outcome of lung abscess without sequestration, lung abscess with sequestration, and lung gangrene. The NPI diagnosis was established based on CT images on admission to the hospital.

The conclusion about previous SARS-CoV-2 infection was based on documented PCR test results, regardless of the date. Treatment of COVID-19 was previously guided by «temporary methodological recommendations for the prevention, diagnosis, and treatment of COVID-19» as they were updated.

The selection of patients with NPIs for the study is presented in Fig. 1.

Assessment upon admission to the hospital (Table 1) included patients' demographic characteristics, assessment by comorbidity scales: CCI (Charlson Comorbidity Index) [31] and CIRS (Cumulative Illness Rating Scale) [32], assessments by the SOFA (Sequential Organ Failure Assessment) and APACHE II (Acute Physiology and Chronic Health Evaluation II) scales, and for presence of diabetes mellitus. The severity of pleural infection was assessed using the specialized RAPID scale (Renal, Age, fluid Purulence, Infection source, Dietary — taking into account kidney function parameters (urea), age, presence of pus in fluids, source of infection, albumin content — as a factor related to nutrition) [33]. This scale is important for stratifying the risk of adverse outcomes in patients with pleural empyema.

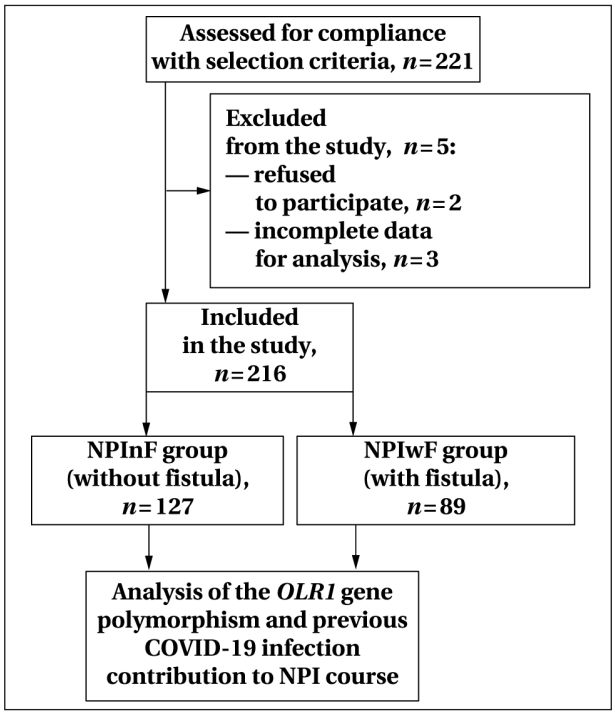

Fig. 1. Flowchart of patient selection for the study.
Note. NPI — necrotizing pulmonary infection

The incidence of empyema with fistula was higher in men than in women ($p=0.0235$; FET; OR = 2.09, 95% CI: 1.12–3.9; OR = 1.586; 95% CI: 1.047–2.4039). There were no differences based on age ($p=0.394$), presence of diabetes mellitus ($p=1$), scores on Charlson ($p=0.694$), CIRS ($p=0.292$), SOFA ($p=0.483$), APACHE II ($p=0.173$), and RAPID ($p=0.218$) scales.

In further analysis, patients with NPIs were divided into two subgroups: those who had previous COVID-19 ($n=81$) and those who had not ($n=135$).

The control group of «conditionally» healthy individuals included 155 people without HIV or viral hepatitis.

The CAP group included 101 patients. Patients' mean age, *Me* (IQR) was 66 (47–81) years, the SOFA score on admission, *Me* (IQR) was 2 (1–4), and the CIRS score, Me (IQR) was 11 (6–16). Women accounted for 49.5% of the cohort.

Laboratory assessments and instrumental examinations.

a) Clinical and laboratory parameters:

• Complete blood count:

— frequency: 1–3–5–7–last day of hospitalization;

— tubes: EDTA K3E/2.7 ml;

— device: ADVIA 2120i.

• Genetically polymorphic markers:

— frequency: 1st day of hospital stay;

— DNA for genotyping was extracted from 200 µl of whole blood using Diatom DNA Prep 200 kits, according to the instructions provided

Allele variants of *OLR1* rs11053646 were determined using a tetraprimer polymerase chain reaction followed by electrophoretic separation and identification of stained

Table 1. Demographic characteristics, morbidity and comorbidities in patients with NPIs.

Parameters	Values in cohorts				
	All patients	With fistula, NPIwF	Without fistula, NPInF	With previous COVID-19	With no history of COVID-19
Age, years, *M (IQR)*	54 (40.7–66)	54 (40–63)	56 (41–66)	52 (40–64)	56 (41–67)
Men, *n* (%)	151 (70)	70 (79)	81 (64)	57 (70)	94 (70)
Women, *n* (%)	65 (30)	19 (21)	46 (36)	24 (3)	41 (30)
CCI comorbidity index value, score, *M (IQR)*	2 (1–4)	2 (1–4)	2 (1–4)	2 (1–3)	2 (1–4)
CIRS comorbidity score, score, *M (IQR)*	10 (7–13)	10 (8–13)	10 (7–13)	10 (7–13)	10 (7–13)
DM, *n* (%)	33 (15)	14 (16)	19 (15)	8 (10)	25 (19)
SOFA score on admission, points, *M (IQR)*	2 (2–2)	2 (2–3)	2 (2–2)	2 (2–2)	2 (2–2)
APACHE II score on admission, *M (IQR)*	5 (3–8)	5 (3–8)	5 (3–7)	5 (3–8)	5 (3–8)
Assessment of pleural infection using the RAPID scale, points, *M (IQR)*	2 (1–3)	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–2)

products in a gel. Using the Primer-BLAST program (https://www.ncbi.nlm.nih.gov/tools/primer-blast/), the following primers were selected and synthesized at Eurogen LLC.

OLR1 1for 5`TACAGAGCCTGTCCGTCCA-3`

OLR1 2for 5`-GACAAGCACTTCTCTTGGCTC-3`

OLR1 2rev 5`-GGCTCATTTAACTGGGAAAAC-3`

OLR1 1rev 5`-ATGCACGTGAGAGAACTAAGG-3`

The amount of oxidized low-density lipoproteins (OxLDL) in blood plasma was measured by enzyme-linked immunosorbent assay using ELISA Oxidized Low Density Lipoprotein kits (Cloud clone Corp, PRC). The median OxLDL content in patients plasma, M(IQR) was 88 (80–95) ng/ml.

b) Instrumental examination:

- Chest CT:

— frequency: 1st day of hospital stay;

— Equipment: Siemens SOMATOM Perspective 64 computerized tomography scanner, Germany.

The diagnosis of CAP was established within the first 48 hours after admission based on CT scans, and the diagnosis of NPI was made based on CT scans at hospital admission.

Patient management protocol. Within 2 hours upon admission to the hospital, pleural cavity drainage was implemented using G. Bülau technique. After drainage was established, pleural empyema without fistula (PlEnF, NPInF) and pleural empyema with fistula (PlEwF, NPIwF) were differentiated. The presence of air discharge through the drain indicated PlEwF. In the thoracic department or ICU, patients were managed with corrective i/v fluids, antimicrobial therapy according to current antibiotic stewardship strategy, therapy for prevention of thromboembolic complications (anticoagulants + elastic compression of lower legs for VTE/DVT control), stress ulcers therapy, adequate pain relief, symptomatic therapy, and respiratory support if necessary. Laboratory tests included complete blood count, full biochemistry profile, coagulogram, ABB. Further tactics were determined based on the results of initial therapy after 48–72 hours. When indicated, video-assisted thoracoscopic surgery (VATS) was implemented to drain fluid out of the pleural cavity. VATS was performed under general anesthesia with separate intubation of the bronchi using a double-lumen tube. Single-lung ventilation was necessary for complete lung collapse to create free space, which allowed for a thorough and complete examination of the chest cavity. Effectiveness of antibiotic therapy was assessed 72 hours after its initiation.

In patients with pleural empyema and fistula with continued air leak, a decision was made to temporarily occlude the bronchi (bronchial blocker placement) in order to close the bronchopleural fistula. Subsequently, the bronchial blocker was removed and air leak was assessed.

In the absence of purulent discharge and air leak, the degree of lung tissue expansion confirming the absence of pneumothorax, was assessed after clamping the drainage tube using chest X-ray. When clinical and laboratory parameters and lung tissue aeration normalized, the drain was removed and the patient was discharged from the clinic.

Statistical analysis of the obtained results. The Shapiro-Wilk test was used to assess if quantitative dataset follows a normal distribution. Variables with normal distribution were described using arithmetic means (*M*) and standard deviations (*SD*), as well as 95% confidence intervals (95% CI). In the case of abnormal distribution of quantitative data, they were described using the median (*Me*) and lower and upper quartiles (*Q1–Q3*). Variables with normal distribution were compared in groups using the Student's *t*-test, provided that the variances were equal. If the distribution differed from normal, the Mann–Whitney *U* test was used.

Categorical data were described using absolute values, which were compared using four-field contingency tables and the χ^2 test with Yates' correction for continuity of the sample and Fisher's exact test (FET). As a quantitative measure of the effect when comparing relative indicators, odds ratios (*OR*) and relative risk (*RR*) with 95% confidence intervals (*CI*) were used. Differences were considered significant at $p < 0.05$. The Bonferroni correction was used for multiple comparisons.

SPSS Statistics software (IBM SPSS Statistics for Windows, Version 27.0.1, IBM Corp., Armonk, NY) was used for statistical data processing. Microsoft Office Excel 2019 software platform was used to create graphs, scatter plots, and tables. OR was calculated using MedCalc software, version 11.6.

Results

A study of the genetic diversity in groups of patients with CAP and NPIs, as well as conditionally healthy individuals, based on the distribution of single nucleotide polymorphic variants rs11053646

of the *OLR1* gene revealed the following genotype frequencies: *OLR1* CC — 81%, *OLR1* CG — 17.6%, *OLR1* GG — 1.4% $n=216$, which was consistent with Hardy-Weinberg law ($\chi^2=0.319$, $p=0.572$) and did not differ statistically significantly from the distribution in the group of patients with CAP (CC — 88.1%, CG — 11.9%, GG — 0%, $\chi^2=0.403$, $p=0.526$, $n=101$, and the group of conditionally healthy individuals (CC — 87.8%, CG — 10.9%, GG — 1.3%, $\chi=2.7$, $p=0.10$, $n=155$ (Fig. 2).

In patients with NPIs and the minor G allele of *OLR1* rs11053646 polymorphism (genotypes CG, GG), encoding the 167N *OLR1* variant, the course of the disease was less frequently complicated by fistula ($p=0.0015$; FET; OR=3.55, 95% CI: 0.12–0.64; OR=2.37, 95% CI: 1.24–4.50; $n=216$; Fig. 3, *a*). For patients who had recovered from COVID-19, this association remained ($p=0.0058$; FET; OR=7.27, 95% CI: 1.54–34.3; RR=4.28, 95% CI: 1.31–16.23; $n=81$; Fig. 3, *b*). Among patients who had not had COVID-19, the pattern was not significant ($p=0.1065$; FET; $n=135$; Fig. 3, *c*). Thus, the minor G allele of *OLR1* rs11053646 protects against more severe NPI course in patients who have had COVID-19.

The frequency of minor *OLR1* CG and GG genotypes was also higher in patients with NPIs without fistula compared to the cohort of patients with community-acquired pneumonia ($p=0.0114$, FET, OR=2.6, 95% CI: 1.3–5.4).

We have previously shown that decreased lymphocyte counts and increased neutrophil counts and the neutrophil-to-lymphocyte ratio (NLR) values are significantly associated with NPIs outcome [28]. It was interesting to find out whether the two predictors — the *OLR1* genotype and immune cell counts in the circulation — were interrelated in patients with NPIs. Taking into account the potential influence of previous COVID-19 on manifestation of this association, for further analysis the participants were divided into two groups based on presence or absence of previous COVID-19 infection (COVID-19 confirmed by PCR results). We compared neutrophil, lymphocyte, and monocyte counts in patients with NPIs with and without fistulas and different *OLR1* rs11053646 genotypes on the 1st, 3rd, 5th, 7th, and last days of hospital stay in these two groups.

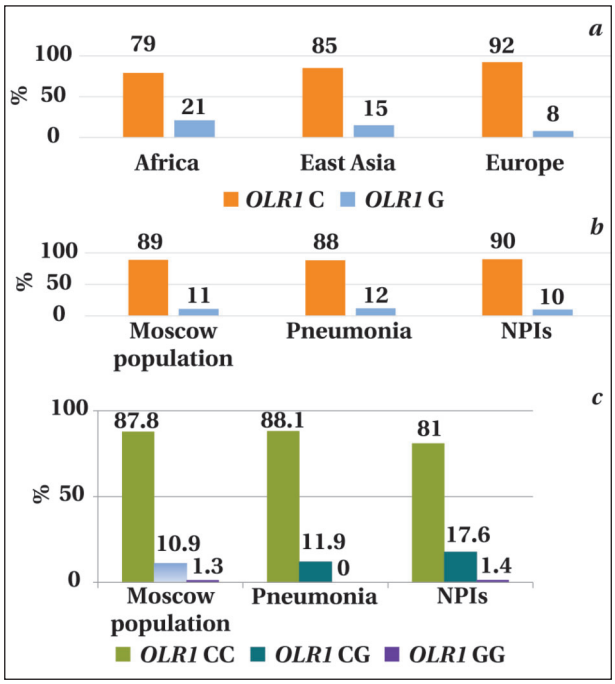

Fig. 2. Distribution of *OLR1* rs11053646 allele and genotype frequencies.
Note. Allele frequencies: *a* — literature data; *b* — conditionally healthy individuals (Moscow population) and patients with CAP and NPIs. Genotype frequencies: *c* — conditionally healthy individuals (Moscow population) and patients with CAP and NPIs.

Neutrophils. For subgroups of patients with NPIs with and without fistulas and different *OLR1* rs11053646 genotypes, no differences in circulating

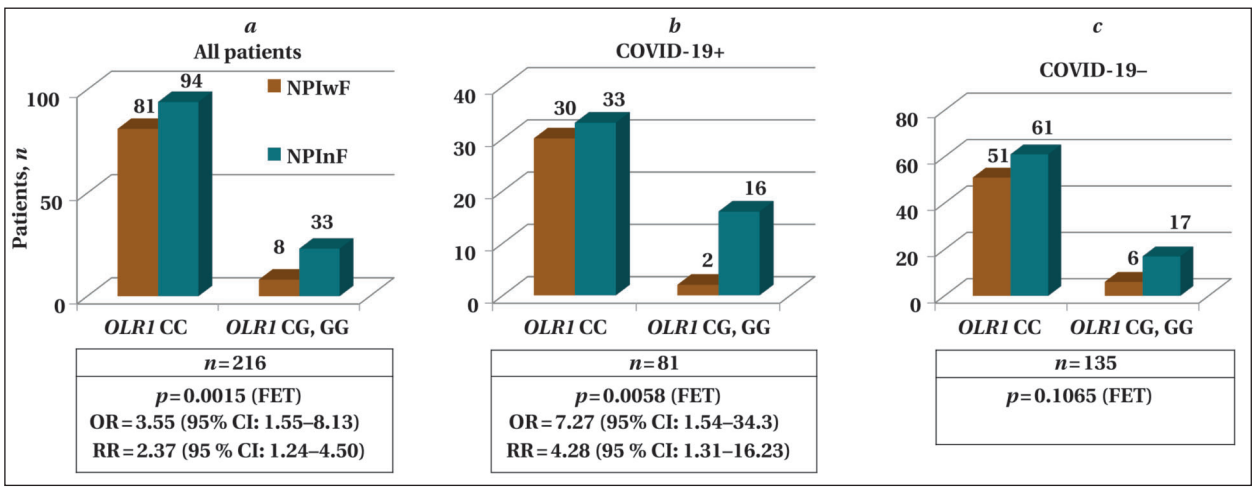

Fig 3. Development of fistula depending on the *OLR1* rs11053646 allele.
Note. *a* — incidence of fistula in all patients; *b* — incidence of fistula in patients with history of COVID-19; *c* — incidence of fistula in patients who did not have COVID-19.

neutrophil counts were found on the 1st, 3rd, 5th, 7th, and last days, regardless of whether they had had COVID-19 (Table 2).

Lymphocytes. No differences in lymphocyte counts were found between subgroups of patients with NPIs with fistula and different *OLR1* rs11053646 genotypes on the 1st, 7th, and last days of hospital stay. Differences in this group were found only on the 3rd and 5th days of hospital stay: patients with minor *OLR1* CG and GG genotypes had higher counts of circulating lymphocytes (Table 3).

In cases complicated with fistula and no previous COVID-19 infection, a difference in counts of circulating lymphocytes was found only on the 5th day. Thus, for patients who had not had COVID-19, the lymphocyte counts in carriers of the minor *OLR1* G allele was higher than in patients with the major *OLR1* CC genotype. In post-COVID-19 patients developing fistula the calculation was skipped given the small number of the minor *OLR1* G allele carriers. When using the Bonferroni correction (assessment based on neutrophil, lymphocyte, and monocyte counts), the significance of the differences was not preserved.

For subgroups of patients with NPI without fistula and different *OLR1* rs11053646 genotypes, lymphocyte counts did not differ on any day of hospital stay, regardless previous COVID-19 infection status (Table 3).

Monocytes. The monocyte counts in the subgroup of NPInF patients who had had COVID-19 and various *OLR1* rs11053646 genotypes, were the same on the 1st, 3rd, 7th, and last days of hospital stay. On the 5th day of hospital stay, patients with minor *OLR1* CG and GG genotypes had significantly higher monocyte counts.

In the subgroup of patients developing fistula and no history of COVID-19 infection, no difference in monocyte counts was found on the 3rd, 7th, and last days of hospital stay. On days 1 and 5, the difference in monocyte counts was linked with different genotypes: in patients with minor *OLR1* CG and GG genotypes, monocyte counts were significantly higher than in carriers of the CC genotype.

Next, we compared the monocyte counts in the subgroup of post-COVID-19 NPInF patients with different *OLR1* rs11053646 genotypes. There was no difference in monocyte counts on the 1st, 5th, 7th, and last days of hospital stay. However, on the 3rd day, the monocyte counts were significantly lower in carriers of the minor *OLR1* G allele compared to the major *OLR1* CC carriers. When using the Bonferroni correction (assessment based on neutrophil, lymphocyte, and monocyte counts), the significance remained for the 1st ($p=0.03$) and 5th days ($p=0.027$) of hospital stay in patients with NPIwF and no previous COVID-19.

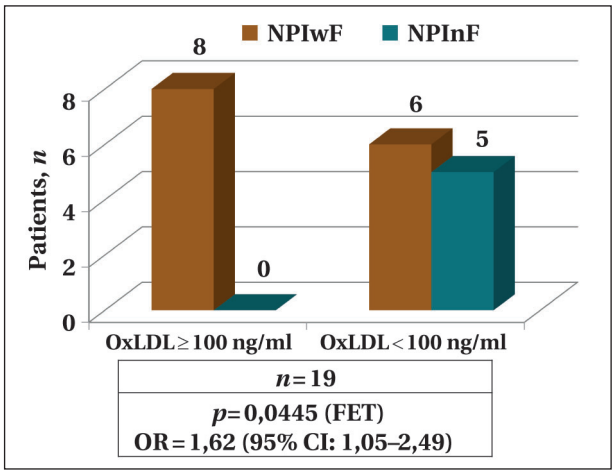

Fig. 4. OxLDL content in the plasma of patients with NPIs depending on the presence of fistula.

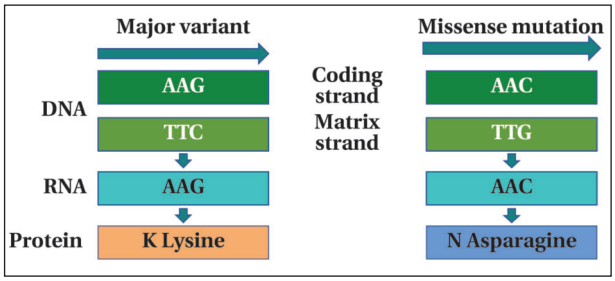

Fig. 5. Single nucleotide substitution *OLR1* rs11053646 (author's drawing).

In patients who had not had COVID-19, the monocyte count did not differ (Table 4).

Keeping in mind the *OLR1* gene potential role in inducing complications of pneumonia, OxLDL levels were measured in a limited number of plasma samples ($n=19$) from COVID-19-expirienced patients. Relatively high OxLDL levels (over 100 ng/mL) were associated with development of fistula ($p=0.0445$; FET; OR = Infinity; RR = 1.62, 95% CI = 1.05–2.49; $n=19$, Fig. 4).

Discussion

We examined genetic markers that predict the NPI course. We showed that the minor allele *OLR1* G (rs11053646) «protects» against development of fistula in patients with NPIs. Since the distribution of *OLR1* genotype frequencies in the cohort did not differ from that in healthy population and among patients with community-acquired pneumonia, the *OLR1* G rs11053646 allele is involved in controlling the course of NPIs, namely preventing development of pneumonia complications such as fistula.

The contribution of the *OLR1* rs11053646 single nucleotide substitution was also investigated, in which the c.501 G > C transversion in exon 4 of the coding strand of the gene leads to the replacement of the amino acid lysine with asparagine at position 167 (p.K167N, Fig. 5) of the LOX-1 receptor. A few

Table 2. Counts of neutrophils in the circulation in patients with NPIs with and without fistulas (×10⁹/L).

NPIs	Genotype *OLR1*	Post-COVID-19	Days			
			1		3	
NPIwF; *M* (IQR)	CC	+	9.2 (6.37–13.6); 89	—	7.8 (5.75–11.1); 89	—
		—		10.5 (6.87–16.05); 57		8.4(5.85–11.1); 57
	CG/GG	+	8.45 (5.8–20.05); 89	—	9.65 (5.85–21.1); 89	—
		—		7.3 (5.2–8.7; 57		6.2 (5.8–12.8); 57
NPInF; *M* (IQR)	CC	+	8.3 (6–13); 127	8.6 (5.82–12.77); 49	7.3 (4.8–10.4); 127	7 (4.3–9.77); 49
		—		8.2 (6.07–13.3); 78		7.5 (5–10.67); 78
	CG/GG	+	9 (6.05–10.3); 127	6.6 (4.85–9.55); 49	7 (4.87–9.12); 127	6.7 (4.35–9.15); 49
		—		9.3 (6.87–12.5); 78		7.2 (5–8.95); 78
			$p_1 = 0.920$		$p_1 = 0.491$	
			$p_2 = 0.411$		$p_2 = 0.638$	
			$p_3 = $ ND		$p_3 = $ ND	
			$p_4 = 0.185$		$p_4 = 0.649$	
			$p_5 = 0.193$		$p_5 = 0.779$	
			$p_6 = 0.837$		$p_6 = 0.799$	

Table 3. Lymphocyte count in patients with NPIs with and without fistula (×10⁹/L).

