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Пневмомедиастинум: новый взгляд на старую проблему в условиях пандемии COVID-19

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Summary

The aim of the study was to identify the risk factors of spontaneous pneumomediastinum and to determine its management strategy in patients with the novel coronavirus infection.

Material and methods. Eighteen patients with spontaneous pneumomediastinum (SPM) hospitalized in the Center for Novel Coronavirus Infection of the Mechnikov Northwestern State Medical University from 2020 to 2021 were examined. The control group consisted of 18 persons selected using matched sampling. We analyzed symptoms, medical and life history, comorbidities, physical examination results, laboratory and instrumental data, and disease management of patients in both groups

Results. The groups were comparable by age and sex. Among all patients hospitalized with the novel coronavirus infection, spontaneous pneumomediastinum was registered in 1.3% (n=18). Analysis of symptoms, medical and life history, comorbidities, physical examination results, laboratory and instrumental data and disease management did not reveal significant differences between the groups. At the same time, the proportion of obese patients in the main group was lower than in the control group. Estimation of HR showed that the risk of spontaneous pneumomediastinum development was significantly lower in obesity (HR=0.14; 95% CI: 0.033–0.63, P=0.010).

Conclusion. The risk of spontaneous pneumomediastinum is significantly lower in obese patients.

Keywords: COVID-19; novel coronavirus infection; spontaneous pneumomediastinum; mediastinal emphysema; obesity

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

The full text version of the paper is available at www.reanimatology.com

Introduction

Since May 2020, the Peter the Great Clinic of the I. I. Mechnikov Northwestern State Medical University has been reassigned to the Covid Center to treat patients with the novel coronavirus infection. During this time, 1,366 patients were hospitalized, including 287 in the ICU. Mortality in the clinic was 9.3%, while in the ICU it reached 44.6%, which indicates the high relevance of identifying predictors of adverse outcomes.

During analysis of fatal outcomes, spontaneous pneumomediastinum (SPM), an uncommon manifestation of spontaneous lung barotrauma in clinical practice, came to our attention.

Pneumomediastinum, or mediastinal emphysema, is a condition in which air is present in the mediastinal tissue [1]. Previously, spontaneous mediastinal emphysema was considered to be a rare stand-alone disease characterized by a benign course and occurring without any particular cause, mainly in young men [2–5]. The first description of SPM was made by Rene Laennec in 1819 in his treatise «De l'auscultation médiate» [6]. Louis Hamman was the first to report SPM as a separate enti-

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ty [7–11], which was later named Hamman syndrome. The first case report of SPM in COVID-19 appeared as early as in the first half of 2020 [12–16]. Most authors identified McLean's phenomenon (increased intrathoracic pressure due to persistent cough combined with decreased pressure in the perialveolar interstitial space) as an essential element of SPM pathogenesis [17]. However, in the last year, more and more frequent clinical case observations of SPM developing in COVID-19 can be found in the literature, where the risk factors included exacerbation of bronchial asthma and chronic obstructive pulmonary disease (COPD) and the use of steroids, which can promote pulmonary interstitial damage, leading to alveolar gas leakage [18]. All authors emphasize the severe course of COVID-19 associated with SPM and accompanied by higher rates of tracheal intubation and mortality [19, 20].

However, whether SPM should be considered a spontaneous or secondary to COVID-19 complication is still unclear, as is the management of such patients [21].

Material and Methods

All cases of SPM in patients with novel coronavirus infection hospitalized at the I. I. Mechnikov University Covid Center from 05.05.2020 to 01.06.2020, from 05.11.2020 to 01.02.2021, and from 01.07.2021 to 27.07.2021 were analyzed. A total of 18 cases of SPM were documented in the patients who comprised the main group. The control group also included 18 patients selected by the matching pair technique (matched by sex, age, and severity of lung involvement).

Patients in both groups were comparable by sex, age, and severity of lung involvement (Table 1).

The mean BMI in the main group was 26 [24; 29] kg/m^2, which was significantly lower than in the control group, where it was 33 [28; 37] kg/m^2 (P=0.0028).

All patients underwent chest CT scan on admission to the hospital. The severity (volume, area, extent) of lung involvement was assessed using an empirical visual semiquantitative scale, considering the approximate volume of lesions in both lungs [22]:

— no typical manifestations was considered as CT-0;

— minimal involvement < 25% of lung volume, CT-1;

— moderate involvement of 25–50% of lung volume, CT-2;

— significant involvement of 50–75% of lung volume, CT-3;

— subtotal involvement > 75% of lung volume, CT-4.

Verification of pneumomediastinum was performed using CT imaging.

Serila pulse oximetry was performed in all patients, starting from admission. If the signs of acute respiratory failure (ARF) and SpO_2 less than 90% were found, an additional arterial blood gases test with measurement of PaO_2, $PaCO_2$ was performed.

The routine clinical examination included complete blood test, urinalysis, measurement of serum C-reactive protein (CRP), AST, ALT, creatinine, urea, glucose, total protein, ferritin, troponin, D-dimer, as well as coagulation test and ECG.

The efficacy of therapy was evaluated by outcomes (recovery or lethal), as well as by documented adverse events associated with the treatment.

The data were analyzed using the Statistica 12 for Windows software package with the assessment of data distribution normality (Shapiro–Wilk's test), calculation of mean values, mean square deviation, medians, lower and upper quartiles, maximum and minimum values. Pearson's χ^2 test was used to examine correlation between qualitative variables; in case of violation of expected frequencies assumption (presence of at least one value less than 10 in 2×2 tables and more than 25% of such values in multifield tables), Fisher's exact test (FAT) was used. The 95% confidence intervals (95% CI) for qualitative characteristics were calculated by Wilson method. Quantitative indices with a normal distribution were ex-

Table 1. Patient characteristics and laboratory data at the time of hospitalization (*Me* [*Q1*; *Q3*]).

Parameter	Values in groups		*P*-value
	Main	Control	
Age, years	73 [67; 78]	72 [63; 81]	0.94
BMI, kg/m^2	26 [24; 29]	33 [28; 37]	0.0028
CT, day from disease onset	8 [4; 9]	9 [6; 10]	0.31
CT % of right lung involvement	35 [15; 68]	57 [32; 78]	0.056
CT % of left lung involvement	33 [11; 66]	63 [41; 78]	0.025
SpO_2, %	94 [91; 95]	85 [76; 89]	< 0.001
Hospitalization, day from disease onset	7 [5; 9]	9 [6; 10]	0.15
Duration of fever, from disease onset	7 [5; 8]	7 [6; 9]	0.28
Transfer to the ICU, days from disease onset	10 [7; 15]	10 [4; 12]	0.59
Hemoglobin, g/l	125 [105; 142]	129 [118; 143]	0.38
Leucocyte count, ×10^9/l	6.0 [4.7; 7.8]	6.6 [6.1; 8.4]	0.48
Neutrophil count, ×10^9/l	4.7 [3.5; 7.8]	4.9 [2.6; 7.1]	0.70
Lymphocyte count, ×10^9/l	0.8 [0.5; 1.0]	0.8 [0.4; 1.1]	0.76
C-reactive protein, mg/l	54 [29; 97]	124 [46; 159]	0.21
D-dimer, μg/ml	0.53 [0.29; 0.88]	0.53 [0.33; 2.73]	0.75

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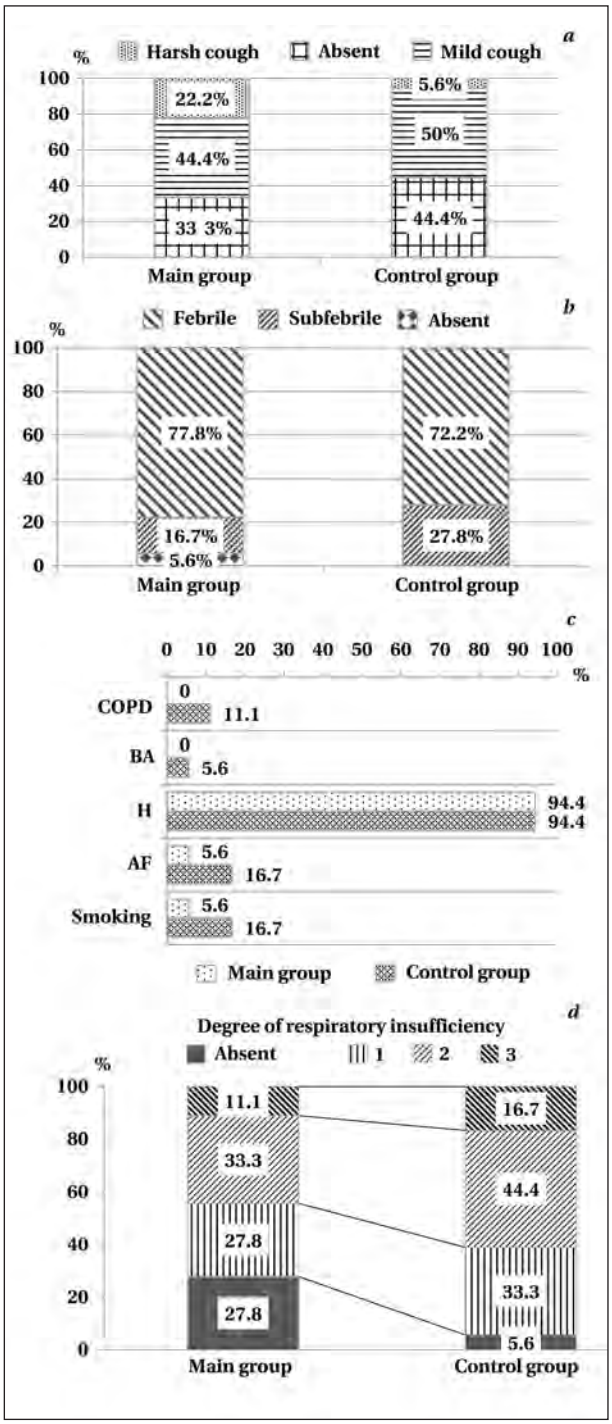

Fig. 1. Patient distribution by presence and severity of cough (*a*) and fever (*b*), by frequency of selected comorbidity signs and history of tobacco smoking (*c*), and by degree of respiratory insufficiency (*d*) on admission.
Note. COPD — chronic obstructive pulmonary disease; BA — bronchial asthma; H — hypertension; AF — atrial fibrillation.

pressed as $M \pm \sigma$, where M is the mean value and σ is the standard deviation. The Student's test was used for their comparison in 2 independent groups. Variables with non-normal distributions were reported as *Me* [*Q1*; *Q3*], where Me was the median, *Q1* and *Q3* were the lower and upper quartiles of the distribution. Mann-Whitney test was used to compare the variables in 2 independent groups. The *P*-value < 0.05 was used as a threshold for significance. Odds ratios (ORs) at 95% confidence interval were used to assess the risk of pneumomediastinum development.

Table 2. Lung tissue involvement in the main group on the day of SPM diagnosis.

Parameter	Patients, *n* (%)	95% CI
CT grade 2	2 (11.1)	3.1–32.8
CT grade 3	5 (27.8)	12.5–50.9
CT grade 4	11 (61.1)	38.6–79.7
Pleural effusion	6 (33.3)	16.3–56.3

Results

When evaluating the symptoms, persistent cough was observed in 4 (22.2%) patients in the main group and in 1 (5.6%) in the control group, the differences between the groups were not significant (Fig. 1, *a*).

The majority of patients in both groups had febrile fever: 14 (77.8%) in the main group, and 13 (72.2%) in the control group, *P*>0.05 (Fig. 1, *b*).

No differences were found between the groups in the timing of hospitalization and duration of fever before admission (Table 1).

There were also no differences in the frequency of selected comorbidity signs and history of tobacco smoking in the groups (Fig. 1, *c*).

History of surgical interventions requiring mechanical ventilation was recorded in 7 patients (38.9%) in the main group and in 3 patients (16.7%) in the control group (*P*=0.14).

No significant differences between the groups were found in severity of respiratory failure (Fig. 1d), but SpO_2 values differed with Me reaching 94 [91; 95] in the main group and 85 [76; 89] in the control group (*P*<0.001).

Comparison of laboratory parameters at the time of admission showed no significant differences between the groups (Table 1).

During hospitalization, all patients were started on a treatment in accordance with the current guidelines of the Russian Ministry of Health, including oxygen therapy through nasal cannulas with a flow rate of up to 10 l/min.

Later, with increasing severity of the condition, the patients underwent control chest CT scan, and 18 of them were found to have SPM (Table 2).

The severity of their disease required transfer to ICU and initiation of different types of respiratory support. There was no significant association between the day of initiation of respiratory support, its duration and the occurrence of SPM (Table 3). However, the obtained data indicate a tendency to a more severe disease in patients of the control group.

The types and parameters of respiratory support in the SPM group are shown in Table 4.

Table 3. Timing of initiation and duration of respiratory support from the moment of hospitalization ($M\pm\sigma$).

Parameter	Values in groups		*P*-value
	Main	Control	
High-flow oxygenation, days from the disease onset	13±7	11±3	0.51
Duration of high-flow oxygenation, days	6±4	3±2	0.16
Noninvasive lung ventilation, days from disease onset	19±11	14±5	0.095
Duration of noninvasive ventilation, days	3±3	4±3	0.72
Mechanical ventilation, days from disease onset	22±9	17±6	0.083

Table 4. Respiratory support in the SPM group.

Variable	Value	
Type	**Patients, *n* (%)**	**95% CI**
Nasal cannula oxygenation	4 (22.2)	9.0-45.2
High-flow oxygenation	1 (5.6)	1.0-25.8
Noninvasive lung ventilation	4 (22.2)	9.0-45.2
Mechanical ventilation PCV	4 (22.2)	9.0-45.2
Mechanical ventilation PCV+	5 (27.8)	12.5-50.9
Parameter	$M\pm\sigma$	
PIP, mbar	16±3	
PEEP, mbar	10±2	
FiO_2, %	86±21	
P/F, mm Hg	110±74	
C_{stat}, ml/mbar	33±12	
Flow, l/min	20±2	
SpO_2, %	92±10	
PO_2, mm Hg	82±61	
PCO_2, mm Hg	40±17	

Table 5. Laboratory values of patients at the time of development of SPM.

Parameter	Me [Q1; Q3]
Hemoglobin, g/l	109 [91; 133]
Hematocrit	0.330 [0.280; 0.402]
Leucocyte count, $\times10^9$/l	11.3 [9.5; 13.0]
Neutrophil count, $\times10^9$/l	10.0 [7.4; 12.0]
Lymphocyte count, $\times10^9$/l	0.5 [0.3; 1.1]
Platelet count, $\times10^9$/l	226 [162; 282]
Total protein, g/l	54 [50; 63]
Serum albumin, g/l	29 [26; 32]
LDH, U/L	543 [468; 772]
ALT, U/L	33 [25; 53]
AST, U/L	33 [19; 42]
Total bilirubin, mmol/l	10 [8; 15]
C-reactive protein, mg/l	77 [10; 182]
Ferritin, µg/l	994 [299; 1 803]
Procalcitonin, ng/ml	0.399 [0.124; 1.840]
D-dimer, µg/l	1.79 [0.79; 7.50]
IL-6, pg/ml	534 [160; 769]

Laboratory values of patients at the time of SPM development are summarized in Table 5.

No significant association was found between the occurrence of SPM and duration of systemic steroid use or timing of administration of such drugs as JAK1/JAK2 inhibitors or anti-IL-6 monoclonal antibodies (Table 6).

When analyzing the clinical variants of spontaneous lung barotrauma, we found that subcutaneous emphysema was present in 5 (27.8%) patients, whereas in 1 (5.6%) patient it was associated with a pneumothorax and in another 1 (5.6%) with a tension pneumothorax. Isolated SMP was revealed in 10 (55.5%) patients. All patients with SPM underwent diagnostic bronchoscopy, which revealed no visible defects of trachea and bronchi (Fig. 2).

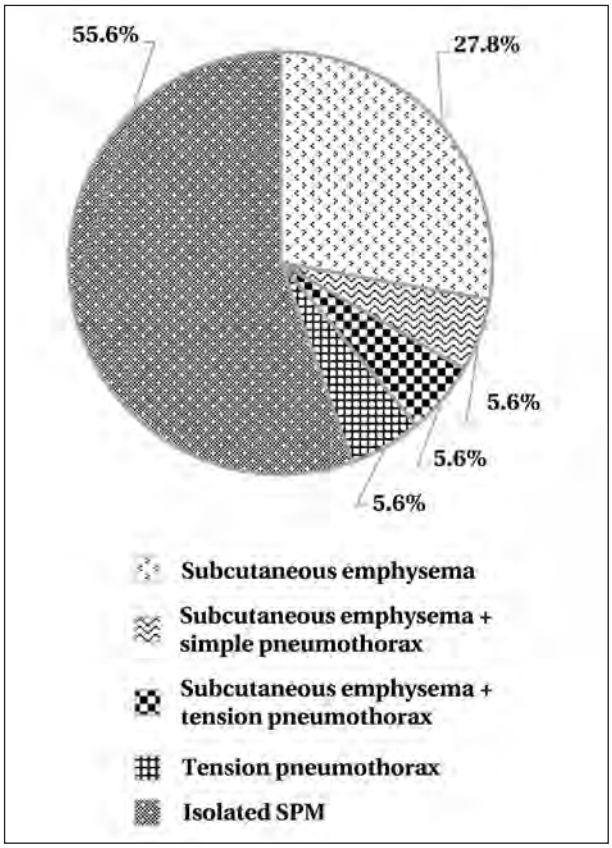

Fig. 2. Types of spontaneous pulmonary barotrauma.

Lethal outcome in the SPM group occurred in 16 (88.9%) patients, on average on day 26±10 of hospitalization (Table 7).

When determining the risks of SPM development, obese patients were found to have a signifi-

Table 6. Analysis of relationship between SPM development and timing and duration of pathogenetic therapy (*Me* [*Q1*; *Q3*]).

Parameter	Values in groups		*P*-value
	Main	Control	
Duration of steroid use, days	10 [5; 12]	8 [6; 10]	0.38
Baricitinib, day from disease onset	8 [6; 10]	13	
Tocilizumab, day from disease onset	11 [10; 15]	11 [10; 15]	0.44

Table 7. Timing of outcomes among patie (*M*±*σ*).

Parameter	Values in groups		*P*-value
	Main	Control	
Lethal outcome, day of disease	20±7	26±10	0.074
Discharge, day of disease	25±1	32±11	0.48

Table 8: Risk assessment of SPM development in patients with/without obesity.

Parameter	Odds ratio [95% CI]	*P*-value
No obesity (reference)	1	
Obesity	0.14 (0.033–0.63)	0.010

cantly lower likelihood of SPM development (OR=0.14; 95% CI: 0.033–0.63, *P*=0.01) versus the patients with normal body weight.

Discussion

Thus, the issue of factors influencing the occurrence of SPM is relevant and still controversial, which requires more detailed studying. The scope of studies in this area is still limited, which is due to the low incidence of SPM in patients with the novel coronavirus infection. In our study, it was 1.3%, with a mortality rate of 88.9%, which is comparable with the available data [23].

Interestingly, the proportion of obese patients in the main group was lower, while the subsequent estimation of OR showed that in obesity the risk of developing SPM was statistically significantly lower. According to Rodriguez-Arciniega T. G. et al. [24], the mean BMI value was slightly lower in SPM group (28 versus 29.5 kg/m^2), but no significant differences compared to the control group were observed. It is worth noting that the authors found SPM only in 9 out of 271 patients.

In an attempt to explain the results obtained, obesity was considered to be an unfavorable predictor for any respiratory complications [25, 26], but on the other hand, the fact that low nutritional status is critical in COPD, especially its emphysema phenotype, shoul not be underestimated. The emphysema phenotype is well known to be associated with a decreased nutritional status [25, 27, 28]. In addition, there is evidence of an inverse relationship between adipose tissue mass and the emphysema progression [29–31]. These data could partially explain the results of our study and can serve as a basis for further research to identify risk factors of SPM in patients with the novel coronavirus infection involving larger number of participants.

Conclusion

The risk of spontaneous pneumomediastinum is significantly lower in obese patients.

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Synthetic Analogue of Leu-Enkephalin in COVID-19 (a Prospective Clinical Study)

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Синтетический аналог лей-энкефалина при COVID-19 (проспективное клиническое исследование)

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Summary

One of the main problems facing intensivists when treating patients with COVID-19 is severe and critical acute respiratory distress syndrome (ARDS) with the underlying viral pneumonia. The current guidelines of the Russian Ministry of Health (Version 15 of 22.02.22) do not include drugs with a lung protective effect. This issue could be solved by administration of a synthetic analogue of leu-enkephalin.

Aim. Study the efficacy of a synthetic analogue of leu-enkephalin in ARDS in patients with COVID-19.

Materials and methods. The study included 35 patients divided into 2 groups. Group 1 (main) patients (*n*=15) in addition to standard therapy received a continuous infusion of synthetic analogue of leu-enkephalin at a rate of 5 **μ**g/kg/hour for 5 days. Patients from group 2 (control, *n*=20) were treated according to the Temporary Guidelines of the Ministry of Health (V.15), but without the synthetic analogue of leu-enkephalin. The radiological data, frequency, severity and evolution of respiratory complications, changes in P/F (PaO_2/FiO_2) ratio, as well as changes in the scores of prognostic APACHE II, SOFA, and NEWS scales were evaluated.

Results. In patients taking the studied drug, the percentage of lung damage did not change with the median (IQR) of 0 [–8; 0], while in the control group it increased by approximately 10% with the median (IQR) of +10,0 [+2; +20] (*P*=0.001). The proportion of patients in group 1 with positive disease evolution within 5–9 days after treatment initiation was significantly higher and reached 46.7 [24.8; 69.9]%, whereas in group 2 it was 15.0 [5.2; 36.0]% (*P*=0.04). Also, in group 1, starting from day 4, the median P/F ratio was significantly higher

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than in group 2 reaching 220 [185;245] versus 127 [111;158], respectively (P=0.014). The need for non-invasive lung ventilation in group 1 on day 7 averaged 6.7%, while in group 2 it was as high as 45.0%, which was significantly higher than in the main group (P=0.013).

Conclusions. The use of synthetic analogue of leu-enkephalin according to the specified regimen had a significant impact on the main parameters of the viral pneumonia severity. The results serve as a rationale for the development of a novel effective treatment strategy to supplement the current standard COVID-19 management.

Keywords: COVID-19; pneumonia; ARDS; dalargin; lung protection; intensive care

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Introduction

The coronavirus disease 2019 (COVID-19) is a respiratory infection caused by the SARS-CoV-2 virus. It is generally recognized that the SARS-CoV-2-induced increase in cytokines, often manifested as a «cytokine storm» is associated with worsening of COVID-19 patients [1]. The course of COVID-19 can rapidly deteriorate if complicated by life-threatening pneumonia and acute respiratory distress syndrome (ARDS) [2].

More than 30 years ago, the clinical use of dalargin, a synthetic analogue of leu-enkephalin with delta-opioid activity, began. Early studies revealed the cardioprotective properties in patients operated under cardiopulmonary bypass [3]. Further studies demonstrated lung-protective effects of the drug [4]. Besides, several studies demonstrated reduced frequency of infectious complications [5,6]. However, the mechanism of organoprotective properties of dalargin remained unclear until recently. In 2018, an experimental study demonstrated the protective effect of dalargin in endothelium exposed to the septic shock serum [7], while a recent *in vitro* study revealed a dose-dependent anti-inflammatory effect of a synthetic analogue of leu-enkephalin due to its action on neutrophils activated by bacterial components (lipopolysaccharide and formyl peptide) [8].

Recent *in vivo* studies, in which a synthetic analogue of leu-enkephalin possessed anti-inflammatory effects and reduced mortality in an acute respiratory distress syndrome model in mice, proved particularly interesting [9,10].

Our clinical research was based on the following hypothesis: dalargin efficacy with respect to the rate of clinical symptom resolution in moderate to severe acute respiratory distress syndrome resulting from the novel coronavirus infection SARS-CoV-2 is superior to those of standard treatment recommended by the current Temporary Guidelines of Russian Ministry of Health (Version 15 dated February 22, 2022).

The aim of the study was to examine the efficacy of a synthetic analogue of leu-enkephalin in patients with COVID-19 and ARDS.

Material and Methods

Before a patient was included in the study, the researcher offered to fill out an informed consent form with a detailed explanation of the study goals, objectives, and design, as well as clearly explained all aspects related to dalargin, a synthetic analogue of leu-enkephalin, which was the drug under study.

According to the current instructions for use, dalargin is classified into the «antiulcer drug with antisecretory activity» pharmacological group. The critically ill patients have an extremely high risk of peptic ulcer in general [11, 12] which is even higher if they receive steroids [13], so prolonged infusion of dalargin was administered for gastroprotection by medical team based on indications (history of peptic and duodenal ulcer). The comparison group included patients with similar disease severity and medical history. The study of the organoprotective effects of dalargin was approved by the local ethical committee of the Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology, Protocol 5/21/7 of 23/12/2021.

This prospective study was done in 2 centers:

- Temporary Branch of Clinical Hospital No. 24 of the Moscow City Health Department;
- Dedicated COVID hospital in Sokolniki of the F. I. Inozemtsev Clinical Hospital of the Moscow City Health Department.

The main criterion for primary admission or transfer of patients to the intensive care unit was inadequate gas exchange despite the low-flow oxygen therapy (up to 10 L/min). Additional criteria for transfer included significant worsening on CT scans, deterioration according to the patient's own assessment, unstable hemodynamic parameters and rapidly progressive respiratory failure. All patients were treated in accordance with current Temporary Guidelines for the Treatment of Coronavirus Infection of Russian Ministry of Health (version 15 dated February 22, 2002). The patients were divided into two groups (Table 1). In group 1 (main, n=15), the patients received dalargin intravenously at the rate of 5 μg/kg/hour over 5 days for gastroprotection. In group 2 (control, n=20), only standard treatment was given.

Inclusion criteria were

- Written patient consent for study participation
- Age 18–85 years
- Confirmed diagnosis of severe or critical COVID-19 according to the Guidelines of the Russian Ministry of Health (Version 15 from 22.02.2022).

• Moderate or severe ARDS (according to the Berlin definition)

• Radiological evidence of ARDS (CT grades 2, 3, 4)

The non-inclusion criteria (at least one was required) were:

• History of hypersensitivity to dalargin or any of its components

• Severe, decompensated or unstable conditions (liver cirrhosis, HIV infection, syphilis, hepatitis B and C, decompensated diabetes, uncontrolled hypertension, pheochromocytoma, myocardial infarction or stroke within 6 months before study inclusion, unstable angina, rhythm and conduction disturbances with poor prognosis; severe chronic lung disease (FEV_1 less than 20 ml/kg of ideal body weight), chronic interstitial lung disease with persistent interstitial infiltration on chest x-ray or CT scan, documented chronic CO_2 retention ($PaCO_2 > 50$ mmHg) or chronic hypoxemia ($PaO_2 < 55$ with $FiO_2 = 0.21$) and any other disease or condition hampering the interpretation of treatment results in investigator's opinion.

• Underlying disease with an expected 6-month mortality of 50% and higher.

• Neurological diseases with risk of intracranial hypertension (where hypercapnia should be avoided).

• Neuromuscular diseases that may have required prolonged mechanical ventilation.

• Severe hypotension

• History of allergic reactions

• Acute psychiatric manifestations (psychosis, delirium, hallucinations)

• Current neoplasm or carcinoid syndrome

• Existing tuberculosis

• Liver failure (ALT or AST > 5 times upper limit of normal [ULN] or total bilirubin or alkaline phosphatase > 3 ULN)

• Documented renal dysfunction or severe decompensated renal failure requiring hemodialysis or peritoneal dialysis.