NPIs	Genotype *OLR1*	Post-COVID-19	Days			
			1		3	
NPIwF; *M* (IQR)	CC	+	1.7 (1.07–2.22); 89	—	1.5 (1–2); 89	—
		—		1.5 (1–2.15); 57		1.4 (0.9–1.97); 57
	CG/GG	+	2.4 (1.25–2.9); 89	—	2.35 (1.85–2.65); 89	—
		—		2.4 (1.6–2.7); 57		2.2 (1.7–2.6); 57
NPInF; *M* (IQR)	CC	+	1.9 (1.2–2.3); 127	1.9 (1.1–2.52); 49	1.7 (1.2–2); 127	1.5 (1.2–2.05); 49
		—		1.9 (1.3–2.3); 78		1.7 (1.17–2); 78
	CG/GG	+	1.8 (1.4–2.22); 127	2.25 (1.45–2.75); 49	1.6 (1.175–2.3); 127	1.75 (1.35–2.9); 49
		—		1.6 (1.37–2); 78		1.4 (1.1–1.8); 78
			$p_1 = 0.239$		$p_1 = 0.031$	
			$p_2 = 0.991$		$p_2 = 0.971$	
			$p_3 = $ ND		$p_3 = $ ND	
			$p_4 = 0.164$		$p_4 = 0.116$	
			$p_5 = 0.169$		$p_5 = 0.208$	
			$p_6 = 0.123$		$p_6 = 0.238$	

Table 4. Monocyte counts in patients with NPIs with and without fistula (×10⁹/L).

NPIs	Genotype *OLR1*	Post-COVID-19	Days			
			1		3	
NPIwF; *M* (IQR)	CC	+	0.8 (0.6–1.1); 89	—	0.6 (0.4–0.9); 89	—
		—		0.8 (0.5–1.17); 57		0.6 (0.4–0.97); 57
	CG/GG	+	1.3 (0.65–1.45); 89	—	0.85 (0.4–1); 89	—
		—		1.3 (1.3–1.6); 57		0.95 (0.8–1); 57
NPInF; *M* (IQR)	CC	+	0.9 (0.7–1.2); 127	0.9 (0.7–1.2); 49	0.7 (0.5–1); 127	0.7 (0.5–0.92); 49
		—		0.9 (0.6–1.3); 78		0.7 (0.5–1); 78
	CG/GG	+	0.8 (0.6–1.02); 127	0.8 (0.55–0.95); 49	0.6 (0.5–0.7); 127	0.55 (0.45–0.7); 49
		—		0.9 (0.67–1.1); 78		0.6 (0.5–0.92); 78
			$p_1 = 0.194$		$p_1 = 0.469$	
			$p_2 = 0.195$		$p_2 = 0.043$	
			$p_3 = $ ND		$p_3 = $ ND	
			$p_4 = 0.010$		$p_4 = 0.172$	
			$p_5 = 0.075$		$p_5 = 0.036$	
			$p_6 = 0.823$		$p_6 = 0.380$	

Note. Tables 2–4 are located on pages 20–21 in a two-page format for easier following the dynamics.

studies indicate an increased risk of atherosclerosis, AMI, ischemic stroke, and hypertension for carriers of minor *OLR1* (rs11053646) genotypes [22, 26, 27].

As can be seen in Fig. 2, there is a tendency for the minor allele G *OLR1* rs11053646 frequency to increase in the African population compared to the European population: in the European population, carriers of the major genotype account for 92%, while in the African population, they account for 78% [34]. The incidence of infectious diseases in Africa is higher [35]. It can be assumed that higher prevalence of the minor *OLR1* G allele in the African population is adaptive in nature due to higher rate of infectious diseases. Perhaps the presence of the minor *OLR1* mutation and, accordingly, the carriage of the CG and GG genotypes, provided better protection against infections due to more effective immune mechanisms that prevent the development of life-threatening purulent complications and other infections that can be fatal in circumstances of medications scarcity or untimely treatment. These may be the selection factors contributing to the accumulation of the «protective» minor allele in the population. The price paid for this evolutionary advantage could be an increased risk of cardiovascular disease, which is characteristic of these geno-

Days					
5		7		The last day	
8 (5.1–11.17); 85	—	7 (4.65–11.72); 85	—	6.1 (4.7–7.9); 85	—
	8.5 (5.02–11.82); 54		7.4 (4.55–12.62); 54		6.4 (4.7–8.425); 54
7.8 (4.9–11.5); 85	—	6.7 (3.1–10.5); 85	—	7.55 (4.8–16.7); 85	—
	7.4 (4.8–13.8); 54		7.3 (3.07–13.85); 54		5.6 (4.67–21.4); 54
6.6 (4.47–9.7); 126	7.45 (4.1–11.5); 48	5.8 (4.25–7); 126	7 (4.05–8.2); 48	5.5 (3.75–6.82); 126	5.3 (3.7–6.45); 48
	6.6 (4.72–9.60); 78		5.5 (4.25–7); 78		5.6 (3.75–7); 78
6 (4.17–8.22); 126	5.45 (4.3–8.7); 48	5 (3.9–6.32); 126	5.05 (3.75–6.05); 48	4.5 (3.2–5.9); 126	5.1 (3.35–5.95); 48
	6 (4.07–8.22); 78		5 (3.9–7); 78		4 (3.175–5.9); 78
$p_1 = 0.884$		$p_1 = 0.738$		$p_1 = 0.372$	
$p_2 = 0.457$		$p_2 = 0.208$		$p_2 = 0.074$	
$p_3 = ND$		$p_3 = ND$		$p_3 = ND$	
$p_4 = 0.831$		$p_4 = 0.654$		$p_4 = 0.676$	
$p_5 = 0.432$		$p_5 = 0.177$		$p_5 = 0.634$	
$p_6 = 0.611$		$p_6 = 0.521$		$p_6 = 0.055$	

Days					
5		7		The last day	
1.4 (1–1.87); 85	—	1.4 (1–1.87); 85	—	1.4 (1.02–2.1); 85	—
	1.3 (0.97–1.8); 54		1.2 (0.8–1.72); 54		1.4 (1.07–2); 54
1.95 (1.6–3.2); 85	—	1.4 (1.1–2.0); 85	—	1.45 (1.2–1.8); 85	—
	2 (1.57–3.35); 54		1.5 (1.07–2.5); 54		1.5 (1.3–2.5); 54
1.5 (1.2–2); 126	1.4 (0.95–1.9); 48	1.5 (1.07–2); 126	1.5 (1–2); 48	1.7 (1.17–2.3); 126	1.5 (1.2–1.9); 48
	1.6 (1.27–2.02); 78		1.7 (1.27–2); 78		1.8 (1.1–2.4); 78
1.6 (1.17–2.2); 126	1.6 (1.15–2.45); 48	1.8 (1.37–2.02); 126	1.8 (1.5–2.25); 48	2 (1.3–2.32); 126	2 (1.2–2.55); 48
	1.6 (1.17–2); 78		1.6 (1.2–2.02); 78		2 (1.37–2.22); 78
$p_1 = 0.027$		$p_1 = 0.520$		$p_1 = 0.771$	
$p_2 = 0.472$		$p_2 = 0.262$		$p_2 = 0.376$	
$p_3 = ND$		$p_3 = ND$		$p_3 = ND$	
$p_4 = 0.019$		$p_4 = 0.270$		$p_4 = 0.456$	
$p_5 = 0.135$		$p_5 = 0.084$		$p_5 = 0.114$	
$p_6 = 0.861$		$p_6 = 0.947$		$p_6 = 0.973$	

Days					
5		7		The last day	
0.5 (0.4–0.8); 85	—	0.5 (0.4–0.7); 85	—	0.6 (0.4–0.7); 85	—
	0.5 (0.4–0.62); 54		0.5 (0.4–0.7); 54		0.6 (0.37–0.7); 54
0.95 (0.6–1.1); 85	—	0.5 (0.5–0.8); 85	—	0.8 (0.3–0.9); 85	—
	1 (0.82–1.1); 54		0.5 (0.5–0.85); 54		0.8 (0.27–0.97); 54
0.6 (0.4–0.8); 126	0.6 (0.4–0.85); 48	0.6 (0.5–0.8); 126	0.6 (0.4–0.8); 48	0.6 (0.475–0.7); 126	0.6 (0.4–0.7); 48
	0.6 (0.4–0.7); 78		0.6 (0.5–0.72); 78		0.6 (0.5–0.8); 78
0.6 (0.37–0.7); 126	0.6 (0.4–0.7); 48	0.5 (0.4–0.62); 126	0.55 (0.45–0.6); 48	0.5 (0.3–0.6); 126	0.5 (0.35–0.55); 48
	0.6 (0.37–0.72); 78		0.5 (0.3–0.7); 78		0.5 (0.3–0.6); 78
$p_1 = 0.010$		$p_1 = 0.668$		$p_1 = 0.332$	
$p_2 = 0.775$		$p_2 = 0.090$		$p_2 = 0.030$	
$p_3 = ND$		$p_3 = ND$		$p_3 = ND$	
$p_4 = 0.009$		$p_4 = 0.502$		$p_4 = 0.483$	
$p_5 = 0.599$		$p_5 = 0.743$		$p_5 = 0.238$	
$p_6 = 0.908$		$p_6 = 0.068$		$p_6 = 0089$	

types. Available data confirm that in human macrophages, the presence of the minor G mutation, which promotes the replacement of Lys167Asn, led to a decrease in the binding of the LOX-1 receptor ligand OxLDL and inhibition of the ERK1/2 kinases activated by this ligand [36] — the final molecules of the pro-inflammatory RAS-ERK1/2 signaling pathway in the cytoplasm, which activate transcription factors of genes (including NFkB) in the nucleus that control inflammatory processes. Thus, the pathogenesis of a less severe purulent complication of pneumonia (without fistula formation) associated with a minor variant of *OLR1* with Lys167Asn replacement may be associated with a predisposition to development of a less intense inflammatory reaction in the lungs, which does not result in structural and morphological alterations and a prolonged purulent process with an increased likelihood of a life-threatening condition — sepsis, including septic shock.

It is worth noting that myeloid-derived suppressor cells (MDSCs), which play a key role in the course and outcome of infectious complications of critical conditions, including sepsis, may contribute to NPI pathogenesis depending on the *OLR1* genotype [27, 14, 15, 37]. MDSC generation occurs as a

result of persistent stimulation of myeloid cell precursors in the bone marrow due to prolonged or chronic infection, chronic inflammation, or cancer. Relatively weak but constant signals induce persistent myelopoesis with the release of immature myeloid cells into the bloodstream, followed by their maturation into MDSCs [38, 39]. The main functional characteristic of such cells is their powerful ability to suppress various types of immune responses through different mechanisms [14, 40–42].

There are at least two subpopulations: granulocytic or polymorphonuclear MDSCs (G-MDSCs or PMN-MDSCs, respectively) and monocytic MDSCs (M-MDSCs). Although MDSCs are involved in suppressing the activity of various immune system cells, the main targets of MDSCs are T cells. M-MDSCs and PMN-MDSCs use different mechanisms of immunosuppression. M-MDSC suppress T cell responses in both antigen-specific and non-specific ways, using mechanisms related to the production of NO and cytokines. PMN-MDSCs are capable of suppressing the functional activity of interacting immune system cells predominantly in an antigen-specific manner, causing T cell tolerance due to the modification of their cell receptors when interacting with MDSCs that produce peroxynitrite radicals, as well as arginase and prostaglandins [43, 44].

It has been established that the LOX-1 receptor plays a role in the generation of PMN-MDSC [45], and ERK1/2-dependent signaling mechanisms ensure the accumulation of this subpopulation in the body [46]. A potential association with NPI pathogenesis is supported by evidence of MDSC accumulation in pleural effusion preceding the development of pleural empyema [47]. It is possible that the expected reduced activity of MDSC in carriers of the minor variant of *OLR1* will lead to less immunosuppression and greater effectiveness of the innate and adaptive immune systems, which will manifest in conditions of high probability of developing healthcare-associated infections (HAIs). The role of PMN-MDSC in the development of HAI and the contribution of MDSC to suppression of T-cell immunity against the life-threatening HAI pathogen, hypervirulent *K.pneumoniae*, was demonstrated in the works of F. Uhel et al. [48] and Q. Xu et al. [49], respectively.

It should be noted that in patients with the major CC genotype, the lymphocyte count was lower than in carriers of the minor allele, although the statistical significance was marginal and was detected only on the 5th day of hospital stay. It can be assumed that carriers of the major CC genotype might have reduced ability to develop cellular and humoral adaptive immune responses, including post-COVID-19 cases [50, 51]. These results suggest that patients who carry the minor G *OLR1* mutation have a greater potential for developing effective anti-infective immunity due to higher lymphocyte counts in the blood and reduced risk of developing persistent or chronic inflammatory reactions, predisposing to a more severe course of infection. It is possible that it is precisely the more intense ERK-dependent signaling mechanisms initiated in carriers of the major variant of the *OLR1*-CC gene by the interaction of circulating OxLDL with the LOX-1 receptor that determine the high risk of fistula development.

It's worth noting that the association of the major CC variant with development of fistula in pleural empyema was significant only in the subgroup of COVID-19-experienced patients. It is possible that the increased risk of developing fistula after COVID-19 is associated with both the increased content of the OxLDL ligand and the presence of allele variant of the *OLR1* gene, which provides more frequent ligand-receptor interaction, combined with impaired lung and immune system function as a consequence of COVID-19.

A limited sample showed that increased Ox-LDL content is associated with the development of fistula. The use of PCSK9 inhibitors in patients with NPIs may have potential.

Despite the small size of the group and the marginal statistical significance, the results revealed a tendency toward an association between high plasma OxLDL levels and the actual development of fistulas. This warrants the continuation of the studies determining the value of plasma LOX-1 ligand levels as predictors for patients with NPIs.

It is possible that complementary markers — the *OLR1* genetic variant and high concentration of the gene product ligand LOX-1 receptor — in combination may become the most informative predictors of the risk of adverse pleural empyema progression and be used to select optimal personalized treatment methods.

A limitation of our study is the absence of a registered study protocol and a small number of patients.

Conclusion

Carriage of the C allele of the *OLR1* rs11053646 gene in a homozygous form (CC genotype) is an unfavorable marker of NPI course for patients who have had COVID-19. The presence of the minor G allele of *OLR1* rs11053646 (CG, GG genotypes), on the contrary, protects against the development of fistula. An OxLDL content of $\geqslant$100 ng/ml has the potential to be a predictive marker of a more severe NPI course with development of fistula.

Note. Based on the results of accumulated data, a Russian Federation patent was obtained for «Method for predicting fistula development in necrotizing pulmonary infections» No. 2 845 356 C1, reg. 18.08.2025, priority 19.12.2024 (authors: Pisarev V. M., Chumachenko A. G., Fetlam D. L., Grechko A. V.)

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Argon-Oxygen Mixture as a Multisystem Therapy after Circulatory Arrest: an Experimental Study

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Summary

Cardiac arrest remains one of the leading causes of death worldwide. Even with successful resuscitation, patient outcomes are often poor due to post-resuscitation syndrome, which includes cerebral hypoxia, myocardial dysfunction, microcirculatory disorders, coagulation abnormalities, and systemic inflammation. Argon, an inert noble gas, has neuroprotective and cardioprotective properties, making it a promising candidate for early post-resuscitation therapy.

The aim of the study was to evaluate the organoprotective properties of an argon-oxygen mixture when inhaled in the early post-resuscitation period for 2 hours after asphyxial circulatory arrest in rats.

Materials and methods. A prospective randomized controlled experimental study was conducted on male Wistar rats ($n=43$) using an asphyxial circulatory arrest model. The animals were divided into three groups: sham-operated (SO, $n=12$), circulatory arrest with resuscitation (CA, $n=13$), and circulatory arrest with resuscitation and two-hour inhalation of a 70%/30% argon-oxygen mixture in the post-resuscitation period (CA+iAr, $n=18$). Hemodynamics, microcirculation, blood gas composition, coagulation (low-frequency piezothromboelastography), neurological status, and biomarkers of organ damage were evaluated. Beclin-1 and caspase-3 expression was analyzed immunohistochemically.

Results. Argon inhalation did not have a significant effect on systemic hemodynamics, but it was accompanied by improved tissue oxygenation and metabolism: a decrease in blood lactate ($p=0.043$), an increase in the p/F oxygenation index ($p=0.001$), and stabilization of microcirculation variability (Kv, σ). Statistically significantly increased expression of the Beclin-1 protein in the lungs, myocardium, and hippocampus reflected activation of autophagy. In the CA+iAr group, there was an improvement in neurological status compared to CA ($p=0.02$), a decrease in serum neuron-specific enolase ($p=0.011$), and a decrease in the number of caspase-3-positive cells ($p=0.011$), indicating a reduction in apoptosis and damage to the nervous tissue. Argon had a moderate anticoagulant and antiplatelet effect (coagulation drive intensity — CDI, and maximum clot firmness-MCF reduction), while maintaining normal processes of clot retraction and lysis. The electrophysiological parameters of the heart (QRS, QTc) varied within the physiological range, indicating the absence of pro-arrhythmic effects in argon.

Conclusion. Early inhalation of argon-oxygen mixture after circulatory arrest has a multisystem protective effect: improves oxygenation and microcirculation, promotes activation of autophagy mechanisms in vital organs, reduces the severity of neuronal damage, and modulates blood clotting in some measure. Argon can be considered a promising therapeutic agent for post-resuscitation syndrome. Further clarification is needed to assess argon's molecular mechanisms of action and long-term outcomes after its use.

Keywords: argon-oxygen mixture; circulatory arrest; post-resuscitation syndrome; neuroprotection; cardioprotection; autophagy; Beclin-1; microcirculation; coagulation; apoptosis; neuron-specific enolase

Conflict of interest. The authors declare no conflict of interest.

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Introduction

Cardiovascular arrest remains one of the leading causes of death worldwide, despite significant advances in cardiopulmonary resuscitation (CPR) and intensive care [1–3]. Even with successful resuscitation and return of spontaneous circulation (ROSC), the prognosis for such patients often remains extremely poor due to severe post-resuscitation syndrome (PRS). Post-cardiac arrest syndrome (PCAS) is a multiorgan pathology that includes cerebral hypoxia, myocardial dysfunction, systemic inflammation, and reperfusion injury. All these components together contribute to high mortality in the first 24 hours and the development of adverse neurological outcomes in survivors. In view of this, the search for effective multisystem therapeutic strategies capable of influencing the main constituents in post-resuscitation damage becomes particularly relevant [4–9].

In recent years, there has been growing interest in the use of inert gases, particularly xenon and argon, as potential organoprotectors. Xenon, which has demonstrated a noticeable neuroprotective effect in a number of preclinical and clinical studies, is limited in its use due to its high cost and handling difficulties [10–13]. Unlike xenon, argon is readily available, more stable, and has a favorable safety profile. In addition, argon exhibits a wide range of biological effects, including anti-apoptotic, antioxidant, and anti-inflammatory, making it a promising candidate for comprehensive treatment of systemic ischemic damage [14–20].

Experimental studies on various models of ischemic and traumatic damage to the central nervous system have demonstrated that inhalation of argon reduces the volume of cerebral damage, reduces the activation of microglia and astrocytes, and modulates the expression of pro-inflammatory cytokines [17, 18, 20]. However, the effects of argon on other organs and systems, especially in the context of global ischemia, such as circulatory arrest, remain poorly understood. There are some publications indicating presumable cardioprotection and stabilization of hemodynamics when argon is used, but there is a lack of systematic data on its multisystem effects after circulatory arrest [21–26].

The model of asphyxial circulatory arrest in rats provides a reliable and reproducible platform for assessing both neurological and somatic sequelae of post-resuscitation injury. It allows for the study of the subtle mechanisms of reperfusion syndrome, coagulation disorders, systemic inflammation, and respiratory failure under controlled experimental conditions [27]. The use of this model to evaluate the action of argon provides an opportunity for an objective assessment of its organoprotective effects in conditions closest to clinical resuscitation practice.

It is important to emphasize that modern resuscitation medicine requires not only protocols for successful CPR, but also therapeutic interventions capable of improving the survival and quality of life of surviving patients. Given the high mortality rate within the first 24 hours after ROSC, early intervention in the post-resuscitation period is of particular importance. In this regard, argon, which has high bioavailability and can be rapidly administered by inhalation, appears to be a very convenient and promising agent for use immediately after return of spontaneous circulation.

Thus, based on existing data on the potential organoprotective effects of argon, as well as the limited availability of clinically applicable multisystem therapies in the early post-resuscitation period, there is a need for more in-depth research into this approach. The availability of preclinical data on the neuroprotective and cardioprotective effects of argon requires verification in the context of complex post-resuscitation syndrome, which includes damage to the lungs, heart, and hemostasis systems.

Objective: to evaluate the organoprotective properties of inhaled argon-oxygen mixture in the early post-resuscitation period within 2 hours after asphyxial cardiac arrest in rats.

Materials and Methods

Study characteristics. A prospective randomized controlled experimental study was conducted on laboratory animals in vivo. The study was conducted in accordance with accepted national and international bioethical standards [28]. The study protocol was approved by the local Ethics Committee of the Federal Scientific and Clinical Center for Intensive Care Medicine and Rehabilitology of the Ministry of Education and Science of Russia (1/23/4, 05.04.2023).

Study subject. Male Wistar rats, $n=43$. Weight: 200–250 g. The animals were kept in standard vivarium conditions, in social groups, with unlimited access to filtered tap water and complete feed, under artificial lighting in a 12/12 hour day/night cycle.

Group I ($n=12$) — Sham-operated animals (SO);

Group II ($n=13$) — Asphyxial cardiac arrest with resuscitation (CA).

Group III ($n=18$) — Asphyxial cardiac arrest with resuscitation and argon inhalation in the post-resuscitation period (CA+iAr).

Experimental procedures

Anesthesia. Animals were given combined anesthesia: tiletamine/zolazepam (Zoletil 100, Virbac, France) 20 mg/kg + xylazine («Xylanit», NITA-PHARM LLC, Russia) 5 mg/kg intraperitoneally. If the depth of anesthesia decreased (response to pain stimulus), an additional injection of Zoletil 100 10 mg/kg intraperitoneally was administered.

Catheterization of major vessels. For invasive measurement of blood pressure (BP) and arterial blood sam-

pling, the left carotid artery was catheterized with a PE-50 polyethylene catheter (OD 0.95 mm, ID 0.58 mm, SciCat, Russia). For the purpose of intravenous administration of pharmaceuticals during resuscitation measures, infusion therapy, and maintenance therapy in the post-resuscitation period, the right jugular vein was catheterized. Catheter heparinization regimen: administration of 0.2 ml of unfractionated heparin solution (5 IU/ml) after placement and subsequently 0.1–0.2 ml as needed.