• Alcoholism

• Drug addiction

Exclusion criteria were

• Patient's refusal to continue participation in the study.

• Adverse events preventing further therapy.

• Development of life-threatening conditions.

• Liver function abnormality (i. e., a 3-fold increase in AST, ALT, or AP above the upper limit of normal, or a 2-fold increase in total bilirubin above the upper limit of normal, or development of jaundice).

• Clinically evident kidney dysfunction

• Occurrence of comorbid conditions/manifestations or exacerbation of chronic diseases not related to drug administration (in physician's opinion).

• Other reasons preventing the patient from continuing the study participation (in the opinion of the research physician).

Criteria of efficacy assessment were as follows.

Primary endpoint:

• Percentage of patients with improvement on chest CT (decreased severity and/or area of lung involvement and/or lesions) in the study groups

Secondary endpoints:

• Changes in P/F ratio on days 1–7 in the study groups

• Percentage of patients (%) with clinical improvement by the APACHE II, SOFA and NEWS scales on days 5–7 in the study groups

• Percentage of patients requiring non-invasive ventilation (NILV) in the study groups

• Percentage of patients requiring mechanical ventilation in the study groups

• Percentage of patients (%) who required vasopressor/inotropic support (VIS).

• 28-day mortality in the study groups.

Statistical analysis of the data. Quantitative variables (intergroup comparison and changes within the groups) were analyzed with the aid of AtteStat, STATISTICA, XLSTAT software using the nonparametric statistical methods (Mann–Whitney *U*-test, Wilcoxon test for related samples, Friedman nonparametric analysis of variance, Pearson Chi-square test, Fisher exact test, Freeman–Holton test). The significance level for bilateral tests was α=0.05. The 95-percent two-sided confidence intervals for differences were calculated to prove the superiority of the treatment.

Due to the nature of the study design, «blinding» was performed only at the stage of interpretation of CT images by the radiologist.

Results

The study groups were comparable in demographic and anthropometric characteristics (Table 1).

The groups were also comparable in most clinical characteristics at the beginning of treatment (Table 2), except for the percentage of lung tissue and structural damage, which was higher in the main group than in the control (differences were significant at P=0.048 according to Mann–Whitney *U*-criterion).

On days 5–9 of the treatment, the change in the lung tissue involvement according to CT data in the main group was on average M=+5.8% (SD=11.1%), while in the control group it was +10.1% (16.9%), i. e., 1.7 times less. The median value of this parameter did not change in the main group and increased by 10% in the control group. The upper limit of the 95% confidence interval (CI) of the median difference between the groups was

Table 1. Demographic and anthropometric characteristics of patients.

Parameter	Units	Values in groups		*P*-value
		Main group (*n*=15)	Control group (*n*=20)	
Sex:				
Male	*n* (%)	6 (40%)	13 (65%)	0.142#
Female	*n* (%)	9 (60%)	7 (35%)	
Age (full years)	Median [IQR]	70 [65; 74]	68.5 [61; 74]	0.442*
	min–max	60–86	50–84	
Body weight (kg)	Median [IQR]	82 [78; 98]	85 [72; 93]	0.640*
	min–max	50–138	50–108	
Height (cm)	Median [IQR]	165 [164; 173]	166 [166; 175]	0.471*
	min–max	155–181	155–187	
BMI (kg/m^2)	Median [IQR]	31.6 [26; 35]	28.7 [26; 31]	0.309*
	min–max	20.8–48.9	19.5–45	
Comorbidities				
Diabetes mellitus, %		5 (33.3%)	4 (20%)	0.174#
Hypertension, chronic heart failure		7 (46.6 %)	10 (50%)	0.241#
Bronchial asthma, chronic obstructive pulmonary disease		3 (20%)	5 (25%)	0.221#
Genitourinary diseases		1 (6.6%)	2 (10%)	0.116#
Mental conditions		0 (0%)	1 (5%)	0.165#

Note. For tables 1–4: IQR — interquartile range (first-third), min–max — range. *P*-value calculated using the χ^2 test (#) or Mann–Whitney *U*-test (*).

Table 2. Comparison of groups by clinical aspects of the underlying disease.

Clinical aspect	Statistical units	Groups		*P*-value
		Main (*n*=15)	Control (*n*=20)	
Instrumental investigation results				
Lung tissue involvement:				
CT grade 1	*n* (%)	0 (0%)	1 (5%)	0.545##
CT grade 2		2 (13%)	4 (20%)	
CT grade 3		7 (47%)	11 (55%)	
CT grade 4		6 (40%)	4 (20%)	
Percentage (%) of lung involvement based on CT scan	Median [IQR]	62.5% [55%; 78.1%]	54.4% [45%; 67.8%]	0.048*
	min–max	27.5–85.0%	10.0–80.0%	
SpO_2, %	Median [IQR]	88.0% [85%; 91%]	86.5% [83%; 87%]	0.192*
	min–max	76–94%	60–92%	
Oxygenation index (PaO_2/FiO_2)	Median [IQR]	196.0 [177; 237]	194.5 [166.25; 227]	0.828*
	min–max	150–262	105–290	
Respiratory rate (per min.)	Median [IQR]	24 [22.5; 24]	23 [21; 24]	0.400*
	min–max	21–26	18–29	
Clinical assessment of severity based on scales				
WHO scale:				
4 points	*n* (%)	0 (0%)	3 (15%)	
5 points		15 (100%)	17 (85%)	0.244**
APACHE II (points)	Median [IQR]	15 [13; 19]	16 [15; 24]	0.133*
	min–max	9–20	3–38	
SOFA (points)	Median [IQR]	4 [3; 4.5]	6 [4; 6]	0.066*
	min–max	2–7	2–10	
NEWS (points)	Median [IQR]	6 [4.75; 7]	7 [5; 8.25]	0.351*
	min–max	2–9	3–14	
Comorbidities				
Obesity (BMI⩾35 kg/m^2):				
yes	*n* (%)	5 (33%)	2 (10%)	0.088#
no		10 (67%)	18 (90%)	
Age ⩾60 years				
yes	*n* (%)	15 (100%)	16 (80%)	0.119**
no		0 (0%)	4 (20%)	

Note. For tables 2–7: *P*-value calculated using the Fisher exact test (**); Freeman-Halton test (##); Pearson χ^2 test (#); or Mann–Whitney *U*-test (*).

7.5%, which proved the positive effect of dalargin (Table 3).

The reduction in lung lesion percentage based on CT scan on day 5-9 was considered as «improvement». Among the patients in the main group, CT improvement was observed 3.2 times more frequently than in the control group, the lower limit of the 95% CI of the difference in percentage between the groups being +1.3% (Table 3).

When comparing the changes in lung involvement severity (CT grades 1, 2, 3, and 4 according to a semiquantitative visual scale used in Russia), no sig-

Table 3. The studied parameters on days 5–9 from the beginning of treatment.

Parameter	Values in groups		Difference between the groups, % [95% CI]	*P*-value
	Main (*n*=15)	Control (*n*=20)		
% lung tissue involvement, median [IQR], min–max	0 [–8;0] –28.8; +6.3	+10.0 [+2; +20] –35.0; +37.5	–15.0 [–27.5; –7.5]	0.001*
Percentage of patients with CT improvement, % [95% CI]	46.7 [24.8; 69.9]	15.0 [5.2; 36.0]	+31.7 [+1.3; +56.9]	0.040#
Severity of lung tissue and structural damage, % [95% CI]	20.0 [7.0; 45.2]	5.0 [0.9; 23.6]	+15.0 [–7.7; 40.5]	0.292**

nificant differences between the groups were found at *P*=0.292 using the Fisher exact test (Table 3).

In both groups, significant changes in the P/F ratio were seen with its drop on day 2 and gradual increase in the following days (Fig.). Significance of the changes in both groups was confirmed by Friedman's analysis of variance at *P*=0.001 in the main group and at *P*=0.013 in the control group.

There were no differences in oxygenation index values between the groups from day 1 to day 4 of treatment but starting from day 5, the lower limit of 95% CI of the median difference was significantly higher in the main group than in the control one (Table 4). On day 7 of treatment the mean value of P/F ratio was 211.9 (SD=80.5) in the main group, and 147.2 (54.9) in the control group, i. e., was 1.4 times higher.

There were no significant differences between the main and control groups in the percentage of patients with clinical improvement on days 3 and 7 as assessed by both the APACHE II and the SOFA and NEWS scales (*P*>0.05) (Table 5).

The main and control groups were comparable in terms of the need for mechanical ventilation (no significant differences at *P*>0.05, Table 6).

The main and control groups did not differ significantly at *P*>0.05 in the percentage of patients who required NILV from day 2 to day 5 of treatment

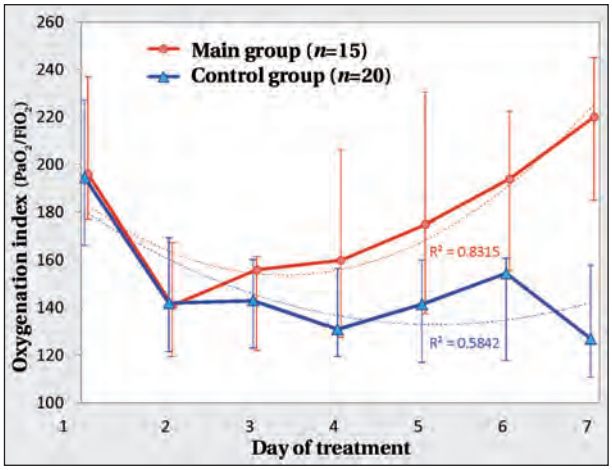

Fig. Changes in the P/F ratio (median ± quartiles, R² — coefficient of determination).

(Table 6). On days 6 and 7 of treatment, the difference between the groups became significant at *P*<0.05 according to Pearson χ^2 test. On days 6–7 of treatment, the rate of NILV use was 4.9–6.7 times lower in the main group than in the control one.

The main and control groups did not differ significantly in the percentage of patients who required VIS (*P*>0.05) (Table 6).

The 28-day mortality rate in the main group was 1.9 times lower than in the control one. However,

Table 4. Changes in the P/F (PaO_2/FiO_2) ratio depending on the day of treatment.

Day of treatment	P/F ratio in groups, Median [IQR], min–max		Difference between the groups, % [95% CI]	*P*-value*[1]
	Main (*n*=15)	Control (*n*=20)		
1	196 [177; 237] 150–262	194.5 [166; 227] 105–290	+4.5 [–24; +41]	0.828
2	141 [120; 168] 108–256	142 [122; 170] 111–277	–1.5 [–26; +21]	0.920
3	156 [122; 162] 92–258	143 [120; 157] 102–240	+2 [–26; +22]	0.777
4	160 [128; 207] 105–330	131 [117; 160] 89–194	+33 [0; +65]	0.040
5	175 [138; 231] 105–323	141.5 [117; 160] 95–213	+41 [+8; +82]	0.020
6	194 [156; 245] 95–310	154.5 [118; 161] 94–190	+55.5 [+24; +95]	0.004
7	220 [185; 245] 150–355	127 [111; 158] 98–320	+64.5 [+15; +114]	0.014
P-value[2]	0.001	0.013		

Note. [1] — intergroup comparison; [2] — *P*-value calculated using the Friedman analysis of variance.

Table 5. Percentage of patients with clinical improvement on assessment scales.

Day of treatment	Scale	Percentage of patients with clinical improvement in groups, % [95% CI]		Difference between the groups, % [95% CI]	*P*-value
		Main (*n*=15)	Control (*n*=20)		
3	APACHE II	6.7 [1.2; 29.8]	10.0 [2.8; 30.1]	–3.3 [–24.2; +20.9]	>0.999**
	SOFA	20.0 [7.0; 45.2]	5.0 [0.9; 23.6]	+15.0 [–7.7; +40.5]	0.292**
	NEWS	26.7 [10.9; 52.0]	10.0 [2.8; 30.1]	+16.7 [–8.9; +43.0]	0.195*
7	APACHE II	33.3 [15.2; 58.3]	10.0 [2.8; 30.1]	+23.3 [–3.8; +49.3]	0.088*
	SOFA	33.3 [15.2; 58.3]	15.0 [5.2; 36.0]	+18.3 [–9.5; +45.1]	0.201*
	NEWS	20.0 [7.0; 45.2]	5.0 [0.9; 23.6]	+15.0 [–7.7; +40.5]	0.292**

Table 6. Percentage of patients requiring MV, NILV, VIS.

Day of treatment	Parameter	Percentage of patients in groups, % [95% CI]		Difference between the groups, % [95% CI]	*P*-value
		Main (*n*=15)	Control (*n*=20)		
2	MV	6.7 [1.2; 29.8]	5.0 [0.9; 23.6]	+1.7 [–17.7; +25.2]	>0.999**
	NILV	20.0 [7.0; 45.2]	50.0 [29.9; 70.1]	–30 [–53.9; +2.2]	0.069*
	VIS	6.7 [1.2; 29.8]	0.0 [0.0; 16.1]	+6.7 [–10.4; +29.8]	0.429**
3	MV	13.3 [3.7; 37.9]	5.0 [0.9; 23.6]	+8.3 [–12.6; +33.2]	0.565**
	NILV	20.0 [7.0; 45.2]	50.0 [29.9; 70.1]	–30 [–53.9; +2.2]	0.069*
	VIS	0.0 [0.0; 20.4]	0.0 [0.0; 16.1]	0 [–16.1; +20.4]	>0.999**
4	MV	—	—	—	—
	NILV	—	—	—	—
	VIS	0.0 [0.0; 20.4]	0.0 [0.0; 16.1]	0 [–16.1; +20.4]	>0.999**
5	MV	13.3 [3.7; 37.9]	10.0 [2.8; 30.1]	+3.3 [–18.9; +28.9]	>0.999**
	NILV	20.0 [7.0; 45.2]	50.0 [29.9; 70.1]	–30 [–53.9; +2.2]	0.069*
	VIS	6.7 [1.2; 29.8]	5.0 [0.9; 23.6]	+1.7 [–17.7; +25.2]	>0.999**
6	MV	—	—	—	—
	NILV	13.3 [3.7; 37.9]	65.0 [43.3; 81.9]	–52 [–71.1; –18.9]	0.002*
	VIS	20.0 [7.0; 45.2]	10.0 [2.8; 30.1]	+10.0 [–13.9; +36.2]	0.403*
7	MV	0.0 [0.0; 20.4]	30.0 [14.5; 51.9]	–30 [–51.9; –4.4]	0.060*
	NILV	6.7 [1.2; 29.8]	45.0 [25.8; 65.8]	–38 [–59.8; –8.3]	0.013*
	VIS	0.0 [0.0; 20.4]	20.0 [8.1; 41.6]	–20.0 [–41.6; +3.6]	0.119**

Table 7. Mortality on day 28.