Tracheal cannulation. The anesthetized animal was fixed in a supine position on a surgical platform. Tracheal cannulation was performed by a surgeon under visual control of the trachea through an incision in the skin and soft tissues on the anterior surface of the neck (during vascular catheterization). Under visual control, tracheal cannulation was performed with a 16G venous catheter. The tube was fixed to the animal's cheek with a surgical suture. The animal was connected to a ventilator. Rocuronium bromide was administered intravenously at a dose of 1.4 mg/kg body weight.

Preparatory measures. After tracheal cannulation and administration of a muscle relaxant, mechanical ventilation of the lungs was initiated in CMV/VC mode (FiO_2 0.21, f 60/min, I:E 1:2, Vt according to the nomogram for rats). The rat was fixed in a supine position on a heated platform of the MouseMonitor S monitor (INDUS Instruments, USA). Central body temperature was measured and monitored using a rectal thermometer. Target temperature values: 36.0–37.0°C. To prevent heat loss, the animal was covered with insulating material. The stabilization period before the start of measurements was 15 minutes.

Blood pressure measurement. An arterial catheter was connected to a Deltran DPT-100 transducer (Utah Medical Products, USA) using a tee-joint and infusion line. The analog pressure signal from the transducer and the BP-100 device was transmitted to a PowerLab16/35 device (ADInstruments, Australia) connected to a PC. The digitized BP signal was stored in the PC hard drive memory and analyzed using LabChart Pro 8 software (ADInstruments, Australia). Based on the BP curve, the mean arterial pressure (MAP) was calculated for the measurement period (5 minutes).

Electrocardiogram (ECG) recording. The analog ECG signal from the surface electrodes of the MouseMonitor S platform (INDUS Instruments, USA) was transmitted to the PowerLab16/35 device (ADInstruments, Australia) connected to a PC. The digitized ECG signal in three standard leads (I, II, III) was stored in the PC hard drive memory and analyzed using LabChart Pro 8 software. Based on the ECG data, the average heart rate (HR) was calculated for the measurement period (5 minutes).

Registration of local skin blood flow. Microcirculation in rat skin was assessed non-invasively using laser Doppler flowmetry (LDF). The rat's tail was wiped with a damp gauze pad to clean the skin surface. The optical probe of the LAZMA MC-3 device (LLC NPP «LAZMA», Russia) was placed perpendicularly at the border between the middle and proximal thirds of the animal's tail (on the ventral side). The duration of LDF registration was 5 minutes. The following parameters were analyzed: average perfusion value (M, p. u.); mean square deviation of blood flow amplitude (σ, p. u.) – a measure of individual temporal variability of perfusion; perfusion variation coefficient (Kv=σ / M, %). Based on the measurements, cutaneous vascular conductance (CVC=M / MAP, p. u. / mm Hg) was also calculated.

Measurement of gas composition and acid-base balance (ABB) of arterial blood. An arterial blood sample (0.2 ml) was taken from an arterial catheter into a heparinized insulin syringe (1.0 ml). Analysis of arterial blood gases and ABB (pH, pCO_2, pO_2, BE, HCO_3^-, SaO_2, lactate) was performed using CG4+ reagent cartridges for the iSTAT 1 analyzer (Abbott Point of Care Inc., USA).

Experimental model of circulatory arrest and resuscitation measures. We used a previously described experimental model of asphyxial circulatory arrest in rats [27], to which we made a number of modifications in accordance with the objectives of this study. After recording the baseline parameters, the animal was re-administered a muscle relaxant (rocuronium bromide 1.4 mg/kg), after which mechanical ventilation was discontinued. ECG and blood pressure monitoring was continued to determine the moment of circulatory arrest. When the mean arterial pressure fell below 20 mm Hg along with extreme bradycardia (or other pathological rhythm), effective tissue perfusion was considered absent, and the time of circulatory arrest was counted. After 2 minutes (no-flow time), resuscitation measures were initiated. Mechanical ventilation was resumed in CMV/VC mode with the following parameters: FiO_2 1.0, f 80/min, I:E=1:2, Vt according to the nomogram for rats. Chest compressions were performed in the anterior-posterior direction with the rat lying on its back at a frequency of 200 per minute. Intravenous adrenaline was administered at a dose of 0.005 mg/kg. After a one-minute cycle, chest compressions were stopped, and heart rate and blood pressure were assessed. If necessary, adrenaline was re-administered at a dose of 0.005 mg/kg. At the same time, ECG, blood pressure, and LDF monitoring continued.

After return of spontaneous circulation (ROSC), we continued mechanical ventilation with 100% O_2, monitoring blood pressure and ECG, and also infusion of 0.9% NaCl solution at a rate of 10 ml/kg/h. Five minutes after resuscitation, the gas composition and CO_2 content of arterial blood were assessed, and the parameters of mechanical ventilation were adjusted accordingly. In cases of severe metabolic acidosis (pH < 7.1, BE < –10 mmol/L), a 5% NaHCO3 solution was infused at a dose of 1 mmol/kg. Next, depending on the group, a mixture of argon and oxygen (70%/30%) or 30% oxygen and air (in the SO and CA groups) was supplied to the ventilator circuit for 2 hours. In the SO group, the same procedures and measurements were performed as in the CA group, except for cardiac arrest and resuscitation (without administration of adrenaline and bicarbonate, but with infusion, anesthesia, and muscle relaxants according to the study plan). Two hours after the resuscitation period (after completing

the measurements), a test for spontaneous breathing was performed: the breathing circuit was disconnected from the endotracheal tube, and the frequency, depth, and pattern of breathing were assessed. Observation of the animal and warming continued for another hour. At the end of this period, the general condition and neurological status were assessed. The general scheme of the experiment is presented in Fig. 1.

Assessment of neurological status. Neurological deficit was assessed using the General Neurological Score (GNS) scale. Motor and sensory tests (vibrissae, vision), reflexes (corneal, pain, ear), balance, and coordination were assessed. The maximum score was 1, the minimum score was 0. The maximum total score was 10.

Euthanasia. The animal was euthanized by intravenous administration of 2 ml of 4% KCl solution under general anesthesia with zoletil (additional dose of 20 mg/kg i/v).

Examination of the hemostasis system using low-frequency piezoelastography. The examination was performed using a Mednord NPTEG thromboelastograph (Mednord–Technika, Russia), with a blood sample volume of 0.5 ml. NPTEG parameters were measured immediately after blood collection. No more than 10 seconds elapsed between blood collection and sample placement in the analyzer. The collected blood was transferred from the syringe to a special test tube for analysis. After placing the test tube in the device, the analyzer needle was inserted into the blood and the curve was recorded by pressing the Start button in the software window that came with the device. The curve recording lasted from 30 to 40 minutes, which allowed most of the recorded indicators to be captured for analysis:

Ai — amplitude (clot density) at a specific time point from 0 to 6, expressed in conventional units.

ti — time of completion of a specific coagulation phase (min.).

ICC — intensity of the contact phase of coagulation; quotient of the difference in amplitudes (A0—A1) for the reaction period t1.

TAC — thrombin activity constant; quotient of the amplitude A2 = (100 const) divided by time (t2—t1).

CDI — coagulation drive intensity; quotient of the difference in amplitudes (A3—A1) divided by blood clotting time t3.

CPI — clot polymerization intensity; quotient of the difference in amplitudes (A4—A3) divided by a constant time = 10 min.

MCD — maximum clot density; the difference between the values (A5—A1) in relative units, characterizes the maximum clot density due to platelet activity and the quantitative/qualitative characteristics of cross-linked fibrin.

CRLI — clot retraction and lysis intensity; determined as the percentage by which the clot amplitude decreases within 10 minutes after reaching MCD: (A5—A6) / A5 × 100%

TAAC — total anticoagulant activity coefficient; quotient of the division of CDI/CPI.

After completing the measurement, the cuvette with blood was disposed of, and the analyzer needle was carefully cleaned with a cotton swab moistened with saline solution. The next measurement was started no earlier than 5 minutes after cleaning the needle.

Study of serum concentrations of biomarkers of brain damage. Serum concentrations of brain injury biomarkers (neuron-specific enolase, NSE) were measured using enzyme-linked immunosorbent assay (ELISA) in accordance with the manufacturer's instructions for ELISA kits (Cloud-Clone Corp., USA). Recording time: once at the end of the experiment.

Immunohistochemical analysis. Fixation was performed in 10% buffered formalin (Biovitrum, Russia) for 48 hours (the volume of the fixing fluid was at least 15 times greater than the volume of the material). Standard processing of the material included washing in tap water, dehydration in alcohols of increasing concentration, and embedding in low-melting paraffin. Sections 2–3 μm thick were prepared on a rotary microtome. The sections were stained with hematoxylin and eosin. Morphometric examination of brain areas highly sensitive to hypoxia (sensory-motor cortex, CA1 and CA4 fields of the hip-

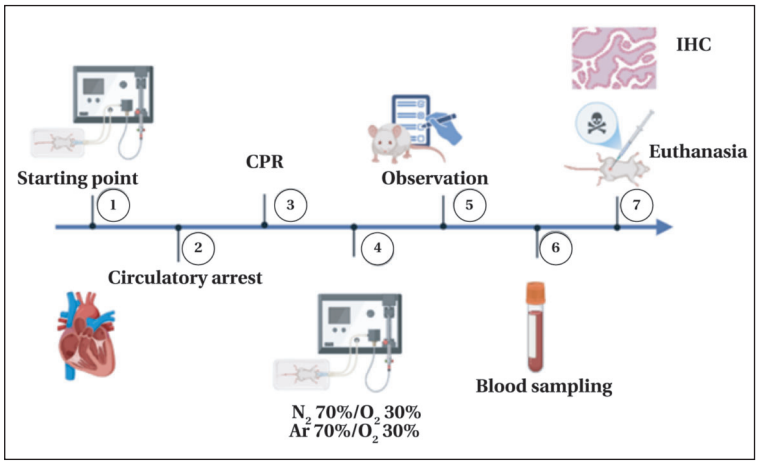

Fig. 1. General experimental setup.
Note.
1. Initial condition (after anesthesia, catheterization, and stabilization). Recording of parameters at the first time point: ECG, blood pressure, local skin blood flow, blood gas analysis, thromboelastography (TEG).
2. Simulation of circulatory arrest.
3. Cardiopulmonary resuscitation.
4. 10 minutes after resuscitation and return of spontaneous circulation. Recording of parameters at the second time point: ECG, blood pressure, local skin blood flow, blood gas analysis. Supply of argon-oxygen or oxygen-air mixture depending on the group being studied.
5. 120 minutes after the resuscitation period, weaning from ventilator and transition to spontaneous breathing after measurements. Recording of parameters at the third time point: ECG, blood pressure, local skin blood flow, blood gas analysis, TEG; assessment of neurological status.
6. Blood tests measuring ABB, thromboelastography parameters, and neuron-specific enolase content.
7. Euthanasia. IHC.

pocampus) was performed using microphotographs taken with a microscope slide scanner (Aperio ScanScope CS, Aperio, Vista, CA, US), a Nikon Eclips Ni-U microscope, and NIS-Elements BR software (Nikon Corp., Japan).

For immunohistochemical analysis, sections were prepared: deparaffinization and antigen retrieval of paraffin sections were performed using Trilogy® Pretreatment Solution Cell Marque, according to the manufacturer's protocol. The sections were then washed twice in PBS for 5 minutes and endogenous peroxidase was blocked with 2% hydrogen peroxide for 10 minutes. The sections were then washed twice in PBS for 5 minutes. To prevent nonspecific binding of primary or secondary antibodies to tissue proteins, Protein Block Serum-free ab64226 Abcam (Cambridge, UK) was used with 30 minutes of exposure in a humid chamber. The sections were then washed twice in PBS for 5 minutes. Antibodies to Caspase-3 (Invitrogen. PA5-77887 1:200) and beclin (Ab62557 1:200) diluted in Antibody and Diluent (ab64211 abcam) were incubated in a humid chamber at 37°C for 1 hour. The sections were then washed twice in PBS for 5 minutes. For visualization, secondary antibodies with peroxidase UMR1000PD-BMS (Diagnostic Biosystems, USA) were used according to the manufacturers' protocol. The sections were then washed twice in PBS for 5 minutes, developed with DAB, stained with hematoxylin for 1–2 minutes, dehydrated with 70%, 96%, and 100% alcohol, and xylene was added in two stages.

The data were statistically processed using SPSS Statistics (IBM SPSS Statistics for Windows, version 27.0.1, Armonk, NY, USA) and GraphPad Prism (version 8.0.1, Boston, MA, USA). The normality of distribution was checked using the Shapiro–Wilk test. The data were presented as the mean and standard deviation, as well as *Me* (*Q1*; *Q3*), where Me is the median, *Q1* is the first quartile (25th percentile), and *Q3* is the third quartile (75th percentile), depending on the type of distribution. For the analysis of quantitative data, the Kruskal–Wallis test with post-hoc analysis (Benjamin–Krieger–Yekutieli adaptive method) and the Mann–Whitney test (Wilcoxon rank sum) were used. To compare categorical variables, we used the χ^2 test or Fisher's exact test (for event frequencies less than 10%). Correlation analysis was performed using Spearman's method, and two-tailed tests were used in all analyses. Values of $p<0.05$ were considered statistically significant.

Results

At the first time point (before induction of asphyxia), two fatalities were registered in the CA group due to complications of anesthesia. Necropsy of the animals revealed no pathological changes in the internal organs. The remaining animals underwent modeling without reaching the criteria for humane euthanasia at any stage of the experiment. The average body weight of rats in the CA+iAr, CA, and SO groups at the time of inclusion in the experiment was 249.3±18.3, 245.6±18.9, and SO 248.1±15.4 g., respectively, and did not differ between groups ($p>0.05$).

Hemodynamic parameters. Fig. 2 shows the blood pressure (BP) and heart rate (HR) parameters in the study groups. At baseline (1), BP and HR values were within the physiological norm and did not show statistically significant intergroup differences (BP: SO 77.0 (73.8; 82.3) vs CA 78.0 (69.3; 88.9), $p=0.825$; SO vs CA+iAr 76.4 (69.3; 83.0), $p=0.752$; CA vs CA+iAr, $p=0.946$. HR: SO 241.6 (209.4; 250.9) vs CA 251.7 (240.0; 259.8), $p=0.545$; SO vs CA+iAr 250.1 (240.5; 261.1), $p=0.281$; CA vs CA+iAr, $p=0.812$).

At the second time point after return of spontaneous circulation, a statistically significant increase in blood pressure and a compensatory increase in heart rate were observed both within the CA and CA+iAr groups and in comparison with the SO group (BP: SO 74.1 (67.2; 92.9) vs CA 125.6 (79.5; 146.3), $p=0.017$; SO vs CA+iAr 122.5 (106.1; 138.9), $p=0.005$. HR: SO 248.1 (226.0; 256.4) vs CA 345.2 (332.8; 368.9), $p<0.0001$; SO vs CA+iAr 334.2 (291.5; 402.9), $p<0.0001$). No differences between the CA and CA+iAr groups were found for these parameters (BP: $p=0.959$; HR: $p=0.927$).

At the third time point, normalization of BP parameters was recorded (SO 79.05 (72.9; 93.9) vs CA 70.6 (64.5; 76.6), $p=0.065$; SO vs. CA+iAr 69.1 (64.5; 73.2), $p=0.231$, CA vs. CA+iAr, $p=0.873$) and of HR, no significant intergroup differences were found (Fig. 2).

Microcirculation and blood flow variability. No significant intergroup differences in the mean microcirculation (perfusion) index M were observed at any time point. It was found that the CVC index differed statistically significantly between the SO group and the CA group at the second time point ($p=0.042$), as well as in the CA group between the first and second points ($p<0.0001$), the 2nd and 3rd points ($p=0.04$), and in the CA+iAr group between the 1st and 2nd time points ($p=0.01$). σ and Kv showed a clear dependence on the experimental conditions. In the SO group, the values of σ and Kv remained relatively stable and were within the physiological norm.

At the 3rd time point, a statistically significant decrease in the values of σ and Kv was noted in the CA+iAr group compared to the CA group ($p=0.002$; $p=0.007$, respectively), as well as with the SO group ($p=0.007$; $p=0.016$, respectively) (Fig. 3).

Acid-base balance (ABB) and tissue metabolism indicators. After return of spontaneous circulation (point 2), statistically significant differences in lactate, BE, p/F, and pH were observed in the CA and CA+iAr groups compared to the SO group (Fig. 4). The condition of the animals at this time point was characterized by mixed metabolic acidosis and impaired tissue perfusion. 120 minutes after resuscitation (point 3), gas exchange and ABB parameters were compensated in all groups of animals.

The content of beclin-1 positive cells in the lung tissue was statistically significantly higher in

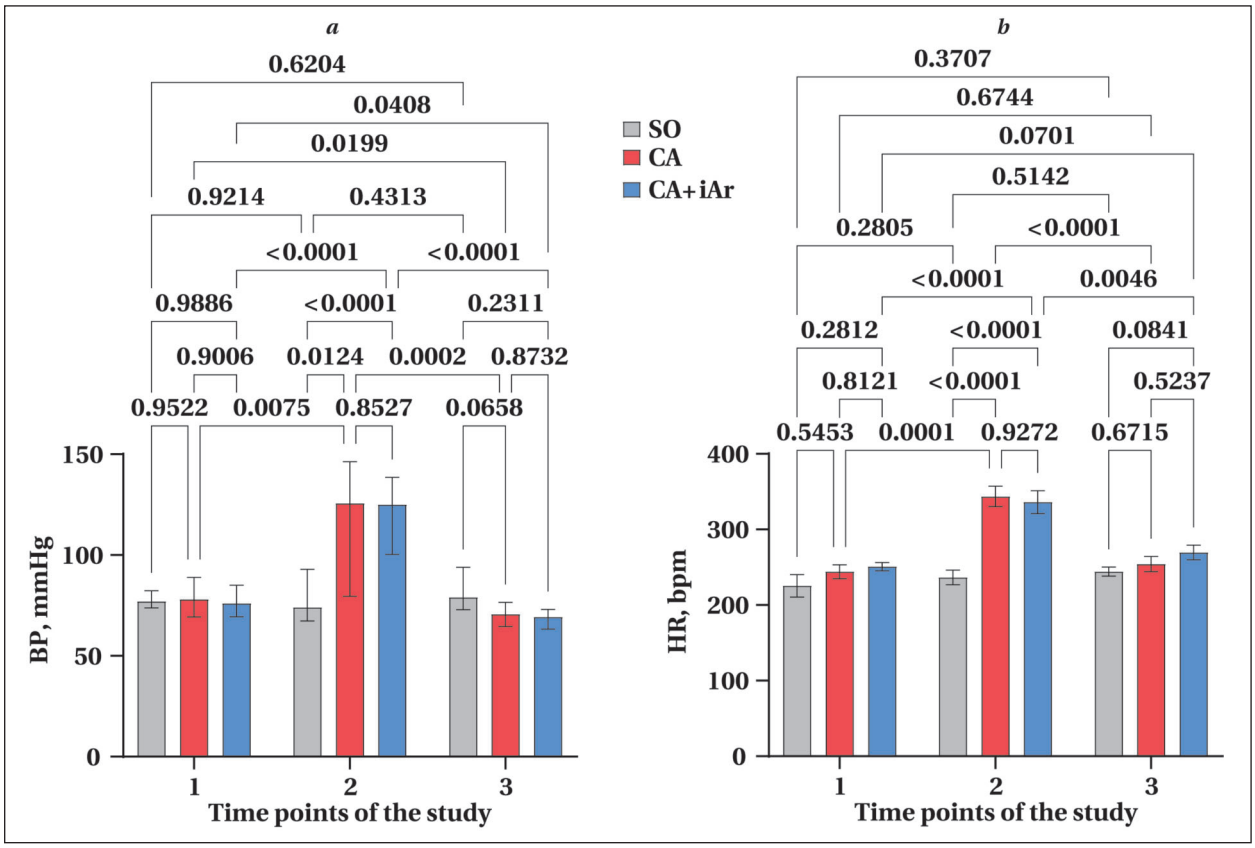

Fig. 2. Blood pressure (*a*) and heart rate (*b*) parameters in the study groups.
Note. In Figs. 2–9, the data are presented as medians and quartiles with indicated *p*-values.

the CA+iAr group (2343 (1558.5; 6528.2) compared to the CA group (1000 (856; 1251.7)), $p=0.028$

Coagulation parameters. The integral parameters of blood coagulation system, reflecting the dynamics of clot formation and subsequent transformation, were analyzed. In the CA+iAr group, we observed a decrease in contact activation intensity (CAI) and a decrease in maximum clot density (MCD), as well as lower polymerization intensity (PI) and coagulation drive (CD) indices (Fig. 6).

Electrophysiological parameters (ECG). The QTc time was longer in the CA+iAr group compared to the SO group (0.120 [0.112; 0.131] s vs. 0.1059 [0.1023; 0.116] s, $p=0.012$), and a difference in QRS duration was found between CA and CA+iAr ($p=0.016$). However, the changes in the intervals were within the reference limits. ST segment changes between groups did not differ statistically (SO 0.17 (0.09; 0.21) vs CA 0.17 (0.15; 0.24), $p=0.321$; SO vs CA+iAr 0.14 (0.11; 0.19), $p=0.423$; CA vs CA+iAr, $p=0.233$) (Fig. 7).

In the CA+iAr group, the content of beclin-1 cells in the myocardium was statistically significantly higher compared to the CA group (2050 (1883; 3582) vs 610.5 (289; 1867.2), $p=0.038$).

Neurological status parameters and markers of organ damage. The total score for the neurological status of animals in the CA group (2 [1.5; 3.5]) was statistically significantly lower than in the CA+iAr group (4.5 [4.0; 5.5]; $p=0.021$) and the SO group (8.5 [6.3; 9.0]; $p=0.0001$) (Fig. 8, *a*).

The beclin-1 protein content in the brain was statistically significantly higher in the CA+iAr group compared to the SO group (3902 (3544; 5212 vs 1080 (379; 1759; $p=0.0003$).

The number of caspase-3+ positive cells was statistically significantly lower in the CA+iAr group compared to the CA group ($p=0.011$). In addition, the content of neuron-specific enolase was statistically significantly lower in animals of the CA+iAr group (16.27 (11.12; 40.7) ng/ml) than in animals in the CA group (29.87 (20.38; 112.19) ng/ml), $p=0.011$ (Fig. 9, *b*).

Discussion

The data obtained indicated the preservation of the basic mechanisms of cardiovascular system regulation under the studied conditions of argon-oxygen mixture inhalation in a model of asphyxial cardiac arrest in rats.

The absence of statistically significant changes in blood pressure and heart rate between the groups allowed us to conclude that the interventions had no effect on macro-hemodynamics, and that identified trends were compensatory in nature.

At the third time point, lactate was statistically significantly lower ($p=0.043$) and the p/F ratio (PaO_2/FiO_2, oxygenation index) was higher ($p=0.001$)

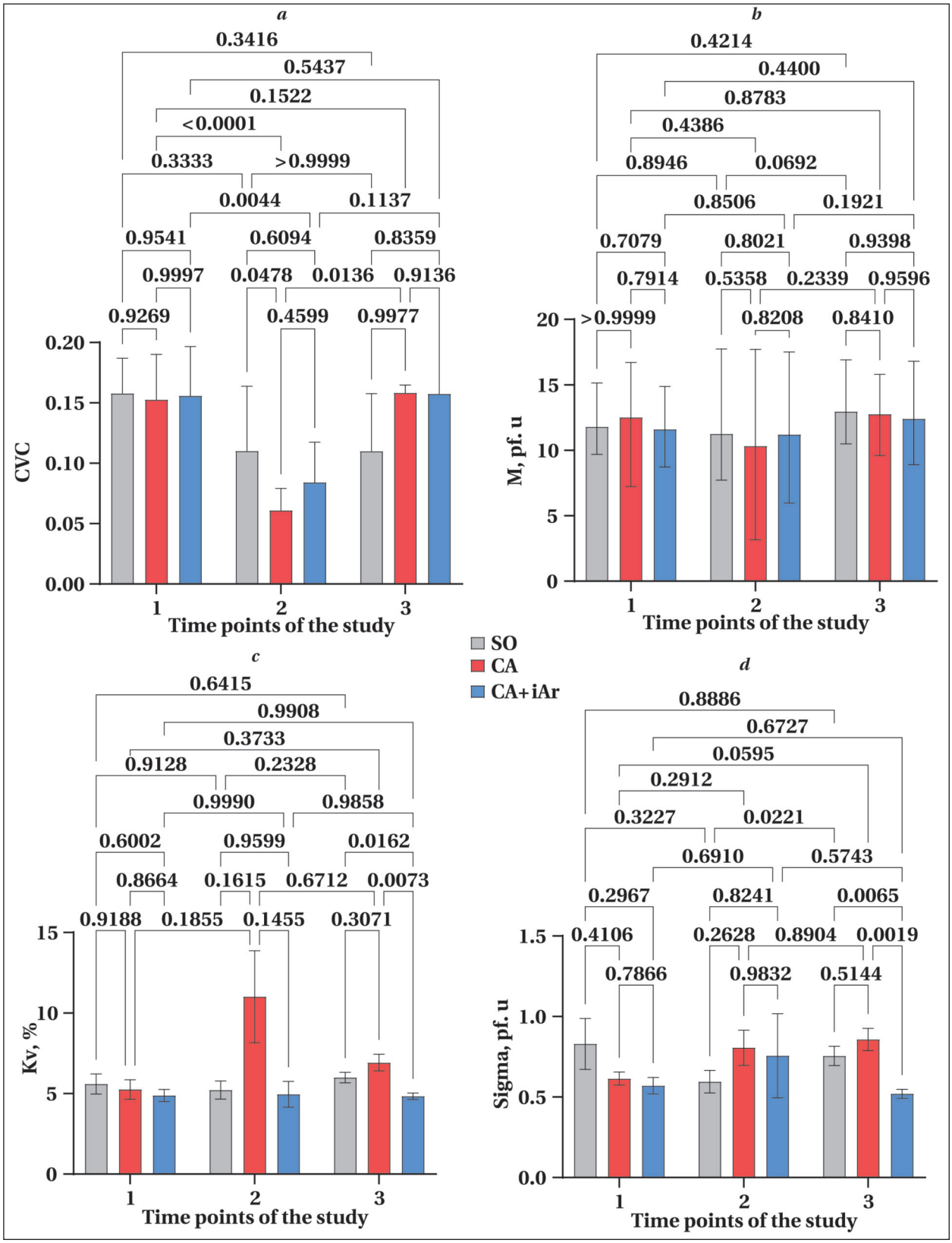

Fig. 3. Microcirculation parameters CVC (*a*), M (*b*), Kv (*c*), Sigma (*d*) in the study groups.

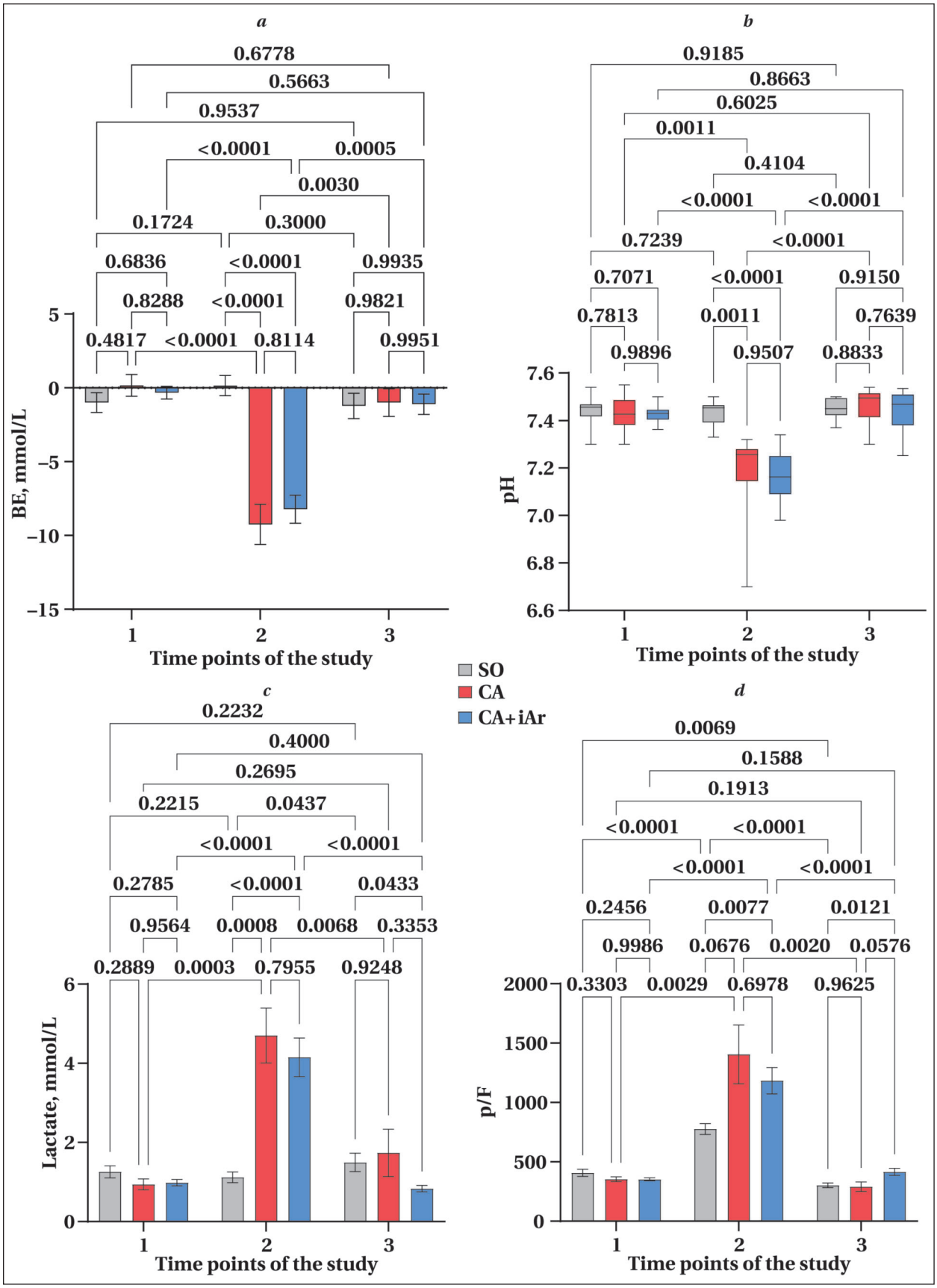

Fig. 4. Indicators of acid-base balance (ABB) and tissue metabolism in the study groups.

in the CA+iAr group than in the SO group (Fig. 4). But there was no significant difference in lactate and p/F between the CA and SO groups. The decrease in lactate combined with an increase in the p/F ratio indicated an improvement in tissue oxygenation and microcirculation following argon therapy.

The decrease in Kv and σ values combined with lower lactate level and increased p/F ratio in the CA+iAr group suggests that argon has a stabilizing effect on microcirculation, optimizing uniform tissue capillary perfusion and reducing blood flow amplitude fluctuations. This is accompanied by optimization of gas exchange and improved tissue oxygenation, by a decrease in anaerobic metabolism, which is confirmed by a decrease in lactate level. At the same time, systemic hemodynamic parameters (BP and HR) remained unchanged, indicating a local, microcirculatory effect of argon that does not affect overall blood flow.

An increase in the amount of beclin-1 in lung tissue in the AC+iAr group may indicate more intense activation of autophagic processes in response to ischemic-reperfusion injury.

The intensification of this process in lung tissue can be interpreted as a manifestation of a protective effect aimed at limiting structural and functional damage. Comprehensive assessment of the respiratory functional parameters confirm this assumption. Increased counts of these cells in the lung tissue after inhalation of argon-containing gas mixture can be considered a marker of protective cellular mechanisms activation aimed at preserving the structural integrity and functional activity of the tissue. In combination with improved gas exchange and oxygen consumption, this indicates a systemic protective effect of argon, actualized through molecular mechanisms of autophagy and through optimization of respiratory and metabolic function.

Thromboelastogram analysis identified changes in coagulation parameters indicating slower clot formation and reduced clot firmness in the presence of argon. At the same time, the thrombin activity constant (TAC) in the CA+iAr group was higher, which indicated a more «compact» and rapid development of the early enzymatic stage of thrombin formation necessary to initiate the coagulation cascade (Fig. 6).

It is important to emphasize that the indicators reflecting clot retraction and subsequent lysis (CRLI), as well as the balance between the rate of amplitude increase and polymerization (TAAC — total anticoagulant activity coefficient), did not show statistically significant changes. This means that argon did not enhance clot lysis processes, and its effect was largely related to how the clot is formed — to the quality of platelet interaction and the structure of polymerizing fibrin.

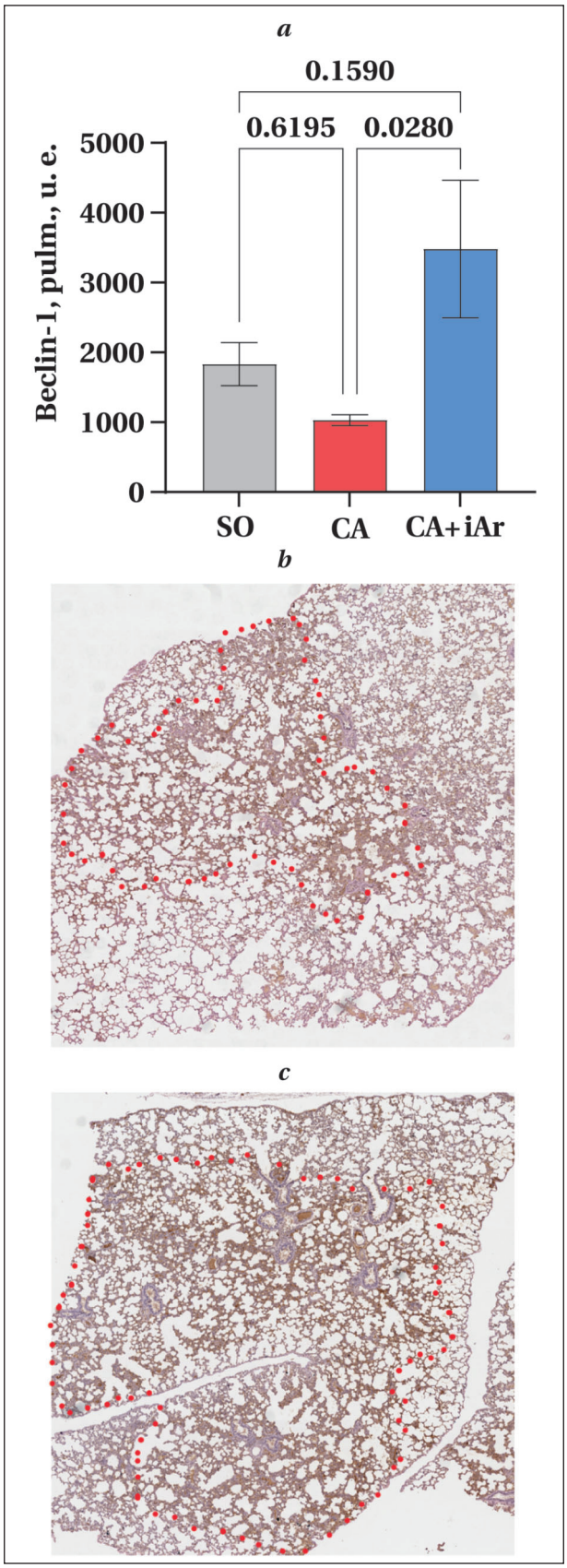

Fig. 5. Number of beclin-1-positive cells in the lungs (*a*). Images representing lung tissue slides in the CA (*b*) and CA+iAr (*c*) groups.
Note. Beclin-1 was evaluated by immunohistochemistry after euthanasia. The red dotted line marks the area that is positively stained for beclin-1.

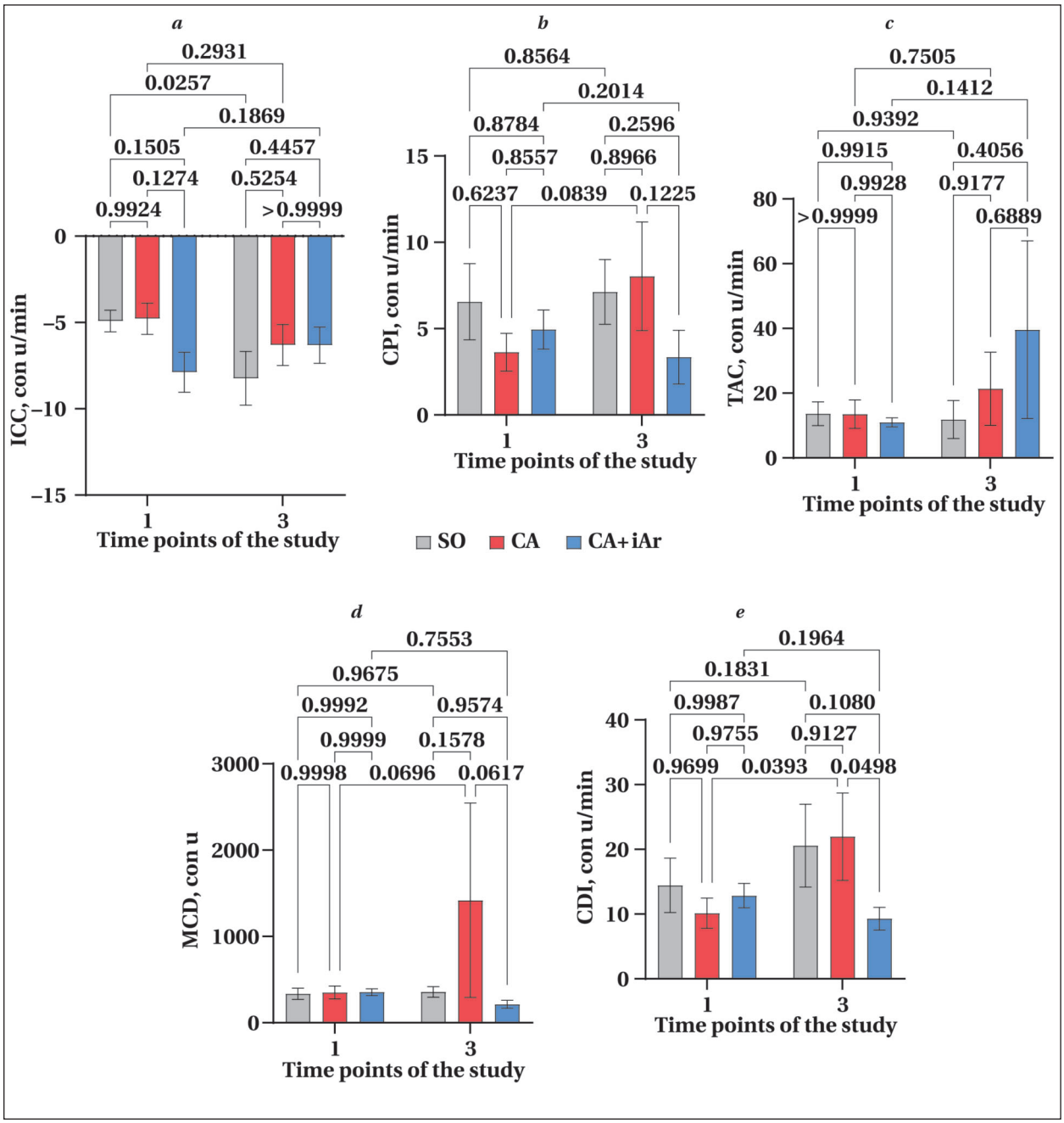

Fig. 6. Coagulation parameters in the study groups.

Thus, the profile observed in the CA+iAr group can be characterized as a selective attenuation of the coagulation response: coagulation is initiated less intensively, clot growth and compaction are slowed down, and the final firmness is lower, while normal retraction and lysis mechanisms are preserved. This pattern of changes can be considered a manifestation of a moderate anticoagulant and antiplatelet effect, directed primarily at the structural and mechanical properties of the forming thrombus.

Such modulation of coagulation can be extremely useful in hypercoagulable status, which often develops in the post-resuscitation period and is associated with the risk of microangiopathy and organ dysfunction [4–6]. However, the number of complications in the CA+iAr group did not differ statistically significantly from other groups. It has previously been shown that inert gases, including argon, can reduce tissue factor expression and platelet activity *in vitro* [19]. Our *in vivo* data confirm this ability of argon under conditions of global ischemic damage.

As for cumulative electrophysiological and molecular data, one can assume that the induction of autophagy (beclin-1 increase) after argon therapy contributes to myocardial cytoprotection, reduces

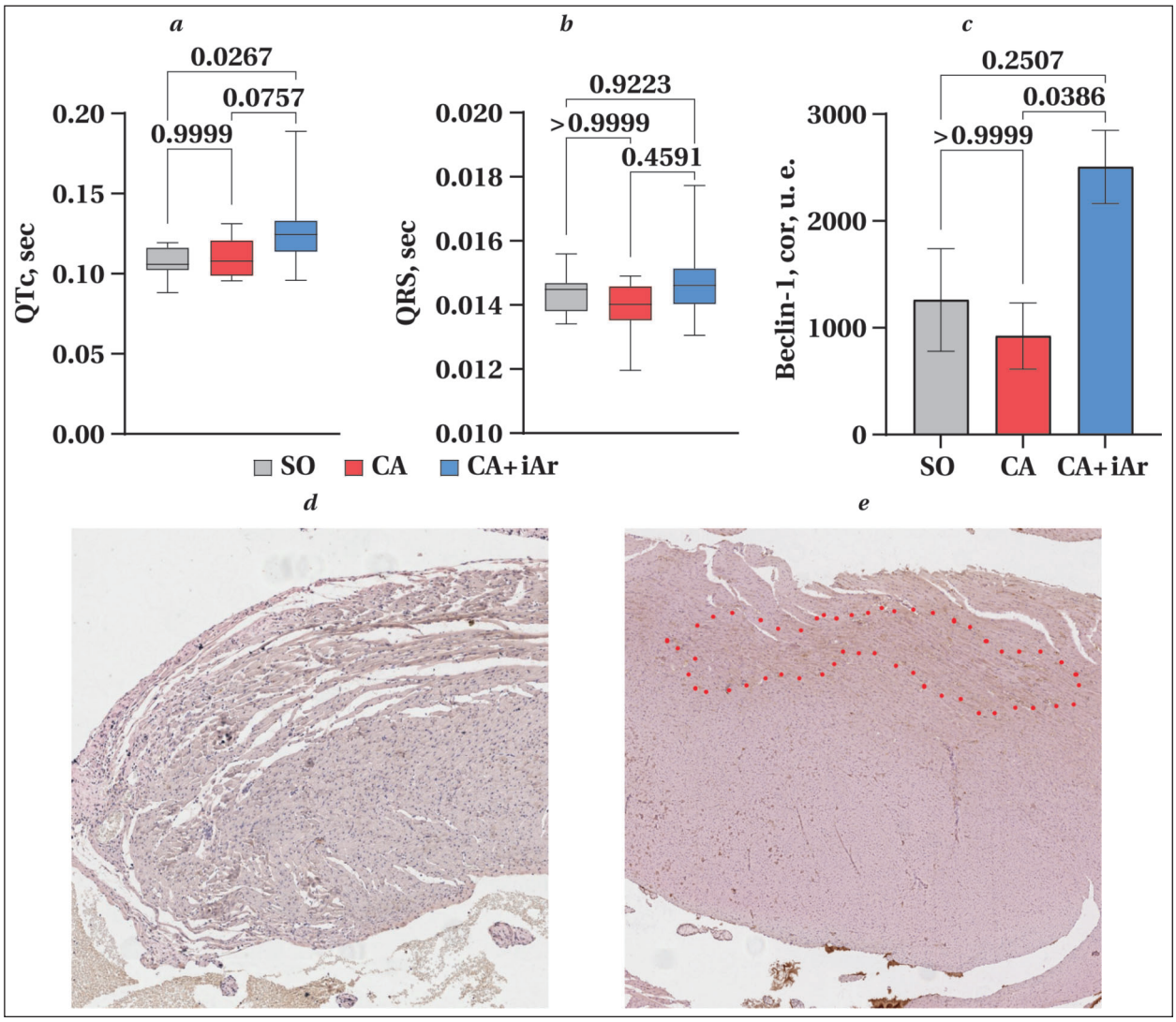

Fig. 7. Electrocardiogram readings at the third time point (*a*, *b*). Number of beclin-1-positive cells in the myocardium (*c*). Images representing myocardial slides in the CA (*d*) and CA+Ar (*e*) groups.
Note. The red dotted line marks the area that is positively stained with beclin-1. * — $p < 0.05$.

damage and variability of myocardial electrical properties, manifested by moderate prolongation of repolarization (QTc) and changes in conductivity (QRS) within normal limits with an intact ST segment. This corresponds to a cardioprotective profile without signs of proarrhythmic risk under the conditions studied, which has been previously described in other models [23, 26].

Analysis of the neurological status of the animals showed marked differences between the groups, indicating the influence of experimental interventions on functional recovery after brain damage.

The data obtained indicate the neuroprotective effect of argon and partial recovery of functional disorders.

Comparing functional data with molecular markers allowed us to hypothesize the basis for this effect of argon. Beclin-1 is a key regulator of autophagy, and its increase in the presence of argon may indirectly reflect the activation of cellular self-regulation and defense mechanisms. Given that autophagy can reduce cellular stress and prevent neuronal apoptosis, the increase in beclin-1 may be one of the factors contributing to the improvement in neurological status of animals in the CA+iAr group.

Thus, the data obtained demonstrate the neuroprotective properties of argon, which has also been shown in other studies [21, 22, 29] and consistent with the concept of argon's multifaceted effect on post-traumatic brain injury: it simultaneously alleviates neurological disorders and activates internal mechanisms of self-regulation and neuron survival.