Frequency of lethal outcome in groups % [95% CI]		Difference between groups, % [95% CI]	*P*-value*
Main (*n*=15)	Control (*n*=20)		
26.7 [10.9; 52.0]	50.0 [29.9; 70.1]	–23.3 [–48.9; +8.9]	0.163

Table 8. The Berlin definition of acute respiratory distress syndrome.

Timing	Within 1 week of a known clinical insult or new/worsening respiratory symptoms
Chest imaging	Bilateral opacities — not fully explained by effusions, lobar, lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload; need of objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present
	Oxygenation impairment
Mild	$200 < PaO_2/FiO_2 \leqslant 300$ with PEEP or CPAP $\geqslant 5$ cmH_2O
Moderate	$100 < PaO_2/FiO_2 \leqslant 200$ with PEEP $\geqslant 5$ cmH_2O
Severe	$PaO_2/FiO_2 \leqslant 100$ with PEEP $\geqslant 5$ cmH_2O

no significant differences of this parameter values between the groups at P=0.163 (Pearson χ^2 test) were found (Table 7) presumably due to a relatively small sample size.

Discussion

The epidemic of the novel coronavirus infection SARS-CoV-19 has drawn the attention of clinicians and researchers around the world to the phenomenon of rapidly developing lung damage, which requires timely and reasonable intervention. To develop and implement new management principles, the understanding the pathophysiological mechanisms of ARDS underlying the lung tissue damage in this category of patients is required.

In 1988, one of the first classifications of ARDS was proposed and introduced into routine practice, which was based on clinical and laboratory data and identified 4 stages of the condition [14]. Later, in 2007, a new classification was proposed, which was based both on clinical and experimental diagnostic findings and morphological examination of lung tissue as well as its correlation with clinical manifestations [15]. This classification was directly related to morphological classification of ARDS which also included the exudation, connective tissue proliferation, and pulmonary fibrosis stages [16, 17]. Nowadays, the Berlin definition (Table 14) adopted in 2012 and used to for severity assessment in ARDS, including that developing in COVID-19-associated pneumonia, is considered most relevant [18].

The current guidelines on the treatment of COVID-19 were driven by the necessity to control the key links in the development of ARDS.

However, according to the current guidelines. the treatment of pneumonia caused by the novel coronavirus infection does not include drugs with lung-protective effects [19]. Opiates are worth mentioning when considering the drugs that could be efficient in this aspect being a part of comprehensive therapy. They are a fairly extensive group of drugs intended for cytoprotection in critical conditions [20, 21]. Among the entire range of opiates used in clinical practice, dalargin stands out because of its unique delta-opioid blocking effect. The latter is suggested to underlie the opioid-induced organoprotection [22]. The use of dalargin in a series of experimental studies was clearly associated with cytoprection when exposed to a wide range of unfavorable factors.

Besides, the presence of delta-opioid receptors practically in all organs and tissues favores a certain versatility of its effects [7, 23, 24].

Earlier patent-pending experimental data [25, 26], as well as the vast clinical experience with the drug provided a rationale for a prospective pilot study of its lung-protective potential in patients with severe COVID-19 associated pneumonia. Impaired air-blood barrier underlies ARDS pathophysiology, while the targeted action of dalargin on key elements of this process could reduce the severity of lung tissue damage.

The most significant effect of dalargin administration was the reduction of lung tissue involvement area, which probably resulted in clinical improvement. The increase in the oxygenation index on days 4–7 after the start of dalargin suggests that further research with the drug will help clarify the timing and scheme of its administration. In addition, a decrease in the frequency and duration of NILV associated with dalargin suggests that the patients with «borderline» severe acute respiratory distress will benefit most from its use.

Conclusion

Improvement on chest CT scans was observed 3.2 times more frequently in patients who received dalargin (the main group) than in the control subjects (P=0.040).

In patients on dalargin, starting from the day 5 of treatment, the P/F ratio was significantly better compared with the control group, which indicates an improved pulmonary oxygenation.

The NILV was used 4.9 times less frequently on day 6 (P=0.020) and 6.7 times less frequently on day 7 (P=0.013) than in the control group.

The results of the pilot study of dalargin use in patients with moderate to severe acute respiratory distress syndrome with the underlying severe and critical novel coronavirus infection SARS-CoV-2 have been promising. This appears to warrant the initiation of a phase III clinical trial of dalargin for new indications. We hope that adding dalargin to the current therapy will significantly improve the prognosis in patients with severe and critical SARS-CoV-2.

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Impact of Anesthesia Method on Immune Response in Patients Undergoing Radical Surgery for Breast Cancer (a Meta-Analysis of Comparative Clinical Studies)

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Влияние выбора метода анестезии на иммунный ответ пациенток, перенесших радикальную операцию по поводу рака молочной железы (мета-анализ сравнительных клинических исследований)

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Summary

Introduction and aim. Recent evidence suggests that inhalation anesthesia (IA) is associated with higher cancer mortality than total intravenous anesthesia (TIVA), possibly due to a modulation of the immune response.

The aim of this study was to determine the impact of anesthesia techniques on selected parameters of patient immunity considering the evidence of relationship between the anesthesia methods and immune status and, consequently, the incidence of cancer recurrence.

Methods. We performed a meta-analysis of clinical studies published in PubMed, Google Scholar, and Cochrane databases, aimed at assessing the impact of anesthesia on the postoperative immune status of patients undergoing breast cancer (BC) surgery. Five randomized and three observational studies were included (a total of 637 patients, of which 320 (50.2%) in the TIVA group). Data on leukocyte counts, matrix metalloproteinases (MMP) 9 and 3, interleukins (IL) 6 and 10 levels, and neutrophil-lymphocyte index (NLI) values were retrieved.

Results. Patients after breast cancer surgery who underwent TIVA had significantly lower white blood cell counts (standardized mean difference (SMD)=–0.32; 95% CI: –0.58 to –0.06; I^2=58%, P=0.020) and MMP-9 (SMD=–0.35; 95% CI: –0.67 to –0.03; P=0.030; I^2=0%) in the postoperative period compared with patients re-

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ceiving IA. No significant differences in the levels of MMP-3, IL-6, IL-10, and NLI values were found between the two groups.

Conclusion. The patients who underwent breast cancer surgery under TIVA had lower blood leukocyte counts and levels of MMP-9, which is involved in the remodeling of extracellular matrix, compared with those operated on under IA, suggesting that the anesthesia method may have an impact on the immunity of breast cancer patients.

Keywords: anesthesia; breast cancer; surgery; immunomodulation; inhaled anesthesia; intravenous anesthesia

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

The full text version of the paper is available at www.reanimatology.com

Introduction

Radical surgery remains the most effective and widely used method of treatment of solid tumors. It is recommended for at least 80% of newly diagnosed cancer patients [3]. Moreover, recent tendency points to a highly probable rise of this parameter, at least for the foreseeable future [3]. For example, the need for surgical treatment of breast cancer (BC) worldwide will increase from 3,022,883 operations in 2015 to 3,810,168 operations in 2030 [3].

Most surgical interventions for malignant tumors have been performed under general anesthesia, and most studies in the area of intraoperative protection have been limited to the study of anesthesia parameters in different types of surgeries. Today, however, new data appear indicating that the use of inhalational anesthesia (IA) may be associated with a greater frequency of adverse outcomes in the long term after radical operations, which, in turn, can be explained by allegedly higher frequency of tumor recurrence [4]. Halogenated anesthetics are considered to contribute to the initiation of tumor regrowth due to impact on cell apoptosis, systemic inflammatory response, and immunosuppression [5-8]. Thus, the immune system seems to be the main link underlying the possible negative effect of anesthesia on postoperative survival rate in cancer patients. This elegant hypothesis, however, has not yet been sufficiently confirmed by the results of evidence-based studies [9]. Perhaps one of the significant limitations of previous meta-analyses was the attempt of bringing together heterogeneous groups of patients with various stages of cancer, major differences in the extent and area of surgery, as well as different levels of baseline mortality within a single study.

Therefore, the aim of this systematic review was to determine the impact of anesthesia method (TIVA vs. IA) on the serum levels of proinflammatory cytokines and matrix metalloproteinases in patients who underwent surgery for breast cancer.

Material and Methods

This meta-analysis follows the guidance outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [10-13] and is registered in PROSPERO (CRD42021255272).

The strategy for study search and selection. Two independent investigators (M. Ya. and K. K.) performed a search in PubMed, Cochrane, and Google Scholar databases for articles published in the past 10 years. The meta-analysis included randomized controlled trials published in peer-reviewed journals, prospective and retrospective cohort studies comparing the effects of IA and TIVA on the immunity of breast cancer patients. Experimental animal studies, studies with insufficient information for performing meta-analysis (e.g., lacking absolute values of quantitative parameters) were excluded. After elimination of duplicates, two reviewers selected publications suitable for full-text analysis to decide on inclusion/non-inclusion according to predetermined criteria. The final decision was made by consensus, if there was a discrepancy, by the Principal Investigator. Searches were conducted in the form of queries using the following keywords: [anesthesia breast cancer / total intravenous anesthesia versus volatile anesthetics breast cancer / TIVA inhalation anesthesia breast cancer / breast cancer propofol / neutrophil-lymphocyte ratio breast cancer anesthesia / anesthesia immune cell / anesthesia immune response]. In addition, the review of literature sources in the analyzed papers was used.

A flowchart of the paper selection is presented in Fig. 1. Of the 1861 publications initially identified in the databases, only five randomized and three non-randomized studies met the inclusion/exclusion criteria (637 patients: 320 in the TIVA group and 317 in the IA group) and were analyzed.

Data collection. The following data were retrieved from each study: design, method of anesthesia (IA or TIVA), quantitative immune parameters (measured by the authors of each original study).

Statistical analysis. Data were analyzed using the RevMan v.5.3 tool (Nordic Cochrane Center, Cochrane Collaboration).

When the authors presented the data as median (interquartile range) or mean (confidence interval), the recommended conversion methods of «mean ± standard deviation» were applied [14, 15]. Heterogeneity of the studies was assessed using the I2 heterogeneity coefficient and the Cochrane coefficient Q. Continuous data were compared using standardized mean difference (SMD) and its 95% confidence interval (CI). Two models (fixed and random effects ones) were used to summarize the magnitude of the standardized difference in mean values [16]. The random effects model was used if moderate to high heterogeneity (defined as I^2>60%) was present.

The primary endpoint of the study was the neutrophil-lymphocyte ratio (NLR) on day 1 post-surgery.

Secondary endpoints were the leukocyte count and the levels of IL-6, IL-10, MMP-3, MMP-9 at the above-mentioned time points.

Assessing the risk of systematic bias. Appropriate Cochrane tools for randomized (RoB 2) [17] and non-randomized studies (ROBINS-I) [18] were used to assess the risk of systematic bias. Papers included in the meta-analysis were independently assessed for the risk of bias by two reviewers (K. K. and M. Ya.) and reviewed by the third (L. B.). Two statistical tests, the Egger [19] and Begg test (MedCalc Statistical Software, version 19.5.6) [20] were used to assess the risk of bias in the publication. Funnel plots were used for visual assessment of publication bias [21].

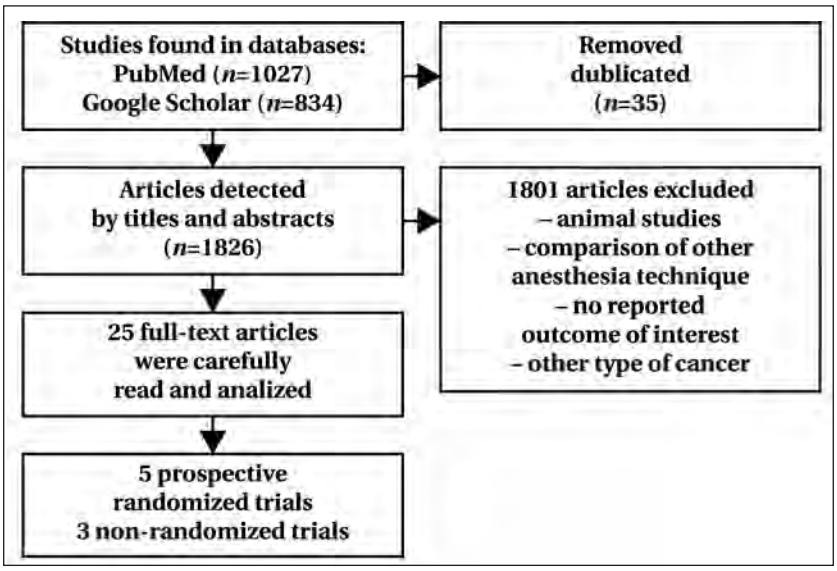


Fig. 1. Flowchart of study selection for the meta-analysis.

Results

Study characteristics. The characteristics of the studies included in the paper are presented in the table.

Data analysis. No significant intergroup differences were found for the primary endpoint (Fig. 2, *a*): the mean NLR in the TIVA group was 2.45±1.32 versus 2.74±1.72 in the IA group (SMD=–0.25; 95% CI: –0.65 to 0.17; *P*=0.240, I^2=71%; three studies included).