The decrease in the number of caspase-3+ positive cells in the CA+iAr group compared to the

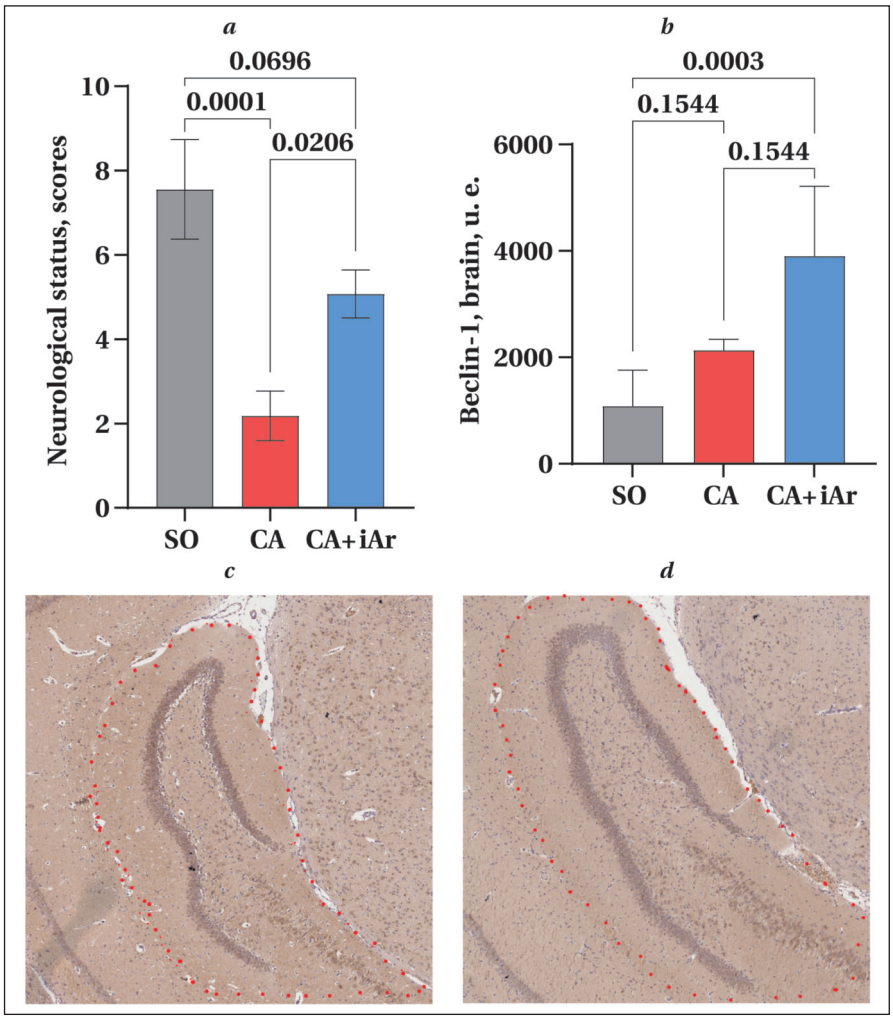

Fig. 8. Neurological assessment parameters at the third time point (*a*). Number of beclin-1 positive cells in the hippocampus (*b*). Images representing hippocampal slides in the CA (*c*) and CA+Ar (*d*) groups.
Note. The red dotted line marks the areas where the count was performed.
* — $p < 0.05$; *** — $p < 0.001$.

CA group indicates the suppression of apoptotic cell death after treatment with argon-oxygen mixture, which is consistent with the known anti-apoptotic properties of argon [14, 16]. Simultaneous decrease of serum neuron-specific enolase (NSE) levels means lower release of this neuronal damage marker, indicating a lower degree of nerve tissue destruction. Taken together, these data suggest that argon inhalation promotes maintenance of cell integrity and reduces the severity of neuronal damage by limiting both apoptosis and necrotic processes, which can be considered a manifestation of its neuroprotective effect.

Limitations and prospects of the study. It should be noted that the study was limited by a short observation window (3 hours after ROSC) and did not allow for the assessment of long-term functional and morphological outcomes. Markers of systemic inflammation and specific molecular pathways (e. g., PI3K/Akt or Nrf2 signaling cascades) that could clarify the targets of argon action were also not investigated. Finally, the choice of dosage and duration of argon therapy was based on preliminary studies and requires further optimization.

Nevertheless, the results of the study suggest that argon may be a promising means of modulating the cellular response to brain injury, providing functional improvement while preserving cellular structure and activating autophagic pathways.

Further research should focus on clarifying the time- and dose-dependent effects of argon use, its molecular targets and mechanisms of action, and in particular the relationship between beclin-1 activation and signaling pathways that provide neuroprotection. It is also necessary to evaluate the long-term outcomes of argon use.

Conclusion

Inhalation of argon-oxygen mixture in the early post-resuscitation period resulted in:

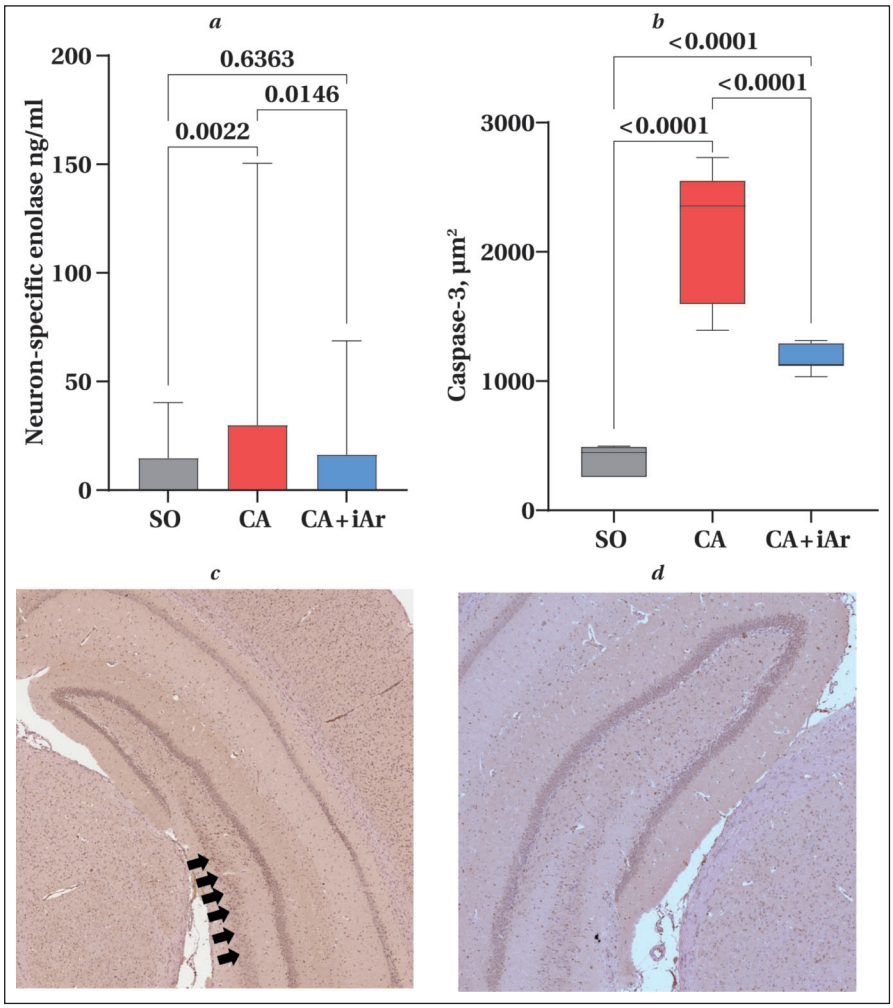

Fig. 9. Neuron-specific enolase (*a*). Number of cas-3 positive cells (*b*). Images representing hippocampal slides in the CA (*c*) and CA+iAr (*d*) groups.
Note. Parameters are presented at the third time point. Black arrows indicate the area of cas-3 positive cells. * — $p < 0.05$; ** — $p < 0.01$; **** — $p < 0.0001$.

— no changes in systemic hemodynamics, cardiac repolarization and conduction;

— decreasing Kv and Sigma values, normalization of blood lactate concentration, pH, and BE parameters;

— an increase in the oxygenation index and beclin-1 content in the lungs, myocardium, and hippocampus;

— a moderate anticoagulant and antiplatelet effect;

— improvement in neurological status parametes;

— reduction in neuron-specific enolase and Cas-3+ cell counts.

Although the differences in physiological parameters between the groups at early time points were minimal, further analysis of microcirculation, coagulation, organ damage biomarkers, and neurological status suggests that argon can effectively modulate key pathophysiological mechanisms of post-resuscitation syndrome.

Our data demonstrate that early inhalation of an argon-oxygen mixture after cardiac arrest provides a multisystem protection by improving oxygenation and microcirculation, promoting the activation of autophagic mechanisms in vital organs, reducing the severity of neuronal damage, and moderately modulating the blood clotting.

In this regard, argon can be considered a promising therapeutic agent for post-resuscitation syndrome.

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Comparison of Alteplase and Forteplase Efficacy in Reperfusion Therapy of Ischemic Stroke: a Retrospective Cohort Study

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Summary

The aim of the study. To compare the effectiveness of thrombolytic therapy in patients with ischemic stroke with forteplase and alteplase in clinical practice.

Materials and methods. A single-center retrospective cohort study was conducted using data from the reperfusion interventions registry at the Arkhangelsk regional vascular center. The primary endpoint was patients' functional recovery at discharge from the hospital. The incidence of type 2 intracranial hemorrhages according to the Heidelberg bleeding classification, mortality, and the duration of hospital stay were analyzed as the secondary endpoints. Descriptive statistics were used. Simple and multivariate multiple linear and logistic regression models were constructed to assess the relationship of forteplase use with functional recovery and length of hospital stay.

Results. The study involved 213 patients with the mean age of 68 (60; 76) years, including 111 (52.1%) men. Forteplase was used in 91 (42.7%) patients. Modified Rankin scale scores of 0–2 were documented in 52 (57.14%) and 51 (41.8%) patients in the forteplase and alteplase groups, respectively, $p=0.019$. After correction for potential confounders, no relationship was found between achieving good functional recovery and the use of forteplase: adjusted odds ratio was 1.04 [95% CI 0.54–2.01], $p=0.91$. The incidence of type 2 parenchymal hemorrhages was 3.3% in the forteplase group vs 0.8% in the alteplase group, $p=0.315$, and the mortality rates were 6.59% vs 11.48%, respectively, $p=0.247$. The use of forteplase did not affect the length of hospital stay in a multivariate analysis: B = –0.54 [95% CI –3.74–2.66], $p=0.741$.

Conclusion. Thrombolysis with forteplase is an effective and safe method of treatment in the acute period of ischemic stroke. Rates of achieving good functional recovery, incidence of intracranial hemorrhage, and length of hospital stay were comparable in groups treated with forteplase and alteplase after correction for significant confounders.

Keywords: alteplase; forteplase; ischemic stroke; systemic thrombolysis

Conflict of interest. The authors declare no conflict of interest.

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Introduction

Intravenous thrombolysis (IVT) is at the forefront of acute ischemic stroke (AIS) current management in the «therapeutic window» [1–3]. The use of IVT and mechanical recanalization techniques can improve patients' functional recovery after AIS [4, 5]. Given the high prevalence of ischemic stroke (IS) in the adult population and the significant disability caused by intracranial accidents, extending reperfusion therapy in management of patients with AIS is a crucial task for current practice [6, 7]. In addition, stroke is a major economic challenge in countries with aging populations, leading to a high burden on health care and social protection systems and increasing already high financial and societal costs [8–10].

One of the most promising areas for increasing the number of reperfusion procedures is a widespread use of advanced neuroimaging techniques to select patients for reperfusion outside the classic «therapeutic window» of 4.5 to 6 hours after the onset of symptoms [7, 11].

Currently, computed tomography (spiral CT) or magnetic resonance (MRI) perfusion imaging of the brain is actively studied in clinical trials and has already been included in the up-to-date national

and international guidelines and treatment protocols for patients with AIS [3]. Another available neuroimaging option that can expand the therapeutic window is diffusion weighted imaging – fluid attenuation inversion recovery — DWI/FlAIR mismatch MRI [12, 13]. Currently, this modality is used not only to select patients for reperfusion procedures in cases with unknown symptom onset, but also in cases with large ischemic core volume outside the therapeutic window [14, 15]. Hence, advanced neuroimaging techniques enable expansion of indications for using reperfusion therapy. On the other hand, wider use of reperfusion can be associated with higher rates of symptomatic intracranial hemorrhages (sICH) in this patient cohort due to extended therapeutic window compared to traditional approaches [13, 16]. For these reasons, search for ways to reduce the risk of hemorrhagic transformations (HTs) in the ischemic zone becomes more than relevant, offering employment of innovative thrombolytic agents with adequate safety profile as one of potential solution.

Use of fibrinolysin on January 22, 1986 for management of progressive vertebrobasilar stroke in Marshal of the Soviet Union G. K. Zhukov was one of the first documented cases of systemic thrombolysis in AIS [17]. Routine use of thrombolysis for AIS was not feasible until the end of the 20th century due to the lack of CT scanners in healthcare, which made it difficult to accurately differentiate between different types of stroke. It was not until 1996 that the first thrombolytic drug for the treatment of AIS, alteplase, was approved in the United States [4]. Representing the 2nd generation of fibrinolytic drugs, safe and highly effective alteplase has become the gold standard for managing AIS, although in the meantime, new thrombolytics have emerged in routine clinical practice in the last decade.

Between 2010 and 2025 a number of third-generation thrombolytic tenecteplase (TNK) studies have been conducted, expecting that its higher fibrin affinity would decrease the incidence of hemorrhagic complications associated with IVT. However, the results of these studies showed that TNK efficacy and safety profiles were comparable to those of alteplase [18–20]. According to the results of a systematic review and meta-analysis by the authors of the European Stroke Organization (ESO) clinical guidelines, which included data from three randomized studies, the efficacy and safety of tenecteplase and alteplase in AIS reperfusion therapy are comparable [1].

Forteplase, a recombinant protein containing staphylokinase amino acid sequence is another novel thrombolytic agent [21]. After publication in Lancet Neurology in 2021 the results of FRIDA RCT evaluating clinical effectiveness of IVT with forteplase compared to alteplase in AIS [22], the Russian MoH approved and included the use of forteplase for management of AIS in clinical guidelines [3]. Accumulated since 2021 clinical experience with forteplase substantiates its' compilation and sharing the overview of the results coming from observational studies.

The aim of this work was to compare clinical effectiveness of IVT with forteplase and alteplase in patients with AIS.

Materials and Methods

Data from the reperfusion therapy registry of the Arkhangelsk Regional vascular center (RVC) based at E. E. Volosevich First City Clinical Hospital (Arkhangelsk), which provides medical care to 1,300–1,400 patients with acute cerebrovascular accidents every year, were used for this single-center retrospective cohort study. The analysis included data from January 1, 2023, to July 1, 2025.

The study results were presented according to the EQUATOR network guidance for cohort studies [23].

The protocol for the registry set up was approved by the local ethics committee of the E. E. Volosevich First City Clinical Hospital of the Arkhangelsk Region (Arkhangelsk) on September 21, 2023. Data collection was carried out without obtaining informed consent due to the observational nature of the registry, which does not require additional medical or diagnostic interventions other than routine ones (the «waived informed consent» procedure, which allows for a deviation from the requirement to obtain informed consent).

The registry included patients aged over 18 years with AIS treated with reperfusion procedures (IVT and mechanical recanalization interventions) at the RVC. For the purposes of this study, patients who underwent IVT (either single or staged reperfusion) were included in the analysis. Cases with no data on functional recovery or whatever outcomes at discharge were excluded from the analysis.

IVT was performed based on indications and according to the current Russian MoH national and international clinical guidelines [3, 24]. When onset of AIS symptoms could not be established, patients were selected for the procedure based on DWI/FLAIR mismatch in brain MRI imaging. In all cases, the relevance of IVT was confirmed by joint decision of a neurologist and anesthesiologist-intensivist. All patients included in the registry received alteplase at a recommended dose of 0.9 mg/kg or 0.6 mg/kg for patients aged over 80 years for systemic thrombolysis according to the standard regimen (10% of the calculated dose was administered intravenously as a bolus within the first 60 seconds, and the remaining 90% was administered within 1 hour), or forteplase 10 mg i/v bolus injection. The use of forteplase relative to alteplase was considered as an exposure variable

For the purposes of subsequent analysis, the following potential confounders were selected from the registry: gender, age, concomitant pathology, the interval between AIS onset and IVT initiation, glycemia level on

admission, maximum systolic blood pressure (SBP) on the first post IVT day, use of staged reperfusion (IVT combined with mechanical recanalization procedures), and the severity of neurological deficit on admission according to National Institutes of Health Stroke Scale (NIHSS) [25]. Of the above factors, effect-modifying potential can be attributed to staged reperfusion, but stratified analysis was not done due to the small number of dual interventions in the sample.

Brain imaging was done using Revolution EVO (General Electric, USA), Brilliance CT 64 (Philips, Netherlands), or Sytec-S 2000i (General Electric, USA) spiral tomographs. Hemodynamic parameters were monitored using GE PROCARE B40 (USA) or Comen WQ-002 (China) monitors. Blood pressure was managed according to national and international guidelines: SBP was maintained at less than 180 mmHg. Diastolic blood pressure was adjusted if it exceeded 110 mmHg. Intravenous urapidil and azamethonium bromide were used to control patients' blood pressure.

The primary endpoint was functional recovery on discharge from the hospital, assessed by modified Rankin scale (mRS). The rehabilitation diagnosis and potential were assessed by a multidisciplinary team in all cases. Good functional recovery was defined as a score of 0–2 on the mRS. The secondary endpoints included hospital mortality, the rate of intracranial hemorrhages (ICH) and type 2 parenchymal hematomas (PH class 2) according to Heidelberg bleeding classification [26] separately, along with severe allergic reactions and length of hospital stay.

Statistical analysis of the data. Quantitative variables were presented as the mean (*M*) and standard deviation (*SD*) for variables with normal distribution, and the median (*Me*) and 25th and 75th quartiles for variables with skewed distribution. The normality of distribution was assessed using the Shapiro–Wilk test. Dichotomous variables were presented as absolute values and percentages. The differences between unrelated samples were assessed using the Mann–Whitney test due to non-normal distribution of the variables. Fisher's exact test was used to analyze the differences in qualitative variables.

Univariate and multivariate regression models were used to assess the relationship between the use of forteplase (relative to alteplase) and the attainment of good functional recovery (mRS 0–2 vs mRS 3–6). Univariate models were constructed to select significant confounders by evaluating the association between all demographic, clinical, and laboratory parameters and the functional outcome. The results of this analysis identified the following variables which were significantly associated with the functional outcome: patient age, NIHSS score on admission, maximum SBP in the first 24 hours after IVT, and the use of staged reperfusion. Multivariate regression models were constructed based on the results of this analysis, and all variables were entered into the model simultaneously. The results were presented as odds ratios (ORs) and adjusted ORs (aORs) with 95% confidence intervals (CIs).

To assess the relationship between the use of forteplase and length of hospital stay, we constructed simple and multivariate linear regression models. To select confounders that were significantly associated with the duration of hospital stay, we conducted a univariate analysis, testing all potential confounders. According to the results, only the severity of neurological deficits on admission assessed by the NIHSS, was associated with the dependent variable. We included the variables in the final model simultaneously. The results were presented as regression coefficients B with 95% confidence intervals.

The STATA 14 MP software (StataCorp, USA) was used for statistical analysis.

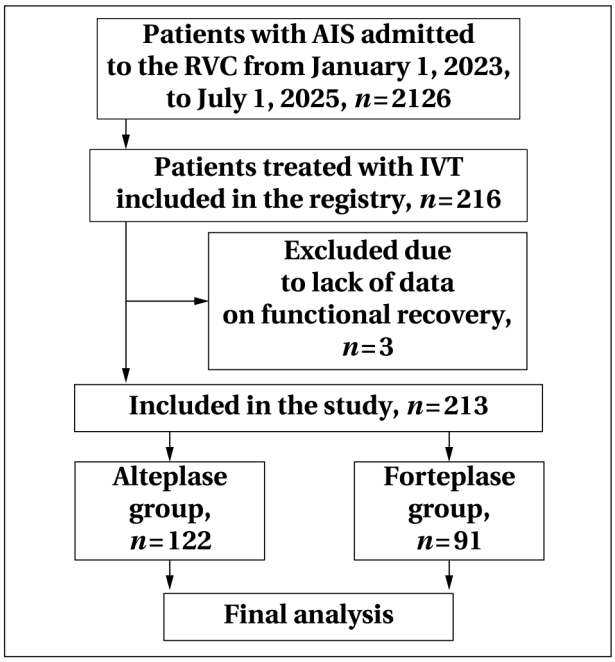

Fig. 1. Patient selection scheme for the study.

Results

During the study, out of 2126 patients with AIS admitted to the RVC 216 patients were treated with IVT (10.2%) and included in the registry. A total of 213 patients were included in the final analysis (Fig. 1).

Of the 213 patients included in the final analysis, 111 (52.1%) were men. The median age was 68 (60; 76) years, and forteplase was used in 91 (42.7%) cases. Detailed clinical and demographic characteristics are presented in Table 1

The median mRS score at discharge in the sample was 3 (1;4), and 103 (48.36%) patients achieved good functional recovery. In the forteplase group, the mRS score at discharge was 2 (1;3) versus 3 (1; 4) in patients who received alteplase, $p=0.016$. Good functional recovery was recorded in 52 (57.14%) and 51 (41.8%) cases in the forteplase and alteplase groups, respectively, $p=0.019$. Assessment of the relationship between the use of forteplase and functional recovery is presented in Table 2.

The mortality rate in the sample was 20 (9.39%). In the forteplase group 6 (6.59%) cases were fatal,

Table 1. Clinical and demographic characteristics of patients.

Parameters	Parameter values in the entire sample and in the groups			*p**
	Entire sample, *n* = 213	Alteplase, *n* = 122	Forteplase, *n* = 91	
Gender, men, *n* (%)	111 (52.11)	68 (55.74)	43 (47.25)	0.267
Age, years, *Me* (*Q1*; *Q3*)	68 (60; 76)	68 (60; 76)	68 (60; 76)	0.978
Time since AIS symptoms onset on admission, minutes, *Me* (*Q1*; *Q3*)	180 (140; 230)	176 (133; 220)	185 (153; 230)	0.128
NIHSS on admission, scores, *Me* (*Q1*; *Q3*)	8 (5; 17)	11 (6; 19)	6 (5; 10)	$p < 0.001$
Max SBP within first 24 hrs, mm Hg., *Me* (*Q1*; *Q3*)	169 (152; 180)	170 (152; 180)	165 (150; 179)	0.221
Glycemia level on admission, mmol/l	6.5 (5.6; 8)	6.5 (5.7; 7.6)	6.3 (5.6; 8.3)	0.863
Staged reperfusion, *n* (%)	19 (8.92)	16 (13.1)	3 (3.3)	0.014
Comorbidities				
Arterial hypertension, *n* (%)	204 (95.77)	115 (94.26)	89 (97.8)	0.306
Diabetes mellitus, *n* (%)	34 (15.96)	18 (14.75)	16 (17.58)	0.577
Arial fibrillation, *n* (%)	45 (21.13)	26 (21.31)	19 (20.88)	1.0

Note. Here and Table 2: NIHSS is the National Institutes of Health Stroke Scale, SBP is systolic blood pressure; * — is the significance of a difference between the Forteplase and Alteplase groups.

Table 2. Relationship between the use of forteplase and attainment of good functional recovery (mRS 0–2).

Predictor	Univariate analysis			Adjusted analysis		
	OR	95% CI	*p*	aOR	95% CI	*p*
Use of forteplase	1.86	1.07–3.22	0.027	1.04	0.54–2.01	0.91
Age	0.95	0.93–0.98	< 0.001	0.96	0.94–0.99	0.006
NIHSS score on admission	0.85	0.81–0.9	< 0.001	0.87	0.82–0.93	< 0.001
Max SBP first 24 hrs	0.98	0.96–0.99	0.002	0.99	0.97–1.0	0.17
Staged reperfusion	0.1	0.02–0.48	0.004	0.36	0.07–1.9	0.232

compared to 14 (11.48%) in the alteplase group, $p = 0.247$.

Three (3.3%) PH 2cases were documented in the forteplase group, compared to 1 case (0.8%) in the alteplase group, $p = 0.315$. The incidence of all ICH types according to Heidelberg bleeding classification is presented in Table 3.

The rate of severe allergic reactions did not differ between the groups: 1 (0.82%) vs. 2 (2.2%) cases among patients who received alteplase and forteplase, respectively, $p = 0.577$.

The duration of hospital stay was 15 (11; 23) days in the alteplase group and 12 (10; 16) days in the forteplase group, $p = 0.005$. The use of forteplase was not associated with shorter hospital stay in a multivariate analysis adjusted for the severity of neurological deficits on admission: B = –0.54 [95% CI –3.74–2.66], $p = =0.741$ (Fig. 2).

Table 3. Incidence of intracranial hemorrhage in the groups.

Parameters	Values in the groups, *n* (%)	
	Alteplase, *n* = 122*	Forteplase, *n* = 91*
No ICH	100 (81.97)	81 (89.01)
Class 1a	5 (4.10)	4 (4.40)
Class 1b	10 (8.2)	2 (2.20)
Class 1c	6 (4.92)	1 (1.10)
Class 2	1 (0.82)	3 (3.30)

Note. ICH — intracranial hemorrhage; * — $p = 0.1$.

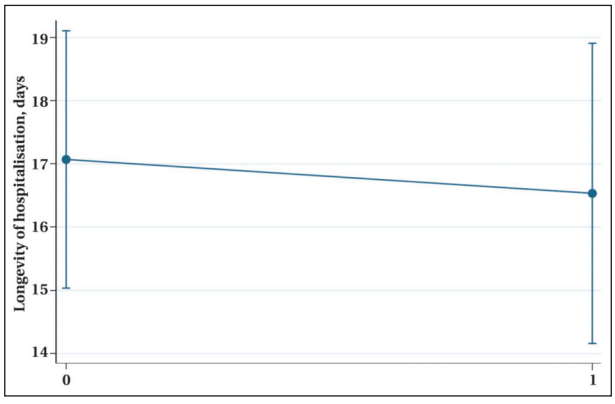

Fig. 2. Marginal average hospital stays by thrombolytic used, obtained in a multivariate linear regression model.

Discussion

The analysis of reperfusion therapy registry of the Arkhangelsk Regional vascular center (RVC) based at E. E. Volosevich First City Clinical Hospital (Arkhangelsk) suggests that forteplase is comparable in efficacy and safety to alteplase in IVT management of AIS.

Less severe cases in terms of neurological deficits on admission in the forteplase group can be attributed to two factors. The first relates to patient screening algorithm for IVT, as the on-call staff selected less severe cases for reperfusion procedure during implementation phase of forteplase bolus administration. The second — to restricted use of forteplase as until December 2024 it was not approved for staged reperfusion based on prescribing information, while clinical guidelines envisaged alteplase-based thrombolysis followed by interventional treatment in patients with large vessel oc-

clusion (LVO) and severe neurological deficits, explaining evermore the difference in rates of staged reperfusion in two study groups.

It should be noted that greater proportion of patients attained functional recovery at discharge in the forteplase group, i. e. 52 (57.14%) patients with mRS 0–2 score versus 51 (41.8%) in the alteplase group, OR 1.86 [95% CI 1.07–3.22], $p=0.027$. Most likely, this is associated with less severe neurological deficit on admission in the forteplase group, as evidenced by NIHSS 6 scores (5; 10) vs 11 (6; 19) scores in the alteplase group. After adjustment for potential confounders (NIHSS on admission, patient age, maximum SBP on the first day after IVT, and the use of staged reperfusion), no association was found between the use of forteplase and achievement of good functional outcome: aOR 1.04 [95% CI 0.54–2.01], $p=0.91$. These findings are consistent with previously published results of other studies [27]. According to Alasheev A. M. et al, patient functional recovery does not depend on the type of thrombolytic used [28]. The results of the only RCT comparing the effects of staphylokinase amino acid sequence-based recombinant protein and alteplase showed that 50% of patients in the forteplase group achieved excellent functional recovery (mRS 0–1), compared to 40% in the alteplase group, but the difference was not statistically significant ($p=0.1$) [22].

The results of M. Yu. Volodyukhin et al. study published in 2023 indicate that efficacy and safety of forteplase in staged reperfusion are comparable to those of alteplase [29]. The results of this study are consistent with the above mentioned with regard to adjusted for the use of endovascular recanalization procedures multivariate analysis, which demonstrated that IVT with forteplase had no significant influence on patient functional outcomes compared to alteplase: aOR 1.04 [95% CI 0.54–2.01] $p=0.91$.

Published data on mortality rates from FRIDA randomized trial were 10% in the forteplase group compared to 14% in the alteplase group, $p=0.032$ [22]. Similar trend is obvious in the presented analysis, with 11.5% mortality in the alteplase group compared to 6.6% in the forteplase group, although the difference was not statistically significant, $p=0.247$.

ICH was reported in 11 (11%) and 22 (18%) patients form forteplase (recombinant protein containing staphylokinase amino acid sequence) and alteplase groups, respectively. According to R. S. Maksimov et al, ICH was reported in forteplase and alteplase groups in equal proportions [27], which is consistent with the results of this study. Published data indicate close to 6% incidence of PH 2 class hemorrhage in patients receiving IVT with forteplase [29]. The 3.3% rate of PH2 in our study can be explained by small sample size. No statistically significant differences in rates of PH 2 and symptomatic ICH between the two thrombolytic agents was found either in this study, or published data from other studies [30]. The incidence of severe allergic reactions did not differ in the groups, which is also consistent with the results of a previously published study [30].

Shorter median hospital stay was reported after treatment with forteplase compared to alteplase — 12 vs. 15 days, respectively, $p=0.005$. Similar results were reported in the study of A. A. Kulesh et al., with 1 day difference in favor of forteplase, $p<0.005$ [31]. However, after adjustment for the severity of neurological deficit on admission, this initial statistically significant difference between the groups in length of hospital stay was lost and became statistically insignificant: B = –0.54 [95% CI –3.74–2.66], $p=0.741$.

The study is limited by its retrospective, single-center design, which makes it difficult to generalize the results onto entire AIS population. Additionally, due to the specific nature of the reperfusion intervention registry, patients' functional recovery was assessed upon discharge from the hospital rather than at 90 days, which is not optimal from the perspective of standardized approaches to assessing outcomes in studies on this topic. However, the sufficient sample size allowed for statistically significant results to be obtained after appropriate statistical analysis.

Conclusion

IVT with forteplase is an effective and safe method of a precise therapy in the acute period of ischemic stroke. Rates of achieving good functional recovery, ICH incidence, and the duration of hospital stay for IVT with forteplase are comparable to those obtained with alteplase.

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Use of Venovenous Extracorporeal Membrane Oxygenation in Status Asthmaticus: Case Reports

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Summary

Bronchial asthma remains one of the most common chronic respiratory diseases characterized by episodes of severe airway obstruction. In cases of refractory status asthmaticus complicated by critical hypercapnia and decompensated respiratory acidosis, conventional methods of respiratory support, including mechanical ventilation, are often insufficient. The use of venovenous extracorporeal membrane oxygenation (VV-ECMO) is considered a promising method for stabilizing gas exchange and minimizing ventilator-induced damage.

Objective: to share clinical experience in successful use of VV-ECMO in patients with refractory status asthmaticus complicated by severe hypercapnia and decompensated respiratory acidosis, resistant to correction by conventional respiratory support and lung-protective ventilation.

Materials and methods. VV-ECMO was used as an extracorporeal alternative for lung gas exchange function in two female-patients with refractory status asthmaticus complicated by severe hypercapnia and decompensated respiratory acidosis.

Results. VV-ECMO reduced the risk of developing ventilator-induced lung injury (VILI) allowing maintenance of lung-protective mechanical ventilation, and therefore, enabling accelerated respiratory rehabilitation. In both presented cases, early initiation of VV-ECMO improved gas exchange parameters and mitigated ventilator-associated complications, thereby confirming the relevance of its' use in patients with severe exacerbations of bronchial asthma complicated by uncontrolled hypercapnia.

Conclusion. Presented experience highlights the importance and feasibility of further VV-ECMO exploration as an intensified approach for management of severe BA exacerbations accompanied by critical hypercapnia and respiratory failure. This might require larger-scale randomized trials to identify optimal indications and protocols for VV-ECMO use.

Keywords: bronchial asthma; extracorporeal membrane oxygenation; bronchial obstruction; respiratory failure; mechanical ventilation; status asthmaticus

Conflict of interest. The authors declare no conflict of interest.

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Introduction

Bronchial asthma (BA) is a chronic inflammatory airway disease, widespread around the world. BA is characterized by episodes of bronchospasm, bronchial hyper-responsiveness and airway obstruction [1]. Bronchial asthma is a heterogeneous disease characterized by chronic inflammation of the airways and a reversible component of bronchial obstruction, consisting of smooth muscle contraction, swelling of bronchial mucosa and luminal obstruction by mucus. This, in turn, can lead to «air trap» phenomenon — an abnormal retention of air in the alveoli when full exhale is not possible. The so-called auto-positive end expiratory pressure (auto-PEEP) is gradually built up, leading to a decrease in the inspiratory reserve volume (IRV), an increase in airway pressure, hyperinflation and a decrease in lung compliance.

The work of breathing increases due to active exhalation, aggravating respiratory failure.

Gas exchange abnormalities in bronchial asthma are characterized by hypercapnia and hypoxemia due to ventilation/perfusion mismatching [2–4].

Basic therapy for severe asthma exacerbation, according to clinical guidelines [5], includes the use of inhaled bronchodilators (short-acting β_2-agonists, M-cholinoblockers), glucocorticosteroids, magnesium sulfate, and heliox [6–8]. Sometimes conservative therapy fails, requiring more intensive respiratory support ranging from low-flow oxygenation to mechanical ventilation (MV) and extracorporeal gas exchange [9, 10].

In order to achieve adequate gas exchange, it is necessary to deviate from the norms of «protective ventilation» in order to overcome high airway pressure and deliver a respiratory volume (RV). These measures often lead to ergotrauma- ventilation-induced lung injury (VILI). Common clinical manifestations of secondary lung injury include development of pneumothorax and pneumomediastinum. The incidence of pneumothorax in patients using mechanical ventilation for severe exacerbations of asthma ranges from 3% to 6% [11]. The mortality rate in patients with asthma undergoing mechanical ventilation is almost 7% [12].

When MV and drug therapy fail to control the BA attack, and respiratory failure (RF) is progressing, it is necessary to consider the initiation of ECMO. ECMO in BA allows to normalize gas exchange parameters, minimize ventilation-induced lung injury and establish favorable environment for recovery of respiratory function [13].

Currently, there are no clear criteria for initiating ECMO in severe BA exacerbations. ECMO is recommended in patients with refractory decompensated respiratory acidosis, accompanied by hemodynamic instability [7, 8, 15]. K. Z. Jonathan et al. identified the following criteria for initiating ECMO in refractory status asthmaticus: plateau pressure $\geqslant$32 cm H_2O, the need to prevent cardiovascular failure, severe respiratory acidosis (pH < 7.2; $PaCO_2$ > 60 mmHg), and a low PaO_2/FiO_2 ratio < 80 mmHg [14].

To date, the use of ECMO in severe BA exacerbations has not been studied in large randomized clinical trials and is limited to case reports or retrospective reviews [14–16]. The aim of this study is to present the experience of VV-ECMO use in patients with refractory status asthmaticus complicated by severe hypercapnia and decompensated respiratory acidosis, which could not be corrected by conventional respiratory support and mechanical ventilation in lung-protective modes.

The patients who participated in the study, gave their voluntary informed consent to participate in the scientific research and to publish the results.

Case report N1

A 22-year-old patient with a body mass index (BMI) of 19 kg/m² and BA since the age of 4, was on basic therapy, but took medications irregularly. On the morning of 11/27/2023, she was brought by an ambulance team to the emergency department of a Moscow hospital with complaints of severe shortness of breath. In 12 hours after admission to the hospital due to the progression of respiratory insufficiency (RI) and increasing cerebral insufficiency (with consciousness reduced to sopor), the patient was transferred to the intensive care unit (ICU), mechanical ventilation was initiated in the VCV mode with the following parameters: tidal volume-V_T — 8 ml/kg, PEEP — 5 mm H_2O, FiO_2 — 50%, T_{insp} — 0.7 sek, Ti:Te 1:4, RR — 12 per minute, P_{plat} — 38 mm H_2O. There were no attempts to initiate noninvasive ventilation.

Due to persistence of decompensated respiratory acidosis, remaining refractory to mechanical ventilation for 24 hours, and emergence of ventilator-associated complications (laboratory and instrumental data: pH — 7.1, pCO_2 — 101 mmHg, pO_2 — 48 mmHg, CT-signs of pneumomediastinum, neck and chest soft-tissue emphysema, bilateral gas accumulations in the interlobar pleura and in the abdominal cavity), the patient was consulted by a visiting ECMO team of the A. S. Puchkov ambulance and emergency medical care station of the Moscow City Department of Health (CDH). The team initiated ECMO on the spot and transported the patient to the ICU of City Clinical Hospital No. 52 (CCH No. 52).

On 11/28/2023, the patient's condition was severe: drug-induced sedation (propofol infusion at 160 mg/h, RASS score of 4). Ventilation through an endotracheal tube (ETT) in V-SIMV mode: tidal volume V_T — 400 ml, inspiration rate — 6 per minute, FiO_2 — 40%, positive end-expiratory pressure (PEEP) — 0 mm H_2O, minute volume (V_E) — 2.4 L/min, while compliance — 15 ml/cm H_2O, resistance — 12 cm H_2O /L/s, auto-PEEP — 23 mm Hg, P_{peak} — 75 mm H_2O, P_{plato} — 34 mm H_2O, pH — 7.19, PaO_2 — 82 mm Hg, $PaCO_2$ — 81 mm Hg. VV-ECMO parameters: flow — 2.4 L/min, speed — 4600 rpm, Foxy — 100%, SGF — 3 L/min in order to gradually reduce hypercapnia and correct hypoxemia. Physical examination revealed neck and upper chest emphysema. There were no other signs of pathology.

Laboratory data indicated a marked systemic inflammatory response syndrome (SIRS): leukocytosis (11.1×10^9/L) with neutrophilia (9.8×10^9/L), and an increase in C-reactive protein (CRP) to 40.53 g/L.

Chest CT (Fig. 1, *a, b*) revealed bilateral polysegmental pneumonia. In the upper right lobe, upper and lower left lobes, there were areas of infiltration and ground glass opacification, as well as

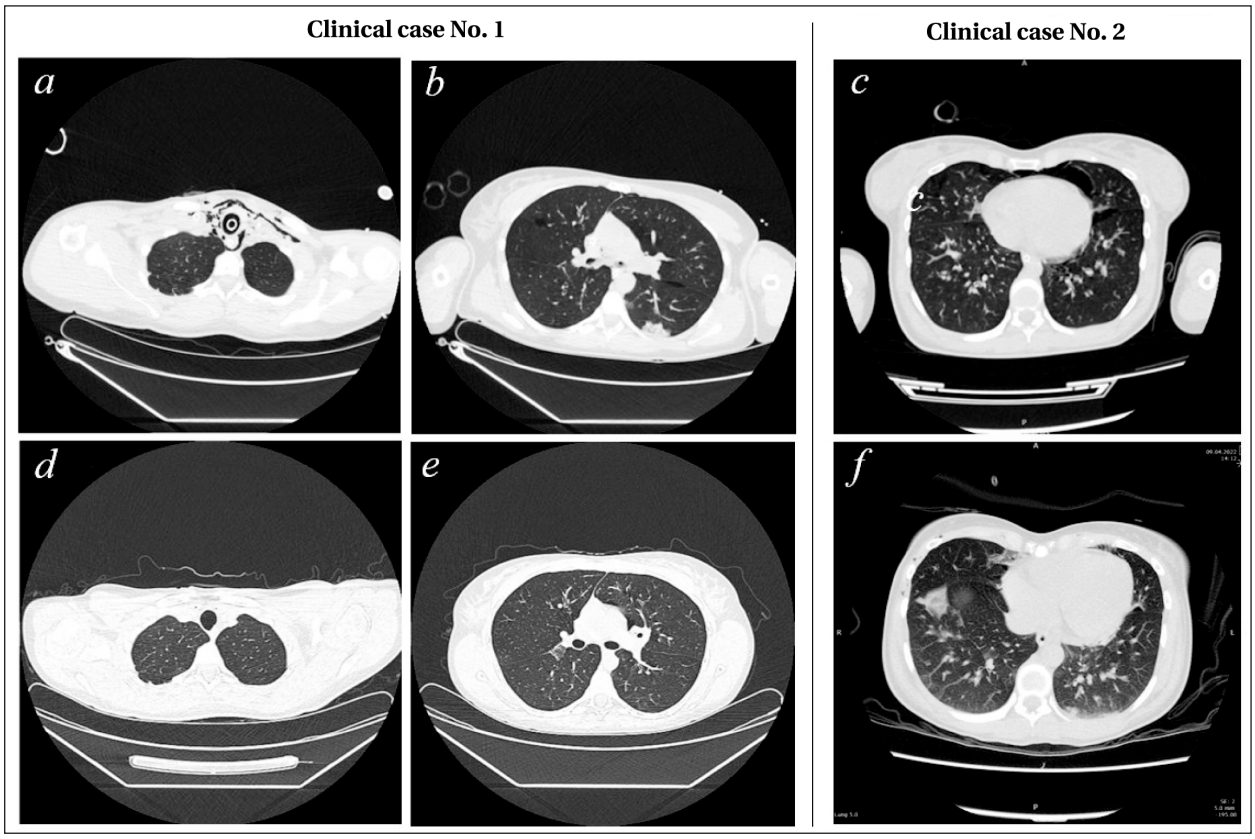

Fig. 1. Dynamics of changes in chest CT scans.
Note. Chest CT before initiation of VV-ECMO (*a, b,* clinical case No. 1); (*c*, clinical case No. 2), on the 6th day of hospital stay (*d* and *e*, clinical case No. 1), and on the 4th day of hospital stay (*f*, clinical case No. 2).

accumulation of mucus with gas bubbles in the main bronchi. There were signs of pneumomediastinum, neck and chest soft tissue emph ysema, and bilateral gas accumulation in the interlobar pleura.

A PCR analysis of bronchoalveolar lavage (BAL) samples revealed the presence of Epstein-Barr virus and rhinovirus, suggesting that acute respiratory infections could be a trigger for exacerbations of asthma.

Pharmacotherapy included β_2-adrenomimetics, anticholinergic drugs, and glucocorticosteroids and empirical antibiotics.

During the first day of therapy with lung-protective mechanical ventilation (tidal volume — V_T — 400 ml, PEEP — 0, RR — 10 per minute, FiO_2 — 21%) and VV-ECMO a slight regression of bronchial obstructive syndrome was documented (compliance — 24 ml/cm H_2O, resistance — 19 cm H_2O,/L/s, auto-PEEP — 18 mm H_2O). After pharmaco-sedation was discontinued, the patient regained consciousness on the third day, tracheal tube was removed and mechanical ventilation was discontinued. Due to persistence of hypercapnia ($PaCO_2$ — 78 mmHg) and infiltrative changes, VV-ECMO was prolonged. VV-ECMO parameters: flow — 2.0 L/min, speed — 3100 rpm, Foxy — 80%, SGF — 2 L/min. On the 5th day, chest CT scans sowed regression of infiltrative changes in the lungs (Fig. 1, *d, e*), a decrease in levels of SIRS markers (Fig. 2), and normalization of gas exchange parameters (pH — 7.34, PaO_2 — 82 mmHg, $PaCO_2$ — 45 mmHg, and no need for respiratory support). The ECMO procedure was discontinued.

The patient was discharged from the hospital in a satisfactory condition on the 8th day after treatment for 2 days with MV and pharmacosedation, continued with life-support ECMO for another 5 days in addition to standard of BA care.

Case report №2

Patient S., 25 years old, BMI — 19.6 kg/m², with a long history of BA with an allergic component, was receiving regular maintenance therapy. Following an asthma attack at night, 04.04.2022 with difficult breathing the patient intensified therapy using salbutamol, ipratropium bromide+phenoterol 6–10 times a day, but failed to cope with the symptoms. The patient called an ambulance and was admitted to the intensive care unit of a Moscow hospital with progressive respiratory failure, was intubated and started on VCV mechanical ventilation with the following settings: tidal volume (V_T) — of 8 ml/kg, FiO_2 of 60%, respiratory rate of

18 breaths/min, and positive end-expiratory pressure of 5 cm H_2O. The patient's Ti:Te ratio was 1:2. Due to ongoing deterioration with further progression of respiratory failure, inapplicability of lung-protective MV mode and emerging ventilator-associated complications (i. e., subcutaneous emphysema, pneumomediastinum, and pneumothorax), the visiting team from the ECMO center was invited for consultation, and the patient was transferred to the ICU of City Clinical Hospital No. 52 for ECMO therapy.

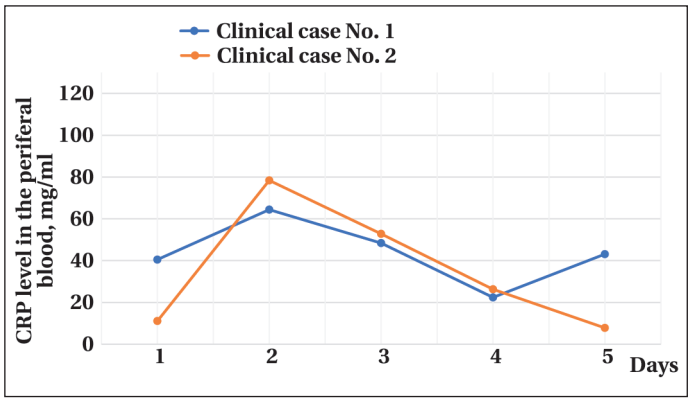

Fig. 2. Dynamics of C-reactive protein (CRP) levels during ECMO procedure.