Figure 2, *b* shows the results of 4 studies comparing the leukocyte counts in the postoperative

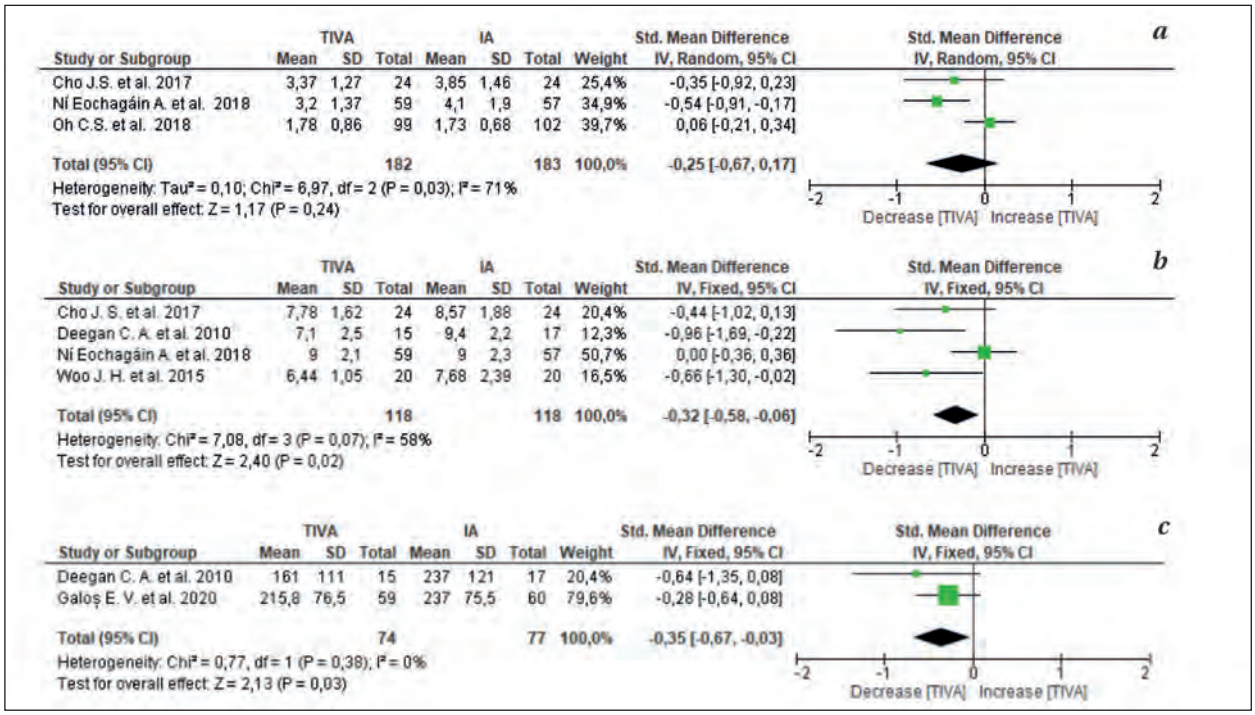


Fig. 2. A meta-analysis of postoperative neutrophil-leucocyte ratio (*a*), leucocyte count (*b*), and MMP-9 level (*c*) in breast cancer patients with inhaled anesthesia (IA) and total intravenous anesthesia (TIVA) (forest plot diagram).
Note. The graphs show study, mean and standard deviation (SD), sample size, study weight, standardized mean difference (SMD), its 95% confidence interval (CI), and estimated heterogeneity and overall effect (*P*-value). The square figure shown for each study represents SMD for the corresponding study and the accompanying horizontal line shows its 95% CI. The diamond-shaped figure represents the pooled SMD for all studies, its horizontal part, 95% CI. The square figures of different sizes indicate the weight of single studies in the overall analysis with respect to sample size and effect size.

period in patients from the TIVA and IA groups. Patients in the TIVA group had significantly lower leukocyte counts compared with patients who received volatile anesthetics (mean leukocyte count in the TIVA group=8.08±2.16–103/ml versus 8.75±2.26–103/ml in the IA group, SMD=–0.32; 95% CI: –0.58 to –0.06; *P*=0.020; I^2=58%) (Fig. 2, *b*). Visual inspection of the funnel plot (supplementary Fig. 1) as well as the Egger (*P*=0.005) and Begg (*P*=0.042) tests suggest the presence of publication bias.

Postoperative levels of matrix metalloproteinase-9 were evaluated in two studies. Patients who received total intravenous anesthesia had significantly lower MMP-9 levels in the postoperative period compared with patients from the IA group (mean MMP-9 value in the TIVA group=204.7±86.6 ng/mL versus 237.0±84.8 ng/mL in the IA group; SMD=–0.35; 95% CI: –0.67 to –0.03; *P*=0.030; I^2=0%) (Fig. 2, *c*).

No significant differences were found in serum levels of the following cytokines:

- IL-6 (mean value of IL-6 in the TIVA group was 215.8±170.5 pg/mL versus 232.8±148.4 pg/mL in the IA group; SMD=–0.34; 95% CI: –0.82 to 0.33; *P*=0.404; I^2=77%; four studies included) (supplemental Fig. 2, *a*),
- IL-10 (mean IL-10 in the TIVA group, 789.9±714.7 pg/mL versus 723.4±470.0 pg/mL in the IA group; SMD=0.16; 95% CI: –0.08 to 0.40; *P*=0.190; I^2=10%; three studies included) (supplemental Fig. 2, *b*)

as well as MMP-3 (mean MMP-3 in TIVA group=341.4±697.1 ng/mL versus 507.3±1120.4 ng/mL in IA group; SMD=–0.10; 95% CI: –0.99 to 0.80; *P*=0.830; I^2=80%; two studies included) (supplemental Fig. 2, c).

The systematic bias risk. The results of the systematic error risk analysis are presented in supplemental Fig. 3.

Overall, the two randomized controlled trials had a low risk of systematic error, while all of the observational studies were characterized by a critical risk of such error.

Table. Characteristics of the included studies (original data are presented).

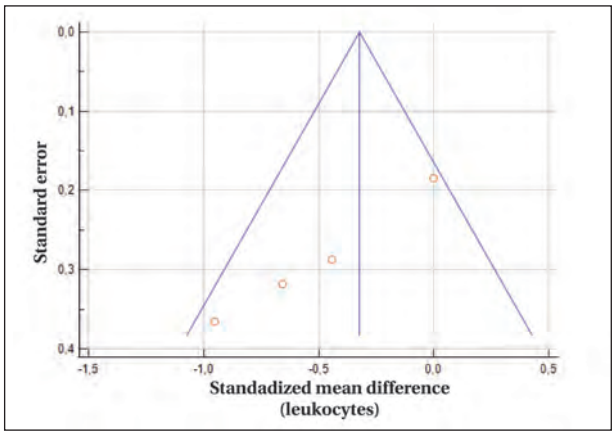
Study and sample size (*n*)	Design	Leucocytes, 10^3/мл	IL-6, pg/ml	IL-10, pg/ml	MMP-3, ng/ml	MMP-9, ng/ml	Neutrophil-lymphocyte ratio
Kim R. et al. 2017, TIVA *n*=21 IA *n*=16	Prospective non-randomized [22]	—	Median and quartiles TIVA: 4.1 [3.2; 8.7] IA: 15.4 [9.6; 23.9]	—	—	—	—
Deegan C. A. et al. 2010, TIVA *n*=15 IA *n*=17	Randomized [23]	Mean and 95% CI TIVA: 7.1 (6.2–8.0) IA: 9.4 (8.6–10.2)	Median and quartiles TIVA: 9.3 [5.5; 19.8] IA: 8.3 [4.4; 11.1]	Median and quartiles TIVA: 2358 [1652; 3245] IA: 1528 [1406; 2344]	Median and quartiles TIVA: 1693 [1361; 1918] IA: 2110 [1562; 3166]	Median and quartiles TIVA: 123 [112; 248] IA: 264 [148; 298]	—
Cho J. S. et al. 2017, TIVA *n*=24 IA *n*=24	Randomized [24]	Mean ± standard deviation TIVA: 7.78±1.62 IA: 8.57±1.88	—	—	—	—	Mean ± standard deviation TIVA: 3.37±1.27 IA: 3.85±1.46
Ní Eochagáin A. et al. 2018, TIVA *n*=59 IA *n*=57	Randomized [25]	Median and quartiles TIVA: 9.0 (IQR=2.8) IA: 9.0 (IQR=3.1)	—	—	—	—	Median and quartiles TIVA: 3.0 [2.4; 4.2] IA: 4 [2.9; 5.4]
Oh C. S. et al. 2018, TIVA *n*=99 IA *n*=102	Randomized [26]	—	Median and quartiles TIVA: 330 [230; 400] IA: 340 [290; 370]	Median and quartiles TIVA: 610 [500; 730] IA: 610 [530; 670]	—	—	Median and quartiles TIVA: 1.62 [1.29; 2.43] IA: 1.68 [1.3; 2.21]
Lim J. A. et al. 2018, TIVA *n*=23 IA *n*=21	Randomized [27]	—	Median and quartiles TIVA: 90 [90; 100] IA: 90 [90; 100]	Median and quartiles TIVA: 470 [430; 570] IA: 470 [440; 500]	—	—	—
Woo J. H. et al. 2015, TIVA *n*=20 IA *n*=20	Prospective case-control [28]	Median and quartiles TIVA: 6.92 [5.54; 6.86] IA: 7.62 [6.22; 9.21]	—	—	—	—	—
Galoș E. V. et al. 2020, TIVA *n*=59 IA*n*= 60	Randomized [29]	—	—	—	Mean ± standard deviation TIVA: 6.90±5.76 IA: 5.30±4.42	Mean ± standard deviation TIVA: 215.8±76.5 IA: 237.0±75.5	—

Discussion

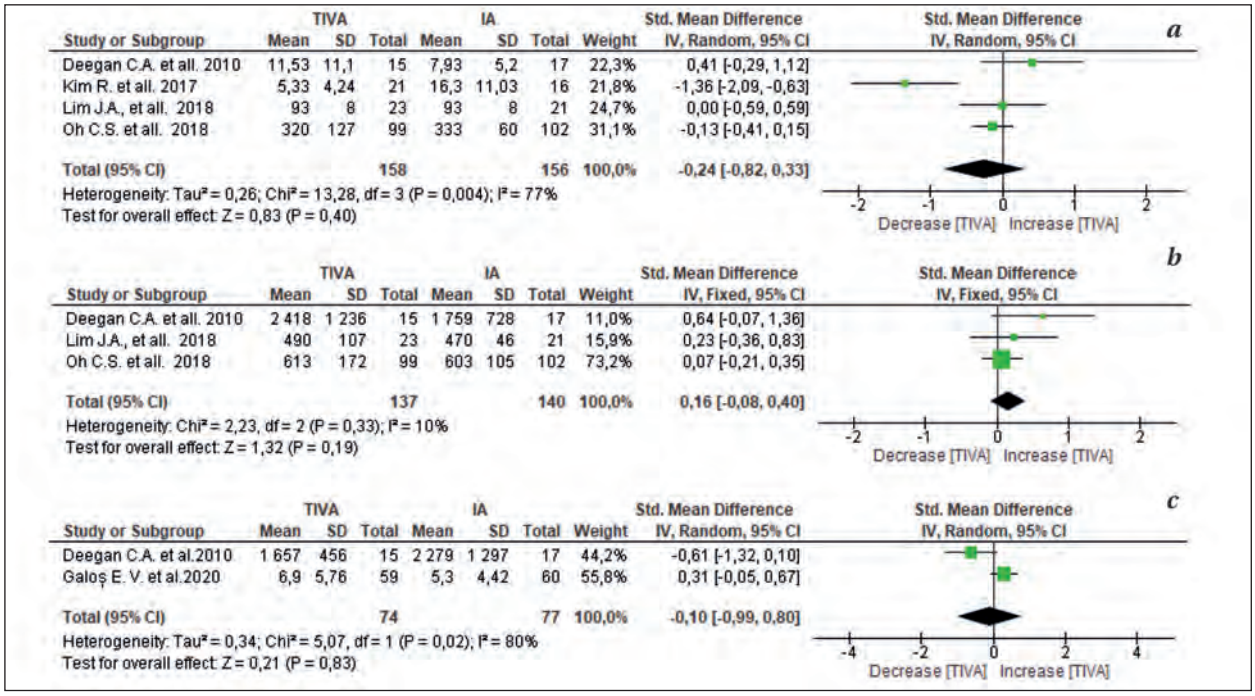
The present study found no differences in postoperative NLR levels in the compared groups. Given the high risk of systematic error in baseline observational studies, the lack of difference in the primary endpoint can be interpreted as a questionable result. We can neither confirm nor deny the effect of inhalation anesthesia on the immune status of patients who have undergone radical surgery for breast cancer. This situation is very similar to the one observed with the study of the effect of inhalation anesthesia on the immune status and mortality in cancer patients in general: some researchers confirm such effect [30, 31], others fail to demonstrate it [9, 32]. Meanwhile, the results of meta-analysis do not provide a definitive answer [33, 34]. Perhaps we should wait for the results of large RCTs, which are currently underway (NCT01975064, NCT04316013) and close to completion.

The observed intergroup difference in leukocyte counts can hardly be interpreted in favor of one or another anesthesia method, because this parameter in both groups hardly exceeds the reference values. This observation only confirms the hypothesis formulated in the previous paragraph.

However, higher postoperative MMP-9 levels were observed in patients with breast cancer who underwent surgery under IA. In an experimental study, Leifler et al. [35] showed that MMP-9 is in-



Supplemental Fig. 1. The risk of publication bias for studies evaluating the post-surgery leucocyte count (funnel-plot diagram).
Note. The graph shows the results of the tests (X-axis) and accuracy (Y-axis). In the figure above, the results are presented as standardized mean difference (SMD) and the accuracy is the standard error of the SMD. Each point on the graph represents a different study. Two lines on each side representing the 95% confidence intervals are also shown. The middle solid line indicates the overall effect of the meta-analysis. A perfect funnel plot is one where the included studies are symmetrically scattered on either side of the overall effect line. In the figure shown, there is a leftward skew, indicating publication bias.