On 05.04.2022, the patient's condition was assessed as severe. Drug-induced sedation (continuous infusion of propofol, RASS score of 4) was initiated. P-SIMV mode mechanical ventilation was maintained with the following settings: peak inspiratory pressure — of 30 mm H_2O), pressure support (PSV) — of 18 mm H_2O, PEEP — of 5 cm H_2O, respiratory rate — of 17 bpm, tidal volume V_T — of 8 ml/kg, minute volume V_E — of 7.4 L/min, FiO_2 — 70%, T_{insp} — 0.8 c, compliance — 20 ml/cm H_2O, resistance — 18 cm of H_2O /L/s. No significant changes were observed in other organ systems parameters.

Laboratory data were indicative of decompensated respiratory acidosis: pH = 7.1; $PaCO_2$ = 140 mmHg, PaO_2 = 46 mmHg, P/F ratio = 0.65 mmHg. CBC showed marked leukocytosis (27.3×10^9/L) with neutrophilia (24.2×10^9/L) and lymphopenia (0.8×10^9/L; 2.9%), CRP was 73.71 mg/L, and LDH was 272.2 U/L. BAL sample contained DNA of types B, C, and E adenovirus and SARS-COV-2 RNA.

Chest CT (Fig. 1, *c*) scans are indicative of pneumomediastinum with extension to the deep cellular spaces of the neck and preperitoneal cellular tissue, with moderate soft tissue emphysema of the neck and interstitial emphysema. A small right-sided pneumothorax. Diffuse thickening of the bronchial walls and narrowed bronchial lumen, presence of mucoid impaction in the distal bronchi.

Drug therapy included β_2-adrenomimetics, anticholinergic drugs, glucocorticosteroids, and initially empirical antimicrobial therapy with subsequent adjustments and transition to targeted therapy based on microbiological culture.

In view of persisting respiratory acidosis VV-ECMO was initiated with the following settings: flow — 2.6 L/min, speed — 5000 rpm, Foxy — 100%, SGF — 5 L/min with the intent to correct hypercapnia and hypoxemia. Because of anticipated prolonged mechanical ventilation a tracheostomy was performed on 06.04.2022.

On April 7, 2022, a regression of bronchial obstruction syndrome (Fig. 1, *f*) and systemic inflammatory response syndrome (Fig. 2) were documented, as well as an improvement in gas exchange parameters: pH — 7.35, $PaCO_2$ — 61 mmHg, PaO_2 — 92 mmHg, compliance — 62 ml/cm H_2O, and re-

Table. Clinical description of VV-ECMO use in patients with status asthmaticus

Parameters	Parameter values	
	Case No. 1	Case No. 2
Age, years	22	25
BA onset	18 years ago	Unknown
Adequate basic/maintenance therapy before admission	Irregular	Regular
Time from the start of mechanical ventilation to the initiation of ECMO, days	< 1	1
Duration of ECMO, days	5	3
Decannulation from ECMO during mechanical ventilation/spontaneous breathing	spontaneous breathing	MV
Viral infection (BAL examination upon admission):		
Adenovirus	Not found	Found
EBV	Found [D1]	Not found
HSV 1	Not found	Not found
HSV 2	Not found	Not found
Rhinovirus	Обнаружен	Not found
SARS-CoV-2	Not found	Found
Bacterial infection	Found	Not found
Airway compliance upon admission, ml/cm H_2O	10	14
Airway resistance upon admission, cm H_2O/L/s	12	18

Note. BA — bronchial asthma; BAL — bronchoalveolar lavage; HSV — Herpes simplex virus; EBV — Epstein Barr virus; MV — mechanical ventilation; ECMO — extracorporeal membrane oxygenation.

sistance — 8 cm H_2O/L/s. The ventilator FiO_2 was reduced to 30%, and after one day of running VV-ECMO, Foxy was reduced to 30%, SGF was reduced to 1 L/min, and weaning from VV-ECMO was initiated. On 08.04.2022, the patient was successfully disconnected from ECMO, the ventilator was turned off, and humidified oxygen was insufflated through a heat exchanger. On 10.04.2022, the trachea was decannulated.

The patient was discharged from the hospital 14 days after the initial asthma attack, of which 4 days were spent on ECMO and mechanical ventilation.

Discussion

In the presented cases, both patients had complaints of fever and dry cough, which are typical for acute respiratory disease. Microbiological analysis of BAL confirmed the presence of viral infections (rhinovirus, Epstein-Barr virus, adenovirus, SARS-CoV-2), which probably acted as triggers for BA exacerbation.

The initiation of VV-ECMO enabled stabilization of patients' condition and prevented the deterioration of ventilator-associated complications in patients with refractory status asthmaticus resistant to pharmacotherapy and mechanical ventilation. Both cases highlight the importance of considering early initiation of VV-ECMO in patients with refractory hypercapnia and ventilator-associated complications.

In the first case, mechanical ventilation was discontinued during the ongoing ECMO procedure due to the rapid clinical regression of bronchial obstruction syndrome in a patient with only lab signs of hypercapnia, which was compensated by extending VV-ECMO procedure. The second case of prolonged and resistant for 2 days to medical treatment status asthmaticus required prolonged mechanical ventilation and tracheostomy. Only after partial regression of the bronchial obstruction syndrome, improvement in gas exchange parameters and markers of the systemic inflammatory response, the drug-induced sedation, VV-ECMO and mechanical ventilation were discontinued 4 days after initiation.

Latest advances in BA management have reduced the mortality rate for BA to 6.5–10.3% [7]. The use of ECMO for refractory RF in patients with BA demonstrates positive results in terms of survival (85%) [17], minimizing ventilator induced lung injury and expanding diagnostic and treatment options [15]. T. McLellan et al. described 6 cases of ECMO use for life-threatening status asthmaticus, with positive clinical response on the 7th day [18].

Research by J. K. Zakrajshek et al. showed that VV-ECMO reduces mortality, but not the duration of ICU or hospital stay [14].

Conclusion

The presented experience with two clinical cases highlights the importance and prospects of considering VV-ECMO as a meaningful therapeutic modality for severe BA exacerbations with critical hypercapnia and RF. Implementation of VV-ECMO in practice requires further randomized trials to optimize indications and protocols.

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ECMO-Assisted Radiofrequency Ablation for Recurrent Ventricular Tachycardia: Case Series

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Summary

Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) has emerged as a viable modality for supporting circulation in patients with severe ventricular arrhythmia and high risk of acute hemodynamic instability during radiofrequency ablation (RFA) procedure.

Objectives: (a) To demonstrate the feasibility and effectiveness of VA-ECMO as a mechanical circulatory support during radiofrequency ablation in patients with sustained-recurrent ventricular tachyarrhythmia, which allows to achieve control of arrhythmia and improves survival in this high-risk cohort; (b) to determine the patient-selection criteria for VA-ECMO.

Case reports. We analyzed 5 cases of sustained-recurrent ventricular tachycardia in patients (all men, mean age 59 years) who were hospitalized in the intensive care unit. All patients had multiple episodes of ventricular tachycardia despite continuous conservative therapy. Four patients underwent radiofrequency ablation of the arrhythmogenic substrate with VA-ECMO support, resulting in complete elimination of tachyarrhythmia. The patients were successfully weaned from ECMO and subsequently discharged. In the fifth patient with left ventricular ejection fraction of 17–20% due to dilated cardiomyopathy the invasive procedure was excluded due to the terminal stage of heart failure, extremely high perioperative risk, and anticipated RFA failure. After patient's condition stabilized, he was referred to a tertiary center for orthotopic heart transplantation (OHT).

Results. All patients who underwent ECMO-assisted RFA achieved complete control of arrhythmia without recurrence during the entire follow-up period. Successful weaning from ECMO and discharge from the hospital confirmed the effectiveness of this strategy. One case demonstrated the limitations of the method, i. e. in a patient with terminal myocardial damage RFA was considered palliative.

Conclusion. ECMO support during ablation procedure allows the use of RFA in patients with severe structural myocardial pathology and high risk of hemodynamic instability. Scrupulous selection of patients with localized arrhythmogenic substrate and the potential for restoring myocardial function after RFA are the key components for procedural success.

Keywords: extracorporeal membrane oxygenation; recurrent ventricular tachycardia; electrical storm; radiofrequency ablation; mechanical circulatory support

Conflict of interest. The authors declare no conflict of interest.

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Introduction

Ventricular tachycardia (VT) remains one of the most dangerous forms of arrhythmia, associated with a high risk of sudden cardiac death [1].

According to modern registries, in patients with ischemic heart disease (IHD) and postinfarction cardiosclerosis, persistent VT develops in 5–10% of patients, while in patients with severe congestive heart failure (CHF) and reduced left ventricular ejection fraction (LVEF) reaches 20–25% [2].

Continuously recurring (resistant) VT — a term applied to clinical scenarios where sustained or recurrent VT does not respond to standard emergency therapy (adequate antiarrhythmic therapy, usually

including a β-blocker/amiodarone/lidocaine, and, if necessary, electrical cardioversion), is accompanied by frequent discharges from an implanted cardioverter-defibrillator, or continues despite optimal drug therapy and/or repeated attempts at defibrillation. An «electrical storm» is defined as ⩾3 separate episodes of sustained ventricular tachycardia/ventricular fibrillation within 24 hours, with episodes separated by an interval of at least 5 minutes and requiring either antitachycardia electrocardiostimulation, or electrical cardioversion/defibrillation. Electrical storms occur in 10–20% of patients with implanted devices (ICD/AICD), increasing 2–3-fold the risk of death during the first year [3–4].

Conservative therapy is used for newly diagnosed non-sustained/sustained VT, for potentially reversible causes (acute MI, electrolyte disturbances, drug interactions), and for treatable precipitating factors. Despite the widespread use of antiarrhythmic drugs, the recurrence rate of VT remains high. ICD is indicated for secondary prevention after an episode of VT/VF, as well as for primary prevention in patients with EF ⩽ 35% on optimal therapy. Radiofrequency ablation (RFA) has been considered one of the most effective treatments in recent years. RFA is recommended for recurrent symptomatic VT (despite conservative therapy) and for «electrical storm» [5–6].

Large studies have shown that RFA is successful in 70–85% of cases [2], but in severe structural myocardial pathology (scarring, aneurysms, cardiomyopathies, myocarditis, ventricular remodeling, valvular defects, congenital abnormalities), this procedure is associated with a high risk of acute hemodynamic instability, since such conditions are accompanied by a decrease in cardiac contractility, electrophysiological heterogeneity of myocardial tissue, and a reduced reserve for adaptation to stress [7].

The main feature of performing RFA in patients is the need to induce sustained VT for accurate mapping, which can lead to a sharp drop in cardiac output and collapse [8].

Two approaches are used for such patients:

— general anesthesia with preparation for potential defibrillation;

— general anesthesia with prophylactic use of mechanical circulatory support (MCS) devices: Impella, Tandem Heart, VA-ECMO, IABP.

One of the most accessible types of MCS is VA-ECMO, which allows systemic blood circulation to be maintained and ablation to be performed in patients at extremely high risk. The use of ECMO during RFA in high-risk patients reduces the likelihood of complications and increases the proportion of successful procedures [6].

The aim of this study was to evaluate the efficacy and safety of using VA-ECMO during RFA in patients with refractory ventricular tachyarrhythmia, as well as to determine the criteria for selecting patients for this procedure.

Materials and Methods

It was a retrospective analysis of five VA-ECMO-supported RFA procedures in patients with continuously recurring ventricular tachycardia (VT) who were hospitalized at the V. M. Buyanov City Clinical Hospital and the N. I. Pirogov City Clinical Hospital in 2024–2025.

Inclusion criteria:

— documented episodes of sustained or recurrent VT confirmed by ECG or implantable cardioverter-defibrillator (ICD/AICD) recordings;

— presence of heart failure symptoms of functional class II–IV (NYHA);

— repeated episodes of VT resistant to drug therapy;

— patient's consent to invasive intervention (RFA) or refusal due to high risk.

Preoperative examination. All patients underwent:

— CBC and biochemistry panel;

— echocardiography to assess ejection fraction (EF) and structural changes in the myocardium;

— 12-lead electrocardiography (ECG);

— analysis of data from implanted devices (ICD/AICD);

— CAG, if necessary.

Anesthesiological support: all procedures were performed under general anesthesia with hemodynamic monitoring (Harvard standard) of the patient: invasive blood pressure monitoring via a catheter in the right radial artery, recording of the heart rate, pulse oximetry, arterial blood gas composition and lactate, ventilation parameters, and capnography.

Use of ECMO: The following criteria were used as indication for «preventive» connection of VA-ECMO: presence of continuously recurrent VT resistant to antiarrhythmic therapy (AAT) with the need for prolonged induction of VT during RFA and/or «electrical storm» with unstable hemodynamics. Cannulas for the ECMO system were placed before the start of VT induction according to the standard protocol: the left common femoral vein and artery were used for this purpose in the absence of anatomical restrictions. The right common femoral vein was used as access for RFA electrodes. The distal end of the venous cannula was placed in the right atrium, and the arterial cannula was placed at the level of the common iliac artery.

ECMO was performed using a Henioss Deltastream device (Xenios AG, Germany) with a HILITE 7000 LT oxygenator (Medos, Germany), using BioLine «Maquet» cannulas (Getinge Group, Germany). Cardio-hemodynamic support was provided throughout the procedure, with gradual reduction of parameters intensity after completion of the ablation.

The patients' vital signs were monitored using a GE Carescape B650 monitor (GE HealthCare, USA). A Dräger Perseus A500 anesthesia and ventilation machine (Dräger, Germany) was used for anesthesia.

Electrophysiological study and RFA: the CARTO 3 three-dimensional navigation system (Biosense Webster, Johnson & Johnson, USA) was used for electro-anatomical mapping. The choice of system was based on the availability of equipment and the preferences of the operating electrophysiologist.

For electrophysiological diagnosis and reference rhythm monitoring, a decapolar diagnostic catheter was inserted into the coronary sinus. To speed up the mapping process, multi-electrode mapping catheters (PentaRay, Biosense Webster) were used.

Irrigated catheters with integrated contact force sensor — Thermocool SmartTouch (Biosense Webster) with a 3.5 mm distal electrode — were used as ablation catheters. The use of contact force measurement technology allowed to optimize the effectiveness and safety of ablation, which is especially important when it is necessary to minimize the duration of the procedure in patients at high risk of hemodynamic instability.

The main mapping method in this series was activation mapping performed during ongoing ventricular tachycardia. This strategy was chosen because of the unique opportunity provided by ECMO support — the ability to maintain effective blood circulation during hemodynamically unstable VT for a period of time sufficient to construct a detailed electro-anatomical map.

Unlike other techniques, activation mapping provides direct visualization of the reentry mechanism, allowing precise determination of the sequence of myocardial activation, identification of critical tachycardia cycle bridges, and targeted ablation with the ability to immediately assess its effectiveness in terminating the arrhythmia.

Transseptal access was used to insert electrodes into the left ventricle by puncturing the interatrial septum in the oval fossa area. Programmed ventricular pacing was performed according to a standard protocol to induce tachycardia. Systematic mapping of the right and left ventricles was performed by sequentially moving the ablation catheter along the endocardial surface during ventricular tachycardia, with an emphasis on areas corresponding to scar locations according to previous imaging methods or echocardiography.

In addition to identifying the critical zone (the area of earliest myocardial activation), an analysis of late diastolic potentials and fragmented electrograms was performed. The most valuable finding was the visualization of a relatively narrow isthmus — a conduction corridor between anatomical or functional barriers through which the critical part of the reentry cycle passes. Ablation of such an isthmus usually led to immediate termination of tachycardia.

The following immediate endpoints of radiofrequency ablation were analyzed: termination of ventricular tachycardia during ablation with transition to sinus rhythm or organized paced rhythm; elimination of all target electrograms (disappearance of isolated diastolic and late potentials in the ablation zones); loss of capture during stimulation with an output of 10 mA and a pulse duration of 2 ms in the ablated zones, indicating transmural damage.

A delayed efficacy assessment was performed 30 minutes after completion of ablation (this waiting period was necessary to exclude the transient effect of myocardial stunning). Repeat programmed ventricular pacing was performed using an aggressive protocol. The ultimate goal was complete non-inductibility of any sustained VT.

Endpoints:

— success of the procedure (no induced VT after RFA);

— absence of VT recurrence/ICD activation in the early and medium term (6–12 months);

— complications associated with RFA or ECMO (bleeding, vascular damage, stroke, infection);

— length of stay in the ICU, in the specialized department;

— in-hospital mortality.

The risk of hospital complications was assessed using two prognostic scale, the EuroSCORE II [9], which takes into account the severity of comorbidities, the severity of patient's clinical condition, and the likelihood of surgical complications, and the PAINESD scale [10].

Weaning from ECMO was implemented using the following technique:

1. Verifying conditions under which weaning is possible:

— Stable mean arterial pressure $\geqslant$60–65 mmHg with low/moderate doses of vasopressor and/or inotropic support;

— Lactate within reference values;

— Diuresis greater than 0.5 ml/kg per hour.

2. Fixation of basic parameters: ECMO performance (L/min), ECMO pump speed — (rpm), mean BP (mmHg), pulse BP (mmHg), lactate (mmol/L), pH, PaO_2 (mmHg), $PaCO_2$ (mmHg), PvO_2(mmHg), diuresis (mL/hour), echocardiography parameters (LVOT VTI, LVEF).

3. Flow decrease by 0.5 L/min (or equivalently, decrease RPM by a fixed number corresponding to ~0.5 L/min). After 60 min, re-measure parameters.

4. Subsequent flow reduction by 0.5 L/min every 30–60 min, with repeated assessment of parameters.

5. Final assessment at an ECMO flow rate of 1–1.5 L/min with targeted Echo-CG assessment. Conditions: LVEF > 20–25%, LVOT VTI > 10 cm, TAPSE > 10 cm.

Statistical data processing. Given the small sample size (n=5), the statistical analysis was mainly descriptive. Qualitative indicators were described as absolute values and percentages.

To assess the relationship between the duration of ECMO, the length of stay in the ICU and in the ward with the patient's age, the duration of surgery, and the time of mechanical support, a correlation analysis was performed with the calculation of Pearson's linear correlation coefficient (r). Differences were considered statistically significant at a significance level of $p < 0.05$.

Statistical data processing was performed using Microsoft Excel 2019 software and built-in functions for calculating correlation coefficients.

Ethical aspect. We obtained written consent from patients for the publication of case reports, as well as a

signed «Patient Informed Consent» form (Appendix No. 2, approved by Order of the Ministry of Health of the Russian Federation No. 1051n dated November 12, 2021).

Case reports

The characteristics and clinical data of the patients are presented in Tables 1–3 and Fig. 1.

Patients 1–4 had an extremely high risk of death associated with low LV ejection fraction (31–27%), age over 60 years, and the presence of electrical storm. Despite the high predicted mortality rates, RFA combined with VA-ECMO allowed for temporary stabilization of hemodynamics, effective mapping, and ablation of the arrhythmogenic substrate. This is consistent with current recommendations indicating the need for preventive mechanical support during RFA in patients at high risk of electrical myocardial instability [6].

Patient 5 had the most unfavorable prognosis: LVEF 17–20%, with use-dependence in antiarrhythmics (IV lidocaine 1.5 mg/kg/hour), indicating end-stage chronic heart failure with dilated cardiomyopathy (DCM) with diffuse post-infarction and fibrotic myocardial remodeling. In such cases, the arrhythmogenic substrate is often multifocal or diffuse, making radical ablation technically difficult or impossible, as it requires extensive myocardial involvement, associated with a high risk of procedural complications without a guarantee of long-term success [11, 12]. Although achieving temporary stabilization was possible in this case, RFA (even with ECMO) was considered a palliative measure that would not change the long-term prognosis. Given the extremely high EuroSCORE II and PAINESD scores (Table 1) and the presumed ineffectiveness of RFA, the procedure was declined and OHT was considered as the only radical treatment with a favorable long-term prognosis.

We performed a correlation analysis (Pearson's coefficient) between the duration of ECMO, the length of stay in the ICU/ward, and parameters such as patient age, duration of surgery, and duration of mechanical support (Tables 2, 3). There was no statistically significant correlation between patient's age and length of hospital stay ($p > 0.05$). There was a direct moderate correlation between the length of ICU stay and the total duration of the procedure ($r = 0.72$), and time of complete mechanical support during VT induction ($r = 0.736$). This suggests that the duration of recovery was defined primarily by the extent and complexity of the intervention, rather than by the patient's baseline characteristics.

The diagram shown in Fig. 2 clearly illustrates the key pathophysiological concept: the «electrical storm» is sustained by a vicious cycle in which arrhythmia exacerbates ischemia, and ischemia, in turn, provokes new arrhythmia. The hybrid treatment strategy (ECMO + RFA) effectively breaks this loop on two sides: RFA eliminates the electrophysiological cause (the source of the arrhythmia), and VA-ECMO eliminates the hemodynamic consequences (decreased cardiac output and coronary perfusion).

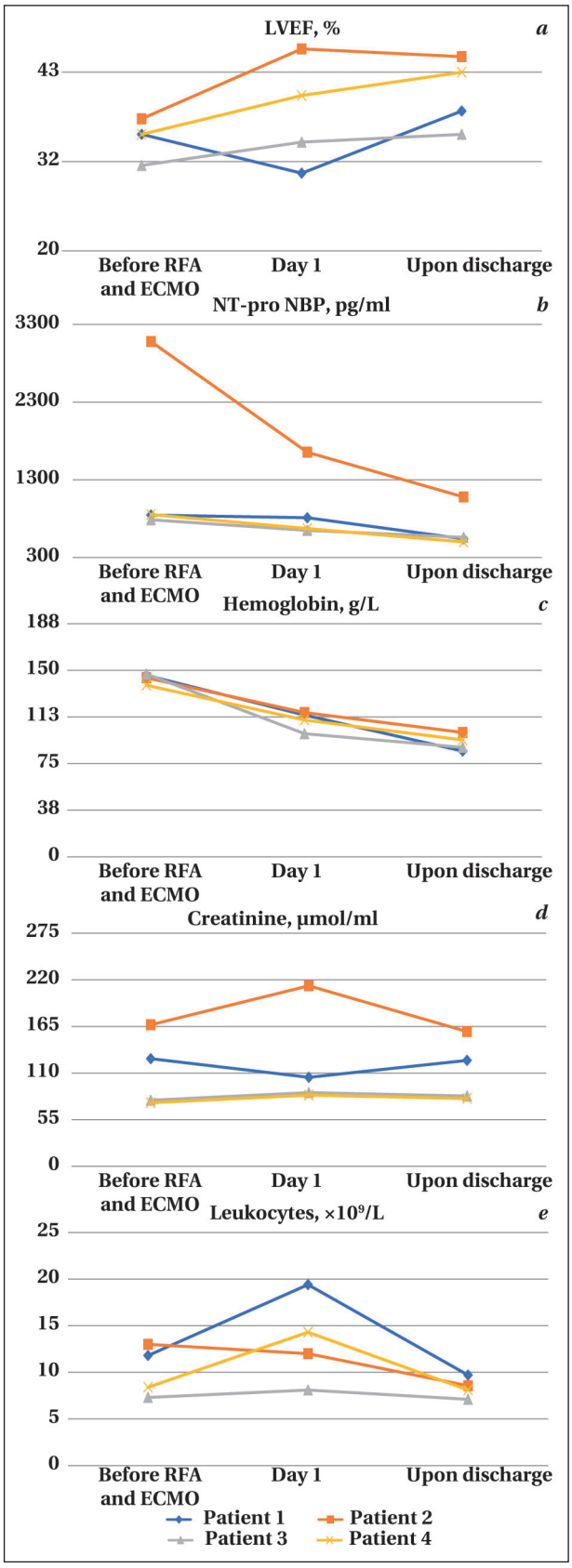

Fig. 1. Dynamics of key instrumental and laboratory parameters at the stages of analysis.