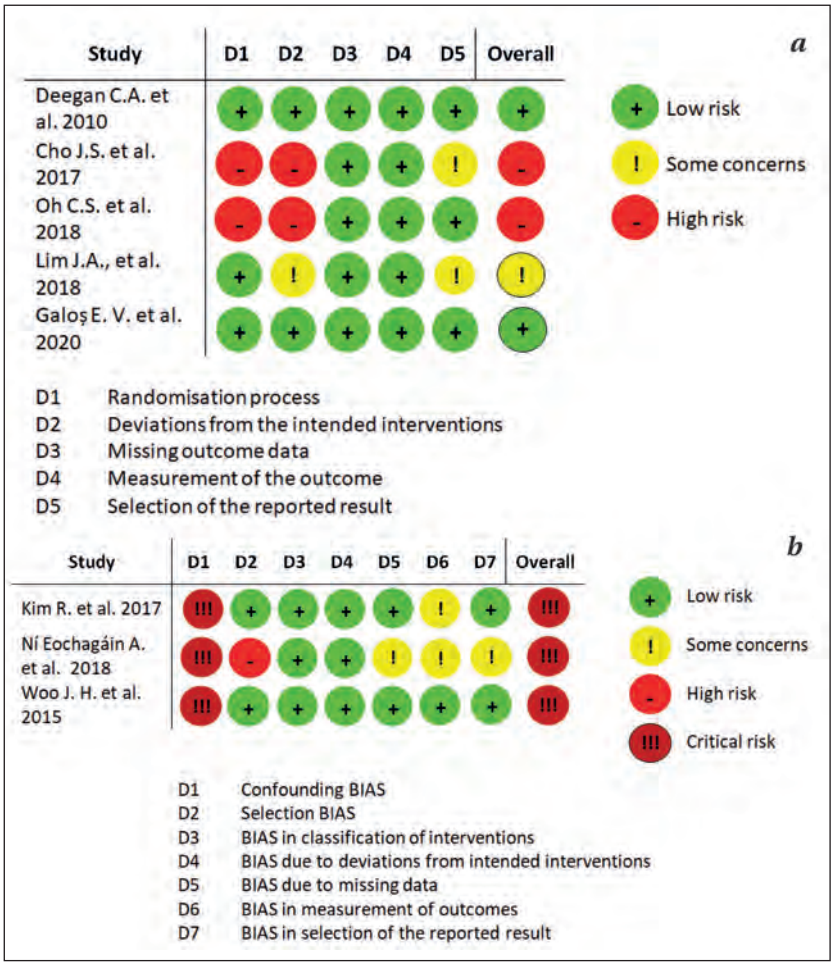


Supplemental fig. 2. A meta-analysis of postoperative serum IL-6 (*a*), IL-10 (*b*), and MMP-9 level (*c*) in breast cancer patients with inhaled anesthesia (IA) and total intravenous anesthesia (TIVA) (forest plot diagram).
Note. The graphs show study, mean and standard deviation (SD), sample size, study weight, standardized mean difference (SMD), its 95% confidence interval (CI), and estimated heterogeneity and overall effect (*P*-value). The square figure shown for each study represents SMD for the corresponding study and the accompanying horizontal line shows its 95% CI. The diamond-shaped figure represents the pooled SMD for all studies, its horizontal part, 95% CI. The square figures of different sizes indicate the weight of single studies in the overall analysis with respect to sample size and effect size.

volved in the regulation of antitumor innate immune responses, thus influencing the metastatic activity of malignant neoplasms. The undoubted importance of MMP-9 expression level as a prognostic marker of survival in breast cancer was also confirmed in a large meta-analysis including 15 studies (from 2001 to 2012) with 2344 participants. This meta-analysis showed that positive MMP-9 expression was associated with lower overall survival (adjusted hazard ratio (HR): 1.70, 95% CI: 1.41–2.04) and recurrence-free survival (adjusted HR: 1.54, 95% CI: 1.17–2.01) in BC patients [36]. More recently, Ren et al. performed a meta-analysis of 28 studies involving 4,944 patients (including 9 MMP-9 studies, *N*=1,044), confirming the negative effect of increased MMP-9 expression on overall survival (relative risk (RR)=1.694, 95% CI: 1.347–2.129, *P*<0.001; HR=1.611, 95% CI: 1.419–1.830, *P*<0.001) [37].

Thus, the differences in MP-9 levels in the compared groups observed in this study do not allow us to dismiss the possible effect of IA on the immune status of patients with breast cancer and confirm the limited knowledge of the problem under discussion.

We did not evaluate the impact of the compared methods of anesthesia on the levels of IL-6, IL-10, and MMP-3, which may argue against the hypothesis of a negative effect of IA on the systemic inflammatory response and immunity, in general.



Supplemental fig. 3. Risk assessment of bias in randomized trials using the ROB-2 tool (*a*) and in non-randomized trials using the ROBINS-I tool (*b*).
Note. The figure illustrates the distribution of risk estimates of bias for randomized (*a*) and non-randomized (*b*) trials across individual domains that could potentially affect the study quality. In (*a*) the success and adequacy of randomization process (D1), the presence of potential differences in patient management between groups (D2), possible missing data (D3), the objectivity and standardization of endpoint assessment in the study groups (D4), and possible selective presentation of results (D5) are assessed. In (*b*), the impact of confounding factors potentially affecting the study endpoint (D1), bias in study patient selection (D2), possible bias in classifying interventions (D3) and bias in assigning patients to certain interventions in various groups (D4), missed data (D5), non-standardized and biased assessment of endpoints in the study groups (D6), and selective presentation of results (DR7) are assessed.

Thus, contradictory data have been obtained that make it difficult to unambiguously evaluate the impact of anesthesia method on the immune status of patients after radical surgery for breast cancer.

Limitations. A marked heterogeneity of data was found while pooling of IL-6 levels and NLR scores from various studies in the meta-analysis, which may have affected the significance of the results.

Only 3 of the 8 studies included in the meta-analysis had a «low» or «moderate» risk of systematic bias, which limits the clinical significance of the results and necessitates a multicenter RCT to evaluate the impact of anesthesia on the immune parameters of patients with BC.

In addition, the results come from single-center RCTs, which are known to overestimate the effect size of an intervention compared to the multicenter ones [38, 39].

Nevertheless, a large multicenter RCT for a comprehensive evaluation of the impact of IA on inflammation and immune system in patients who underwent breast cancer surgery is currently needed to definitively answer the question of whether the anesthesia method affects the immune status of such patients. Only a study evaluating early postoperative complications and long-term survival will provide a rationale for using IA or avoiding this method of anesthesia for breast cancer surgery.

Conclusion

Patients with breast cancer operated under TIVA had lower MMP-9 levels compared to those operated under IA, which could suggest that IA has a negative effect on the immune status of patients with breast cancer.

The impact of different anesthesia methods on the immune status of patients should be further investigated by measurement of classical immune parameters such as immunoglobulins, complement components, acute phase proteins (in particular, high-sensitivity C-reactive protein), cellular immunity characteristics.

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Correction of the Elevated Blood Pressure in Patients Undergoing Robot-Assisted Radical Prostatectomy

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Коррекция гипертензии у пациентов при выполнении робот-ассистированой радикальной простатэктомии

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Summary

The aim of the study was to evaluate the role of urapidil hydrochloride for the management of abnormal cardiovascular response in patients undergoing robot-assisted radical prostatectomy (RARP).

Material and methods. The total of 93 prostate cancer patients scheduled for elective RARP were included and randomized in two groups: urapidil (n=44) and standard anesthesia control group (n=49). Urapidil was used to control the elevated blood pressure intraoperatively. Central hemodynamic monitoring was performed at 5 steps of the surgery.

Results. In the control group, the step 2 of the procedure was associated with elevated mean blood pressure (by 24.3%, P=0.045) and increased total peripheral vascular resistance (by 46.6%, P=0.011) compared with step 1, while in the urapidil group no significant changes in these parameters were found. In the urapidil group, the blood pressure was lower by 20.2% (P=0.047), afterload by 36.9% (P=0.02) vs the control group values, whereas the cardiac output was higher by 22.2% (P=0.043). Placing patient in the steep Trendelenburg position (step 3) resulted in a 22.4% increase in stroke volume (P=0.38) in the control group and a 19.2% increase in stroke volume (P=0.049) in the urapidil group compared with the previous step. Cardiac output in the urapidil group was higher by 34% (P=0.002) and blood pressure and vascular resistance were lower by 24.4% (P=0.031) and 45.7% (P=0.001), respectively, vs the control group. At steps 4 and 5, gradual stabilization of the hemodynamic parameters and peripheral vascular tone with significantly smaller differences between the groups were revealed.

Conclusion. Urapidil was effective for maintaining central hemodynamic parameters in patients during robotic-assisted radical prostatectomy at step 2 of the procedure, avoiding blood pressure elevation at step 3 and significantly reducing the total peripheral vascular resistance compared with the control group.

Keywords: robotic-assisted prostatectomy; steep Trendelenburg position; urapidil

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

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Introduction

Robot-assisted radical prostatectomy (RARP) has been gradually replacing the open radical surgery and becomes the «gold standard» treatment of patients with localized prostate cancer globally. Primarily, this is due to its minimal invasiveness, better functional results (concerning urine retention and erectile function), as well as to a shorter time needed to achieve clinical success [1, 2].

CO_2 pneumoperitoneum and Trendelenburg position are prerequisites for optimal visualization of the surgical field in RARP. This combination can negatively affect both pulmonary and cardiovascular systems, which necessitates a thorough understanding of the pathophysiology involved, as well as timely feedback of function control to prevent the development of life-threatening conditions.

In addition to pulmonary dysfunction associated with atelectasis and increased airway pressure, RARP results in severe hemodynamic changes [3–6]. According to Lestar M. et al. who evaluated central hemodynamic parameters using Swan–Ganz catheter, the central venous pressure increased almost 3 times compared to the baseline with a simultaneous 2-fold increase of mean pulmonary artery pressure and pulmonary capillary pressure (P<0.01) while the patient was placed in Trendelenburg position at 45°. Meanwhile, the mean arterial pressure, increased by 35% [7].

In the study of Pawlik M. T. et al. the central hemodynamic parameters during RARP were assessed using the PICCO+ (Pulse Contour Cardiac Output with continuous measurement of cardiac output using pulse waveform analysis) invasive technique. The authors reported perioperative cardiac complications in 5.9% of patients, with 11.8% having cardiac deterioration in the intraoperative period with a significant decrease in cardiac index (up to 1.5 L/min/m^2 versus baseline of 2.6 L/min/m^2 (P=0.003)) after the CO_2 pneumoperitoneum and Trendelenburg position and an increase in total peripheral vascular resistance to 6865 dyn×s×sm^{-5} versus 2879 dyn×s×sm^{-5} at baseline (P=0.001) [8].

Thus, hypertension during CO_2 pneumoperitoneum and Trendelenburg positioning of the patient is the most significant hemodynamic complication of RARP. In this regard, studying drugs with a well-controlled hypotensive effect used as a part of anesthesia regimen seems reasonable. We believe that urapidyl hydrochloride possessing strong alpha-blocking activity perfectly meets this goal. In the available literature, we found no studies addressing pharmacological control of hypertension in RARP.

Undoubtedly, the Swan–Ganz catheter is the most objective method for assessing central hemodynamic parameters [7, 9], but due to complexity and possible complications of this invasive method, alternative noninvasive methods of hemodynamic assessment are becoming more and more popular [10, 11]. In our study we employed impedance cardiography using Niccomo® (Medizinische Messtechnik GmbH, Germany) device to assess cardiac contractility, preload and afterload.

The aim of the study was to evaluate the efficacy of urapidyl hydrochloride as a component of anesthesia support for the control of hypertension during robot-assisted radical prostatectomy.

Material and Methods

After approval by the ethical committee (decision of the ethical committee of the Federal Scientific and Clinical Center for Intensive Care and Rehabilitology No. 5/20/6 of December 23, 2020) and written informed consent, 93 patients with verified prostate cancer scheduled for RARP were included in the open randomized prospective study (see Fig.).

Criteria for inclusion were:

— age from 50 to 70 years

— anesthesia risk 1–2 according to ASA (American Society of Anesthesiologists);

— signed patient's informed consent for participation in the study.

Non-inclusion criteria were

— refusal to participate in the study / sign the informed consent;

— anesthesia risk ⩾3 ASA

— body mass index >33 kg/m^2

— chronic nonspecific lung diseases and/or 2–3 degree respiratory failure (dyspnea on moderate and mild exertion),

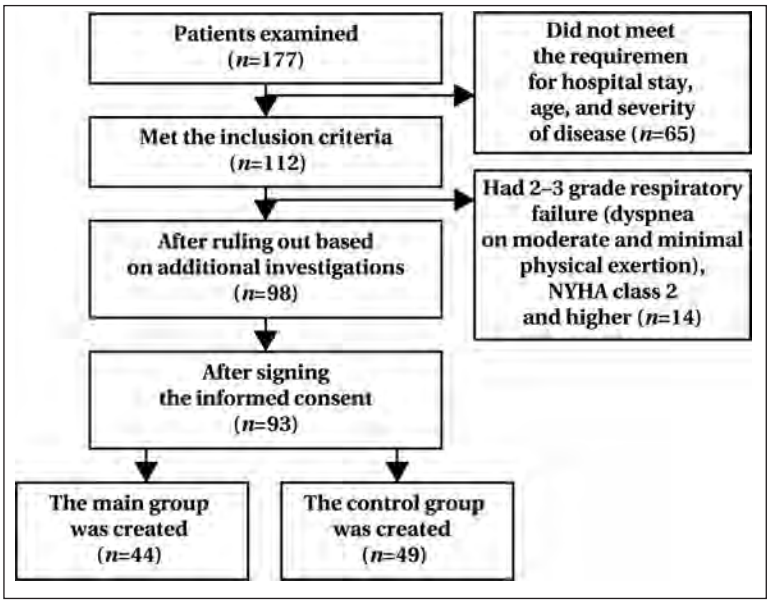

Fig. Scheme of patient recruitment.