Table 1. Assessment of surgical and procedural risk.

Parameters	Parameter values in patients №1–5				
	1	2	3	4	5
Diagnosis	IHD: PICS. LV aneurysm. VSD closure with a prosthesis patch (BASEX-Pach); CABG to the LAD and PDA/PIVVA from 16.05.2024	AH III. Paroxys-mal VT	IHD, ischemic cardiomyopathy PICS (1999, 03.03.2025). RCA stenting. Multiple lesions of the coronary arteries	Idiopathic VT	IHD: PICS (of unknown duration). CAG and PCI: LAD stenting in 2016. Type 2 diabetes mellitus. Dilated cardiomyopathy
Age, years	62	71	64	36	63
LVEF (%)	35	37	31	35	17–20
ICD	Yes	Yes	Yes	No	No
VT type	ES	ES	ES	ES	ES
EUROSCORE II, score	17,35	15,6	8	1,09	14
PAINESD, score	14	14	20	5	26
RFA	Yes	Yes	Yes	Yes	Yes
ECMO	Yes	Yes	Yes	Yes	No
OHT	No	No	No	No	Yes

Note. PICS — post-infarction cardiosclerosis; LVEF — left ventricular ejection fraction, %; ICD — implantable cardioverter defibrillator; ES — electrical storm; RFA — radiofrequency ablation; ECMO — extracorporeal membrane oxygenation; OHT — orthotopic heart transplantation.

Table 2. Localization of the arrhythmogenic substrate and temporal parameters of the hybrid treatment procedure.

Parameters	Parameter values in patients №1–4			
	1	2	3	4
Localization	Posterior basal segment of the interventricular septum, along the border of the LV aneurysm (from the scar/patch to the mitral annulus)	Anterobasal part of the left ventricle outflow tract (LVS — the left ventricle summit)	Interventricular septum, LV aneurysm, and scar area	Interventricular septum
Duration of surgery, hours : minutes	3:20	4:00	3:04	3:10
Duration of VT induction,	2:20	3:00	2:00	2:00
full mechanical support,				
hours : minutes				
ECMO duration, hours	48	120	24	24

Table 3. Endpoints.

Parameters	Parameter values in patients №1–4			
	1	2	3	4
Induced VT after RFA	No	No	No	No
VT recurrence	No	No	No	No
Complications of RFA	No	No	No	No
Complications of ECMO	No	No	No	No
Length of stay in the ICU, days	7	7	3	5
Length of stay in the ward, days	5	8	5	4
Mortality	No	No	No	No

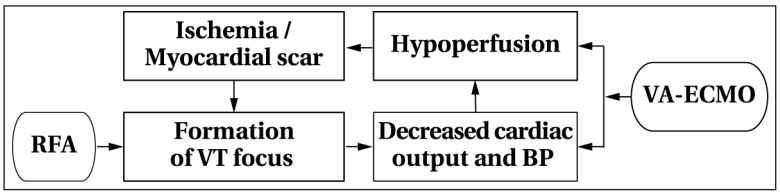

Fig. 2. Pathophysiological loop of «electrical storm» and ECMO and RFA application areas.

Discussion

The selection criteria for the ECMO-supported RFA strategy were:

- Refractoriness to drug therapy. All patients received amiodarone and lidocaine without lasting effect. In the fifth patient, discontinuation of lidocaine infusion immediately led to recurrence of VT, indicating that the drug had only a symptomatic effect.
- Preserved recovery potential: despite the severity of their condition, patients 1–4 showed no signs of multiple organ failure or irreversible neurological damage at the time of decision-making. In patient 5, the main limiting factor was the diffuse nature of myocardial damage and concurrent DCM with a severe decrease of contractile function (LVEF 17–20%), which indicated the terminal stage of CHF, where RFA would be a palliative measure, and the only radical solution would be OHT.

Comparative analysis: The case 5 serves as the «control» in this study. It demonstrates the limitations of hybrid procedure in patients with end-stage heart failure and diffuse myocardial damage: attempting radical ablation in the absence of a localized substrate is unpromising and may worsen the prognosis. This proves that the ECMO support for RFA procedure is not only life-saving but also pathogenetically substantiated, allowing the ES cause to be eliminated only in the presence of a potentially removable electrophysiological substrate.

The analysis demonstrates that the hybrid treatment strategy is a highly effective method of saving the lives of patients with refractory ventricular tachycardia, allowing arrhythmia control to be achieved in 100% of cases, where drug therapy proved ineffective. The results obtained are consistent with data from recent studies confirming that attempts to stabilize the condition of such patients using exclusively conservative methods are associated with extremely high mortality rates of 40–70% [13].

A key aspect of success is the potential of VA-ECMO to ensure stable hemodynamics and adequate organ perfusion, primarily the myocardium, during VT induction and prolonged mapping process. This facilitates accurate identification and subsequent successful ablation of the arrhythmogenic substrate, which was impossible in unstable patients in the era before the widespread use of mechanical circulatory support. As shown by the data presented, no recurrence of VT was recorded after the procedure in all four patients who underwent surgery, which directly corresponds to the conclusion of a large meta- analysis by J. Garg et al. on improved survival with the use of ECMO support during RFA [14].

However, as illustrated by case 5, the use of this tactic requires careful patient selection. High scores on the EuroSCORE II and PAINESD scales objectively reflect the extremely high perioperative risk in patients with end-stage heart failure secondary to dilated cardiomyopathy and serve as an important tool for making a well-considered decision [15].

It is critically important to assess not only the surgical risk, but also the possibility per se of eliminating arrhythmia through ablation. In DCM with total fibrosis and severely reduced EF, the success of RFA is unlikely. In such situations, when radical elimination of arrhythmia may not improve the prognosis of the underlying disease, the method of choice may be to consider OHT.

Hence, presented cases confirm the conclusions of recent international studies about the necessity of ECMO support programs in cardio-surgery hospitals for providing care to the most severely ill patients with life-threatening tachyarrhythmia [16].

Further prospective studies should focus on determining the optimal timeframe for initiating ECMO and developing precise algorithms for selecting patients for this high-tech care.

Conclusion

The presented series of clinical cases clearly illustrates that the combined use of VA-ECMO and radiofrequency ablation is a highly effective and safe strategy for managing patients with refractory «electrical storm» and hemodynamic instability. This approach not only stabilizes the patient's condition, but also allows for the radical elimination of the cause of life-threatening arrhythmia, which is impossible with drug therapy alone. The key to success is making a timely decision to use mechanical circulatory support before irreversible multiple organ dysfunction develops.

Avoiding RFA procedure in case 5 emphasizes the importance of an individual approach and the need to assess the prospects of ablation surgery in

the context of terminal heart failure, when arrhythmia is a manifestation of diffuse irreversible myocardial damage rather than a localized problem. In such cases, OHT may be considered as the method of choice.

The introduction of hybrid technologies (ECMO combined with RFA) requires close collaboration between cardiologists-arrhythmologists, cardiac surgeons, and specialists in extracorporeal support methods in a specialized hospital and should be based on strict selection criteria that take into account the pathophysiological nature of the arrhythmia and the operative and periprocedural risks.

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Phenothiazine-Related Critical Conditions: a Mini-Review

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Summary

Objective. The aim of this review is to summarize the pathological mechanisms associated with the toxicity of phenothiazines in overdose.

Materials and methods. A database search was conducted on PubMed, Google Scholar and eLibrary were used to identify original research articles, clinical reports, review articles, editorials, commentaries, and brief communications. Additional sources not identified through the search of these databases were analyzed after reviewing the reference lists of the selected articles. Articles were selected based on the relevance of the title and abstract to the purpose of this review.

Results. This review analyzes the mechanisms of action of phenothiazines in the context of their long-term clinical use and in overdose, as well as the mechanisms of action of proposed potential areas of application of phenothiazines. Clinical manifestations of phenothiazine poisoning are predominantly characterized by antagonism of dopamine D_1–D_4 receptors, histamine H_1 receptors, α_1–α_2 α-adrenergic receptors and muscarinic acetylcholine receptors M_1–M_2. In addition, phenothiazines are able to increase the permeability of the blood-brain barrier through apoptosis, increase global methylation, effectively enhance chemotherapy of some tumors and provide neuroprotection by reducing GFAP production (PKC-δ/NOX/MnSOD pathway).

Conclusions. Given the potential for new applications of phenothiazines, further study of the effects of phenothiazines on the central nervous system in overdose, with a focus on repeat overdose episodes, is important at the morphological level to identify the underlying morphological substrate. Further study of the mechanisms associated with phenothiazine use is needed to develop more effective therapeutic strategies to improve patient outcome, not only in psychiatry but also in other disciplines.

Keywords: phenothiazines; chlorpromazine; overdose; epigenetics; neuroprotection

Conflict of interest. The authors declare no conflict of interest.

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Introduction

Phenothiazines are used in psychiatry since their discovery in 1951 [1]. Chlorpromazine, a representative of phenothiazines, being the first antipsychotic drug, is widely used in the treatment of various mental illnesses, such as schizophrenia, manic episodes in bipolar affective disorder and various forms of psychosis. It has also found application in other areas of medicine, for example, for the treatment of migraines, nausea, hiccups, etc. The significance of the discovery of chlorpromazine for psychiatry is difficult to overestimate, so much so that, to this day, it remains the reference drug with which all antipsychotic drugs are compared [2].

Haloperidol, synthesized in 1958, became the new first-line neuroleptic due to its less pronounced sedative and more pronounced antipsychotic effect [3]. After the discovery of atypical antipsychotics, the prevalence of first-generation neuroleptics decreased significantly [4].

Despite this, phenothiazines have not been completely replaced by newer antipsychotic medications. They have been used for 74 years, and recent medical research has sparked renewed interest in the potential use of phenothiazines such as chlorpromazine in oncology and emergency care [3].

In all of the areas of medicine listed, patients are at increased risk of potential overdose, both intentional suicide and accidental, such as unintentional overdose due to cognitive impairment.

In 2021, 32,900 cases of drug- related poisoning were registered in the Russian Federation, of which 15,615 deaths were due to suicide [5, 6]. Although the global suicide rates are declining, intentional overdose remains a pressing problem, particularly among the younger segment of the population [7,8]. Worldwide, poisoning remains the most common form of suicide attempts, among which we observe the use of drugs, with psychopharmacological drugs making up the majority (up to 64.28%) [9, 10]. Most

of the drugs used in suicide attempts are those that have been prescribed to the patient, especially in the case of psychopharmacological drugs [11]. In addition, epigenetic factors, such as those responsible for the expression of the serotonin transporter, tryptophan hydroxylase 2 and brain-derived neurotrophic factor, may be one of the causes of suicidal behavior, which must be taken into account when prescribing phenothiazines, in particular, since they can affect gene expression [12]. Furthermore, patients eligible for the proposed expanded use options of phenothiazines, who have suffered ischemic stroke, or who are undergoing chemotherapy are more likely to experience an unintentional overdose of prescribed drugs [13].

Given the potential increase in phenothiazine prescriptions, as well as their existing use in psychiatry, the aim of this review is to analyze the mechanisms of phenothiazine toxicity in acute poisoning.

Materials and Methods

The PubMed, Google Scholar, and eLibrary databases were searched for original research articles, clinical reports, review articles, editorials, commentaries, and brief communications. The search was conducted using the keywords:

- (chlorpromazine) AND (overdose mechanism) OR (overdose)
- (chlorpromazine) AND (blood brain barrier)
- (chlorpromazine) AND (toxicity)
- (antipsychotic) OR (chlorpromazine) AND (epigenetics)
- (phenothiazines) AND (neuroprotection)
- (antipsychotic) AND (apoptosis)

Articles were selected based on the relevance of the title and abstract to the review topic. Additional materials not identified during the main database search were included after manually reviewing the reference lists of the selected articles. The most relevant information was selected. Sources were excluded if they were inappropriate for the review objective and were of low informative value.

Results

Mechanism of action of phenothiazines. The pharmacological properties of phenothiazines, in particular chlorpromazine, have been studied in sufficient detail. Metabolism occurs primarily in the liver (CYP3A4 substrate: CYP450 A12 and 2D6 enzymes) and kidneys. Excretion occurs with urine and bile. More than 40 metabolites have been identified, metabolized through several metabolic pathways, including hydroxylation, demethylation and sulfation, of which the most clinically significant are: Desmethylchlorpromazine, didemethylchlorpromazine, 7-hydroxychlorpromazine, 7-hydroxynorchlorpromazine, 7-hydroxynor-2-chlorpromazine [14]. Being first-generation antipsychotic drugs, phenothiazines exert their neuroleptic effect through antagonism of dopamine receptors, acting on D_1–D_4 receptors, with the most pronounced antagonism being to D_2 receptors. Phenothiazines are also antagonists of histamine (H_1), α -adrenergic (α_1, α_2) and muscarinic acetylcholine (M_1, M_2) receptors, as well as serotonin (5-HT_2, 5- HT_6, and 5-HT_7) receptor antagonists *in vitro*, although the serotonergic effect is not observed *in vivo*, since phenothiazine metabolites do not have serotonergic activity [15, 16]. The brain structures most affected by phenothiazine metabolites are the reticular formation, limbic system, hypothalamus and basal ganglia [17].

Phenothiazine metabolites readily cross the blood-brain barrier (BBB), whereas the parent drug does not, which may be the reason for the aforementioned difference in serotonin antagonism in *in vitro* and *in vivo*. Studies have also shown that high therapeutic doses of phenothiazines increase BBB permeability by increasing the activity of caspases-3, -8, -9, as well as fragmentation and condensation of chromatin in endothelial nuclei, which are signs of apoptosis [18].

In recent studies, antipsychotic drugs have demonstrated epigenetic activity through hypermethylation. In an experimental study by Swathy et al., antipsychotic drugs showed an increase in the expression of genes encoding DNA methyltransferases (by decreasing the expression of microRNAs targeting DNA methyltransferases), methyl-CpG-binding proteins, and TET-methylcytosine dioxygenases [19].

Toxicology. Phenothiazines, being typical first-generation antipsychotics, have a relatively higher association with adverse effect, when compared to second generation neuroleptics. Common side effects include orthostatic hypotension, extrapyramidal disturbances (but less common than with other first-generation antipsychotics), excessive sedation, and ophthalmological complications. Adverse effects with long-term use most often include hepatotoxicity, acute cholestatic liver injury, increased risk of seizures, and corneal damage [20, 21].

The toxic effects of phenothiazines are considered primarily as an extension of their pharmacological activity. The primary mechanism of action of phenothiazines is through antagonism of D_2 receptors in the reticular formation, limbic system, and hypothalamus, which is likely the cause of side effects such as extrapyramidal symptoms and hyperprolactinemia [17]. Phenothiazines have also been shown to inhibit vasomotor reflexes, suppress the secretion of prolactin-releasing inhibitory hormone (PRIH), and reduce the secretion of corticotropin-regulating hormone (CRH), and significant prolongation of the QTc interval [22].

Phenothiazines are characterized by an overlap between therapeutic and toxic doses. The toxic concentration of chlorpromazine in the blood ranges

from 0.5 to 2 μg/ml. The LD50 for rats is 210 mg kg^{-1} for oral administration. The potentially lethal dose of chlorpromazine (3000 mg) is ten times the average daily dose (300 mg); however, the maximum daily dose can reach 2000 mg [23, 24].

Clinical manifestations of acute phenothiazine intoxication, especially in cases of overdose, include severe extrapyramidal reactions, hypotension, and sedation. In the late stages of intoxication, CNS stimulation and seizures are often observed, followed by respiratory and/or CNS depression, as well as cardiovascular conduction disturbances, arrhythmias, anticholinergic effects, impaired body temperature regulation, vomiting, difficulty breathing, pulmonary edema, and coma. Treatment of phenothiazine intoxication consists of symptomatic therapy [23]. Currently, there is no specific antidote for phenothiazine overdose. Regarding extrapyramidal side effects anti-Parkinson's drugs are effective in mitigating adverse effects. Also, S. Naeem et al. [25], in their study using chlorpromazine to model Parkinson's disease-associated cell death in rats, showed that diclofenac exerted a neuroprotective effect, with significant improvement in motor control in treated rats compared to controls.

Discoveries in recent years have renewed interest in the study of the biological aspects of psychiatric disorders. In recent years, the volume of information on morphological, epigenetic, and immunohistochemical studies of psychiatric diseases, particularly suicides, has increased. These studies have revealed morphological changes in microglia, astrocytes, and oligodendrocytes of the central nervous system, as well as in the blood-brain barrier [26].

An important role in understanding the mechanisms of exposure to phenothiazines belongs to the study of autopsy material, which showed a correlation between the occurrence of suicidal behavior and the content of cytokines: IL-4, IL-10, IL-13, TNF-α [12, 27, 28]. S. G. Torres-Platas et al., in their study showed that fibrous astrocytes in the white matter of the anterior cingulate cortex in individuals who died from completed suicide with a history of depressive disorders were twice as large and had 50–60% more branches, compared with controls. Also, studies have shown that in the dorsal part of the anterior cingulate cortex, in completed suicide, there is a significant increase in the ratio of amoeboid to branched microglia, as well as, blood vessels surrounded by macrophages are detected more than twice as often compared to controls. This is accompanied by an increase in the expression of IBA1 and MCP-1 genes and an increase in mRNA and CD45 [29–31]. In the amygdala, a decrease in the density of oligodendrocytes is observed [32]. M. J. Chandley et al. showed that, in oligodendrocytes of the occipital cortex of the cerebral hemispheres and the brainstem, in the context of completed suicide, signs of oxidative stress (decreased expression of SOD1, SOD2, GPX1, and a significant increase in the expression of AGPS) can be observed [33].

It should be noted that signs of oxidative damage to the central nervous system are also observed in cases of phenothiazine poisoning. With prolonged therapeutic use of chlorpromazine, the activity of copper- and manganese-containing superoxide dismutase (SOD), which have a pronounced antioxidant function, decreases, but the concentration of malondialdehyde (MDA) increases, indicating lipid peroxidation [34].

Phenothiazine poisoning is also characterized by organ dysfunction, such as: prolongation of the QT period; ventricular arrhythmias, in particular ventricular tachycardia, which can lead to fibrillation; hypothalamic thermoregulation disorder, mainly in the form of hyperthermia, however, hypothermia is possible; neuroleptic malignant syndrome. In autopsies, agranulocytosis, drug-induced lupus syndrome, rhabdomyolysis, necrotic damage to hepatocytes, myocardial lipomatosis are observed [20, 24, 35].

Use of phenothiazines in other diseases. A statistically significant correlation has been observed indicating that patients with schizophrenia have a lower incidence of certain types of cancer compared to the general population [36]. This difference was long thought to be genetic in nature, but more recent studies have shown a high probability that the cause is related to the use of first-generation antipsychotic drugs in the treatment of schizophrenia.

Studies have identified apoptosis and cytotoxicity as the primary mechanisms by which first-generation antipsychotics, particularly phenothiazines, can influence tumor growth. First-generation antipsychotics have also been shown to modulate the effectiveness of cancer treatments through various mechanisms, including increasing BBB permeability, modulating cellular signaling pathways such as PI3K/Akt/GSK-3β, STAT 3, improving the accumulation of chemotherapeutic drugs in the body, and increasing cell susceptibility to chemotherapy through inhibition of P-gp pumps [37–39].

Another potential application of phenothiazines that has attracted attention in recent years is that phenothiazines, particularly chlorpromazine, have demonstrated neuroprotective effects in ischemic stroke. In their study, H.-J. Li et al., showed that administration of chlorpromazine to rats before induction of middle cerebral artery occlusion reduced infarction size by 20.1% [40]. The proposed mechanism of action was activation of BKCa channels, compared to a reduction of neuroprotective activity with administration of chlorpromazine with a blockade of BKCa channels. Recent studies have shown the efficacy of combined treatment of ischemic stroke using chlorpromazine and promethazine, which have been shown to reduce oxidative stress associated

with the production of reactive oxygen species NADPH via the PKC-δ/NOX/MnSOD pathway [41–43].

Antimicrobial, antiviral, antiprotozoal, antifungal and antiprion activities of phenothiazines have also been reported [38].

Conclusion

Thus, in recent years, there has been increased interest in studying the effects of phenothiazine drugs. Epigenetic factors responsible for the expression of the serotonin transporter, tryptophan hydroxylase 2, and brain-derived neurotrophic factor may be a cause of suicidal behavior. These findings are important for further research.

Given that, patients receiving phenothiazines are at higher risk of poisoning, studies of the direct effects of repeated acute phenothiazine poisoning caused by overdose, both intentional and unintentional, are of particular interest. Although the clinical manifestations of phenothiazine poisoning are well documented, modern morphological and immunohistochemical studies of acute phenothiazine intoxication are scarce.

Given the potential for new applications for phenothiazines, further study of the direct effects of phenothiazines on the central nervous system in overdosing, with a focus on repeated overdose-linked events, is important for identifying the morphological substrate of phenothiazine poisoning. Furthermore, phenothiazines increase global methylation, while suicidal behavior is potentially associated with increased methylation in specific DNA regions, which may serve as a differentiating factor in the study of suicide causes. Research focused on the development of new approaches for treating phenothiazine poisoning, as well as their possible neuroprotective properties in ischemic stroke, offer potential for the field of intensive care. The aforementioned ability of phenothiazines to enhance the effectiveness of cancer treatment offers significant potential for clinical application, not only for symptomatic treatment, but also for mitigating the side effects of chemotherapy for patients with malignant tumors.

Renewed interest in expanding the use of this pharmacological group should lead to further study of the mechanisms associated with the use of phenothiazines, with the aim of developing more effective therapeutic strategies and improving patient outcomes not only in psychiatry but also in other diseases.

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Указатель авторов и статей, опубликованных в журнале «Общая реаниматология» за 2025 год*

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