Table 1. Characteristics of the study groups.

Parameter	Group		*P*-value
	Main (*n*=44)	Control (*n*=49)	
Age, years	57.9±0.72	57.3±0.67	0.99*
Weight, kg	74.1±2.93	73.3±2.34	0.98*
ASA	1.59±0.13	1.68±0.1	0.55**
ASA 1, % patients	38.6	32.7	
ASA 2, % patients	61.4	67.3	
Comorbidities, % of patients			
Coronary heart disease	38.6	44.9	0.32**
Chronic obstructive pulmonary disease	6.8	14.3	0.32
Gastric erosions or ulceration, remission	6.8	20.4	0.08

Note. *— Student's *t*-test; ** — χ^2 test

— chronic heart failure ⩾2 NYHA (New York Heart Association) classification.

The patients were randomized using the envelope method into 2 groups (the main and the control). The patients of the main group (*n*=44) received standard anesthesia support and intraoperative urapidil hydrochloride to correct hypertension, while the patients of the control group (*n*=49) received only standard anesthesia support. The characteristics of the groups are summarized in Table 1.

Patients aged 50–60 years prevailed in both groups. Two thirds of the patients were working at the time of diagnosis, the rest were retired. Differences in age and weight between the groups were not significant, indicating the group comparability (Table 1).

In general, the differences between the groups in the anesthetic ASA risk were not significant (Table 1).

Hemodynamic parameters were analyzed at the following key steps of surgery:

Step 0: Baseline values prior to the intervention;

Step 1: Introductory anesthesia, horizontal position of the patient;

Step 2: Induction of CO_2 pneumoperitoneum, insertion of trocars;

Step 3: Bringing the patient to the 30° Trendelenburg position, 5 min after the start of surgery with robotic assistance;

Step 4: The most invasive step of the operation, 30–60 min after the start of the intervention with robotic assistance;

Step 5: 15 minutes after tracheal extubation.

The following hemodynamic parameters were measured at each of the key steps:

— heart rate (HR), per min;

— systolic blood pressure (SBP), mm Hg;

— diastolic blood pressure (DBP), mm Hg;

— mean arterial pressure (MAP), mm Hg;

— cardiac output (CO), L/min;

— stroke volume (SV), ml;

— total peripheral vascular resistance (TPR), $dyn \times s \times cm^{-5}$.

After the patient was transported to the operating room the standard (electrocardiogram, noninvasive blood pressure measurement, pulse oximetry) and invasive (peripheral venous catheter 18G-20G inserted into a vein of the left upper extremity with the right arm adducted to the torso and fixed during the operation) monitoring were initiated. The Niccomo® device was connected as an additional monitoring component with 4 twin electrodes preoperatively placed on the neck and chest.

The dosage of drugs for combined endotracheal anesthesia was calculated based on the ideal body weight. All patients received standard pharmacological premedication on the operating table together with 100% oxygen insufflation through a face mask at 6–8 l/min consisting of 0.1% atropine sulfate 0.01–0.02 mg/kg, 0.2% clemastine (Tavegil®) 0.03–0.05 mg/kg, midazolam (Dormicum®) 0.02–0.06 mg/kg, 0.005% fentanyl 1–3 mg/kg. Induction anesthesia was initiated by injecting propofol (Diprivan®) 1.5–2.5 mg/kg until the target BIS values of 30–40 were achieved.

After achieving depressed consciousness, the precalculated dose of non-depolarizing myorelaxant rocuronium bromide 0.5 mg/kg was injected and tracheal intubation was performed with 8–9 mm endotracheal tube. Due to the risk of displacement of the distal end of the endotracheal tube toward the carina and single-lung ventilation after placing the patient in Trendelenburg position, obligatory auscultatory control was performed at all stages of patient positioning. After tracheal intubation, a nasogastric tube was placed to minimize the risk of injury to the stomach during trocar placement and to prevent postoperative nausea and vomiting. Anesthesia was maintained by sevoflurane (Sevoran®) inhalation anesthetic with the target BIS values of 40–50. Muscular relaxation was achieved by bolus injection of calculated doses of rocuronium bromide. We used Drager Primus (Dragerwerk, Germany) device for mechanical lung ventilation using oxygen-air mixture at 0.4–0.6 ratio and at a rate of 0.8–1 L/min in PCV (Pressure Control Ventilation) mode with the following parameters: respiration rate 10 per minute, respiratory volume of 6–8 ml/kg, positive end-expiratory pressure (PEEP) of 5 cm H_2O, inspiration-expiration ratio of 1:1 as the most optimal in terms of reducing the risk of lung baro-

Table 2. Hemodynamic parameters of patients from main (*n*=44) and control groups (*n*=49) during the surgery (*M*±*σ*).

Group	Baseline	Step of surgery				
		1	2	3	4	5
Heart rate, per minute						
Control	77.1±2.78	83.1±2.56	67.1±3.45*,#	65.2±2.36*	66.1±1.76*	74.2±2.3
Main	74.1±1.53	81.4±2.26	71.5±2.78*	68.1±1.78*	72.7±2.31*	80.7±3.5
Systolic blood pressure, mm Hg						
Control	125.8±2.32*	102.4±3.4	136.4±1.85*,#	141.3±2.12*	133.2±1.76	126.6±1.3*
Main	129.1±1.78*	99.4±3.2	131.5±1.6*,#	105.7±1.57*,##,#	107.1±2.14*,##	132.4±2.2*,#
Diastolic blood pressure, mm Hg						
Control	80.1±1.48	68.2±1.96	87.5±1.05*,#	92.3±1.34*	84.8±2.15	73.7±1.6
Main	83.3±2.16	72.1±1.46	70.7±1.52##	71.3±1.56##	68.6±1.75##	78.4±2.32*
Mean arterial pressure, mm Hg						
Control	95.4±1.3	80.2±1.8	99.7±1.15*,#	112.6±1.42*	102.3±2.13*	92.6±1.4
Main	91.4±1.6	84.1±1.2	79.6±2.04##	85.1±2.12##	78.7±1.67*,##	93.2±1.9*
Cardiac output, L/min						
Control	6.1±0.23	5.4±0.24	4.5±0.3	4.7±0.14	5.4±0.16*	5.7±0.23
Main	5.5 ±0.41	5.7±0.14	5.5±0.24##	6.3±0.35*,##	5.8±0.24*	5.2±0.35
Stroke volume, ml						
Control	78±2.78*	65±2.85	67±1.98	82±2.63*,#	83±3.02*	77±2.48
Main	74±3.16	71±3.65	78±2.34	93±1.87*,#	91±2.56*	75±3.13
Total peripheral vascular resistance, dyn×s/cm^5						
Control	1254±24.1	1138±29.3	1668±27.2*	1763±19.3*	1418±26.2#	1210±24.2
Main	1275±26.3	1208±24.7	1053±23.8##	957±16.7*,##	1024±20.1##	1094±17.4

Note. Significant differences: * — versus step 1, $P<0.05$, Duncan test; # — versus the previous step, $P<0.05$, Newman–Keuls test; ## — between the main and control groups, $P<0.05$, Student's *t*-test.

trauma and impaired venous return. The respiratory rate settings during anesthesia were adjusted to achieve optimal exhaled carbon dioxide partial pressure of 4.9–6.4 vol%. The constant CO_2 insufflation through robotic trocar port and its leak into the circulation were taken into account and timely adjustment of the ventilator parameters was performed to maintain normocapnia [12].

Urapidyl hydrochloride 25 mg was administered by bolus to patients in the main group at the stage of CO_2 pneumoperitoneum induction and trocar placement (step 2), with further continuous infusion through an infusion pump at a rate sufficient to maintain mean arterial pressure at 75–80% of baseline values.

During the operation, limited volumes (1–2 ml/kg/h) of balanced crystalloid solutions were infused until the urethrovesical anastomosis was created in order to limit the production and leakage of urine into the operating field, as well as to prevent impaired visualization of the area of surgical interest and reduce the likelihood of upper airway obstruction in Trendelenburg position. After the anastomosis was created, an additional 1,000 ml of balanced crystalloid solutions were administered.

The duration of surgical intervention (212.13±11.2 min for patients in the main group and 225.2±13.6 min for patients in the control group) did not differ between the groups (P=0.83, Student's *t*-test). Intraoperative blood loss was less than 100 ml in both groups. After completion, all patients underwent tracheal extubation and were transferred in stable condition to the postoperative ward for symptomatic therapy and clinical and laboratory monitoring. Both groups did not differ statistically in an average hospital stay which was 7±1 days.

The RARP was performed using da Vinci Si system (Intuitive Surgical, Mountain View, USA). After tracheal intubation, the patient was placed in the lithotomy position; special soft fixators were positioned under the patient's shoulders to limit his/her displacement relative to the operating table. Five ports were inserted into the abdominal cavity creating CO_2 pneumoperitoneum with initial CO_2 pressure of 15 mm Hg. After this step was completed and the patient was moved to Trendelenburg position, gas pressure in the abdominal cavity was reduced to the safe 12 mm Hg [6, 9, 13].

Considering the exploratory nature without a primary endpoint, the sample size of the study was not specified. Ninety-three patients were considered suitable for analysis of hemodynamic parameters during RARP. The quantitative data distribution was checked for normality using the Shapiro–Wilk criterion. Taking into account normal distribution of the data, statistical variables were presented as mean values (*M*) with standard deviations (σ). Comparison between the groups was performed using Student's *t*-test. Statistical differences between the mean values in the groups at different steps of the surgery were assessed by univariate analysis of variance (Newman–Keuls criterion for comparison with the same parameter's value at the previous stage and Duncan criterion for comparison with the value of step 1). Pearson's χ^2 test was used to compare frequencies, Yates' correction was applied for expected frequencies less than 10, and Fisher's exact test was additionally calculated for expected fre-

quencies less than 5. Statistical analysis was performed using Statistica 10.0 software package. Differences were considered significant at $P<0.05$.

Results and Discussion

The baseline hemodynamic parameters remained within the reference range (Table) due to premedication with sedatives and a conversation with an anesthesiologist with a detailed description of upcoming events held the day before, which reduced the impact of the emotional component on hemodynamics. After induction anesthesia, mean arterial pressure (MAP) values decreased insignificantly in both groups, remaining within the target values, ensuring adequate microcirculation.

During step 2, where the installation of ports and the induction of CO_2 pneumoperitoneum (with CO_2 pressure -– mmHg) occur, the control group demonstrated cardiovascular changes including an increase in SBP (33.2%, *P*=0.037), DBP (28.3%, *P*=0.041), MAP (24.3%, *P*=0.045), and vascular resistance (46.6%, *P*=0.011), as well as a slight 16.7% decrease in cardiac output (*P*=0.61) versus step 1. The CO_2 pneumoperitoneum obviously had a strong stressful effect on the cardiovascular system, which necessitated additional doses of opioid analgesics at this step. Falabella A. et al. and Meininger D. et al. in their studies obtained similar results [14–16].

In the main group, MAP and TPR decreased by 5.4% (*P*=0.62) and 12.8% (*P*=0.092), respectively, during step 2 compared to step 1.

The DBP in the main group was 19.2% (*P*=0.049) less than in the control group, as were MAP (20.2%, *P*=0.047) and TPR (36.9%, *P*=0.02), while the CO was 22.2% (*P*=0.043) higher versus the control group.

Patient's placement in Trendelenburg posotion (step 3) led to a 22.4% increase in stroke volume (*P*=0.038) and an insignificant increase in MAP (12.9%, *P*=0.62) and afterload (5.7%, *P*=0.83) in the control group vs with the previous step, which is likely due to the increased venous return to the heart as a result of elevation of the lower extremities, increased intra-abdominal pressure and sympathetic activation [8]. These findings agree with the data obtained in the study of Rosendal C. et al. who found a significant increase in TPR at all steps of RARP and its reduction below the baseline values only at the end of the surgery [15].

In the main group, a 19.2% increase in stroke volume (*P*=0.049) and a 19.6% decrease in SBP (*P*=0.049) were revealed at the step 3 vs the previous step. Increases in cardiac output by 14.5% (*P*=0.61) and MAP by 6.9% (*P*=0.23) and a 9.1% decrease in afterload (*P*=0.12) were not significant compared with the previous step.

The CO in the main group was 34% higher vs the control group (*P*=0.002), and MAP and TPR were 24.4% (*P*=0.031) and 45.7% (*P*=0.001) lower, respectively. The stroke volume in the main group was insignificantly higher (13.4%, *P*=0.13) relative to the control group.

The hemodynamic parameters were stable during step 4, which is the most invasive part of the surgery with separation of the seminal vesicles, dissection of the dorsal venous complex and removal of the prostate, followed by urethrovesical anastomosis. Interestingly, the SBP was 24.4% (*P*=0.035) lower in the main group, DBP was 23.6% (*P*=0.039) and MAP 30% (*P*=0.004) lower than in the control group. The TPR was insignificantly lower vs the control group (27.8%, *P*=0.12), while the SV and CO were 9.6% (*P*=0.51) and 7.4% (*P*=0.73) higher, respectively.

Lestar M. et al. and Falabella A. et al. reported similar results in their research [7, 16]. Several studies have demonstrated wide variation of SV and CO changes, from an 11% decrease to significant increase (more than 20%) at the same step of the operation [17, 18].

The final step of the study was characterized by the return of most of the studied parameters to their baseline values in both groups. Only DBP and SV in the main group remained slightly decreased vs the step 1, which was probably caused by limited intraoperative infusion of crystalloids due to the specific nature of the surgery. In the postoperative room, the volume status was corrected in all patients using balanced crystalloid infusion [16].

Thus, the use of urapidyl hydrochloride during anesthesia support in RARP allowed to stabilize hemodynamic parameters at step 2 of surgery, to avoid hypertension at step 3, and to significantly reduce the afterload.

A more stable hemodynamic profile in the patients of the study group during critical stages of surgery such as induction of CO_2 pneumoperitoneum and patient placement into the Trendelenburg position can be suggested [19–22].

Another important effect of urapidyl hydrochloride during anesthesia in RARP was the reduced frequency of «critical» hemodynamic accidents during the surgery. Thus, significant hypertension (more than 40% increase in BP vs the step 1 values) was observed in 25 (51.0%) patients in the control group, while only 3 (6.8%) patients had a similar response in the main group (*P*=0.00001). A significant decrease in CO was seen in 8 (16.3%) patients of the control group, while in the main group this was found only in 1 (2,3%) patient (*P*=0.033). Also, 6 (12.2%) patients in the control group experienced a significant increase in TPR, while in the main group no similar increase in afterload was found (*P*=0.028).

Conclusion

The use of urapidyl hydrochloride as a part of anesthesia support to control the hyperdynamic

cardiovascular response allows to achieve the target MAP values during all steps of surgery by reducing the afterload and maintaining the heart performance without reducing organ and tissue perfusion and compromising the cardiovascular adaptive response.

The use of urapidyl hydrochloride ensures stability of hemodynamic parameters during the whole intraoperative period, which contributes to the adequacy and safety of anesthesia and can be crucial in patients with cardiovascular comorbidities.

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The Antioxidant Effect of Mitochondrially Targeted Antioxidant SkQ1 on the Isolated Rat Heart Model

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Исследование антиоксидантного эффекта митохондриально-направленного антиоксиданта SkQ1 на модели изолированного сердца крысы

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Summary

Mitochondrially targeted antioxidants based on Skulachev ions (SkQ1) are extremely attractive for neutralizing reactive oxygen species directly in the mitochondrial matrix.

The aim was to examine the antioxidant and cardioprotective status of the SkQ1 mitochondrially targeted antioxidant in an isolated rat heart model of ischemia and reperfusion after cold cardioplegia.

Material and methods. The effects of different concentrations of SkQ1 (1200 ng/ml, 120 ng/ml, 12 ng/ml) were explored on isolated hearts of Wistar rats (n=50) during 240-min cold cardioplegia. The levels of oxidative stress, changes in myocardial damage markers (classical and highly specific) and cardiac function (coronary flow velocity, heart rate, systolic pressure) were assessed.

Results. The use of SkQ1 at 12 ng/ml resulted in a significant neutralization of oxidative stress manifestations (P<0.05). The minimum concentration of NO metabolites (nitrates and nitrites) (36.2 [30.8; 39.8] μmol/ml) was maintained at pre-ischemic level throughout the 30-minute reperfusion period, while the malonic dialdehyde concentration (49.5 [41.1; 58.9] μmol/g) was lower compared with SkQ1 use at 120 ng/ml dose. Due to the «mitigation» of oxidative stress, intracellular enzymes and highly specific markers of myocardial damage rose more slowly during reperfusion, while cardiac function recovery occurred at a higher rate and showed stability upon restoration of perfusion.

Conclusion. SkQ1 at 12 ng/ml concentration showed strong antioxidant and cardioprotective properties in an *ex vivo* study.

Keywords: plastomitin; SkQ1; bypass circulation; isolated heart; oxidative stress

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

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Introduction

Open heart surgeries under cardiopulmonary bypass remain in high demand. The comorbidity of cardiac surgery patients, cardiopulmonary bypass, prolonged ischemia/anoxia of myocardium during surgery and reperfusion in combination cause accumulation of metabolic products, development of oxidative stress and systemic inflammatory response, which can lead to various postoperative complications including multiple organ failure [1, 2]. Therefore, intensive research is underway to find active agents and develop methods that can minimize postoperative complications in cardiac surgery. Oxidative stress underlying complications is triggered by altered mitochondrial respiration and leads to the production of reactive oxygen species (ROS), initiating a variety of pathological processes [3]. Local neutralization of ROS located in the mitochondrial matrix may become the most effective way of mitigating oxidative stress.

Mitochondrial-directed antioxidants belong to highly promising agents. Plastomitin is a systemic antioxidant drug based on Skulachev ions (SkQ1). The proprietary formula of a plastoquinone-containing antioxidant (SkQ1) was developed and actively studied by a team of scientists led by Professor Vladimir P. Skulachev [4, 5]. The SkQ1 antioxidant as a market product has already found its place in the pharmaceutical and cosmetic industries: Visomitin eye drops are used for the dry eye syndrome and in early cataract, which both involve oxidative stress, whereas Mitovitan face serum has been used to reduce the manifestations of aging, where ROS play an important role [6–8]. Various branches of human and veterinary medicine and agriculture have expressed interest in studies of SkQ1 efficacy [9, 10]. Specifically, our research group is interested in the development of methods to reduce postoperative complications in cardiac surgery, which in most cases involve oxidative stress, and ways to preserve the viability of the heart transplant [11]. This paper is devoted to the study of the effects of SkQ1 on the isolated heart exposed to prolonged ex vivo anoxia and reperfusion. In this case, the lack of systemic regulation allowed us to evaluate the «pure» effects of the drug itself.

The aim of the study was to evaluate the antioxidant and cardioprotective effects of SkQ1, a mitochondrial-directed antioxidant, in an ischemia and reperfusion model of isolated rat heart under cold cardioplegia.

Material and Methods

Plastomitin (with SkQ1 concentration of 1.7 mg/ml) was provided under a scientific cooperation agreement by OOO Mitotech (Russia). Working solutions of SkQ1 were prepared by diluting Plastomitin with perfusion solution in the appropriate proportion.

The experiments were performed on isolated hearts of healthy male Wistar rats (m = 300±50 g), *n*=50. The animals were kept under standard vivarium conditions without food and water restrictions. Experiments and procedures with laboratory animals complied with the rules of the European Convention for the Protection of Vertebrate Animals Used for Experimental or Other Scientific Purposes (Strasbourg, 1986). The study was approved by the local ethical committee (protocol No. 150 of 16.11.2021).

Perfusion of isolated hearts by the Langendorff method. A similar experimental scheme has already been used in studies of the efficacy of other drugs [12]. Initially, rats were anesthetized by intraperitoneal injection of sodium thiopental (25 mg/kg). Then a thoracotomy was performed, the heart with the necessary segment of the aorta was dissected and immediately immersed in Krebs-Henseleit solution (KHS) at t=4°C. Then the aorta was cannulated to allow a retrograde perfusion of the heart using an original system which included gas and temperature circuits, with standard KHS containing NaCl 118.0 mmol/L, $NaHCO_3$ 25.0 mmol/L, glucose 11.0 mmol/L, KCl 4.8 mmol/L, KH_2PO_4 1.2 mmol/L, $MgSO_4$ 1.2 mmol/L, $CaCl_2$ 1.2 mmol/L, enriched with a gas mixture (95% O_2 and 5% CO_2) with pH = 7.3–7.4. During all phases of the experiment on isolated hearts, a stable temperature of the perfusion solution in the acceptable range from 37°C to 38°C was maintained, as well as a constant pressure of the fluid column at 80 cm H_2O.

Perfusion protocol.

Pilot phase of the experiment. Consisted of cardiac stabilization (20 minutes), normothermic hypoperfusion (20 ml/h) with KHS and SkQ1 (20 minutes), and reperfusion (15 minutes) periods. The hearts of the study groups were hypoperfused using the perfusion solution containing various concentrations of SkQ1: 12 ng/ml for the first (SkQ1-12, *n*=5), 120 ng/ml for the second (SkQ1-120, *n*=5), and 1200 ng/ml for the third (SkQ1-1200, *n*=5) ones. The control group (*n*=5) did not receive SkQ1 during hypoperfusion.

The studied parameters. At minute 20 of perfusion (pre-ischemic baseline level, BL) and the minute 15 of reperfusion, coronary flow rate (CFR, ml/min) was recorded. The activity of enzymes such as creatine phosphokinase, myocardial fraction (CPK-MB, units/L) and lactate dehydrogenase (LDH, units/L) was determined in perfusate flowing from the hearts by enzymatic kinetics method on automatic biochemical analyzer «Konelab 30i» (Thermo Fisher, USA).

Main phase of the experiment. Experiment included following stages: stabilization of heart contraction (20 min); connection of the second flow of perfusion solution with SkQ1 (10 min); hypoperfusion (20 ml/h) with cooled (t=4ºC) cardio-

plegic solution (Custodiol, Dr. F. KOHLER CHEMIE GmbH, Germany) (10 min); global cardioplegic ischemia (240 min); reperfusion (30 min). Hearts of the first study group were perfused with double-flow KHS containing 120 ng/ml SkQ1 (SkQ1-120, *n*=10). The hearts of the second study group were perfused similarly to the first group with SkQ1at another concentration, 12 ng/ml (SkQ1-12, *n*=10). In the control group (*n*=10) SkQ1 was not added to the second flow of perfusion solution.

The studied parameters. At a pre-ischemic level, on minutes 1, 10, 20 and 30 of the reperfusion period, CFR, heart rate (HR, bpm), systolic blood pressure (mm Hg) using bedside monitoring device, BSM-2301K (Nihon Kohden, Japan) were recorded.

The methods of measuring levels of such enzymes as CPK-MB, LDH, aspartate aminotransferase (AST, units/L) were similar to those used during the pilot phase of the study. The levels of heart-type fatty acid-binding protein (H-FABP, ng/ml) and cardiac troponin I (pg/L) were detected by enzyme immunoassay (ELISA) using Hycult biotech (USA) and Cusabio (PRC) kits, respectively. Total levels of nitrite and nitrate, mitochondrial superoxide dismutase (SOD-2), mitochondrial DNA peroxidation damage marker (8-OHdg) were studied by ELISA using Biomedica (Austria) and R&D (USA) kits. Malone dialdehyde (MDA) in the myocardial homogenate was measured using a commercial OxiSelect™ TBARS Assay Kit MDA Quantitation (Cell Biolabs, USA).

The data were statistically analysed using «GraphPad Prism 7.0» program. Differences in the measured parameters were determined using non-parametric Mann–Whitney *U*-criterion for unrelated pairs, and Wilcoxon's criterion for dependent groups. Differences between the groups were considered significant at $P<0.05$. Dunn and Tukey corrections for multiple comparisons were applied where needed. Data are presented as *Me* [25%; 75%] and as the values obtained in the studied range or at a specific point.

Results and Discussion

The unique structure of SkQ1 molecule (10-(6'-plastoquinonyldecyl) triphenylphosphonium bromide) allows the molecule to embed into the mitochondrial membrane in conformationally correct manner (Fig. 1).

Pilot phase of the experiment. SkQ1 is known to exhibit high antioxidant activity at nanomolar concentrations [15]. Another mitochondrial-directed antioxidant, MitoQ, is also known to have a strong antioxidant effect at a concentration of 50 nmol/L in a pig kidney ischemia model, resulting in increased total blood flow and urine output [16]. However, given that our study assumed an extremely prolonged stage of anoxia with enevitable severe impairment of cellular respiration and mitochondrial membrane

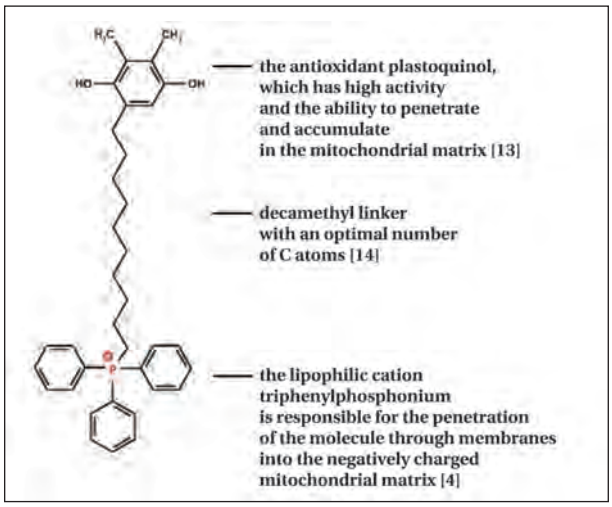

Fig. 1. SkQ1 molecule.

permeability [17], we performed a pilot experiment to select an adequate concentration of SkQ1. Isolated rat hearts were perfused with antioxidant solution of 3 different concentrations, 12 ng/ml, 120 ng/ml and 1200 ng/ml. Initially, the quantity of SkQ1 permeated and deposited in the myocardium was determined.

As expected, the number of ions per 1 g of tissue increased proportionally to the increase in the concentration of ions in the perfusion solution. Thus, the maximum concentration of ions was found in the SkQ1-1200 group at 6234.0 [4569.0; 8867.0] ng/g, in SkQ1-120 at 1059.0 [825.5; 1317.0] ng/g, and in SkQ1-12 at 268.1 [100.2; 293.0] ng/g (Fig. 2, *a*).

Coronary flow rate was restored to baseline in all experimental groups after a period of hypoperfusion and reperfusion. Notably, in SkQ1-120 group, the median AUC (15.1 [14.7; 16.0] mL/min) was significantly higher vs the control group (10.0 [9.0; 14.0] mL/min, $P=0.003$) and 15.8% higher than baseline value of 13.0 [12.1; 15.1] mL/min. However, increasing the SkQ1 concentration in the perfusion solution to 1200 ng resulted in a 3% decrease in CFR relative to baseline (Fig. 2, *b*). No intergroup differences were found in CPK-MB level, but an increase in SkQ1 concentration to 1200 ng/mL was associated with a 38.5% rise in CPK-MB vs the baseline values (Fig. 2, *c*). The level of LDH in the SkQ1-1200 group reached 5.0 [0.0; 8.0] U/L, which was significantly higher than that of the control (1.0 [0.0; 1.0] U/L) and SkQ1-120 (0.5 [0.0; 1.0] U/L, $P=0.003$, Fig. 2, *d*) groups. The increase in both LDH and CPK-MB levels at minute 15 of reperfusion in the SkQ-1200 group may indicate increased intensity of anaerobic respiration, ROC formation and sarcolemma damage of cardiomyocytes in the presence of 1200 ng/ml SkQ1 in perfusion solution, which can be considered as toxic effect of the drug at this concentration.

The pilot phase of the study identified potentially effective and safe concentrations of SkQ1 in

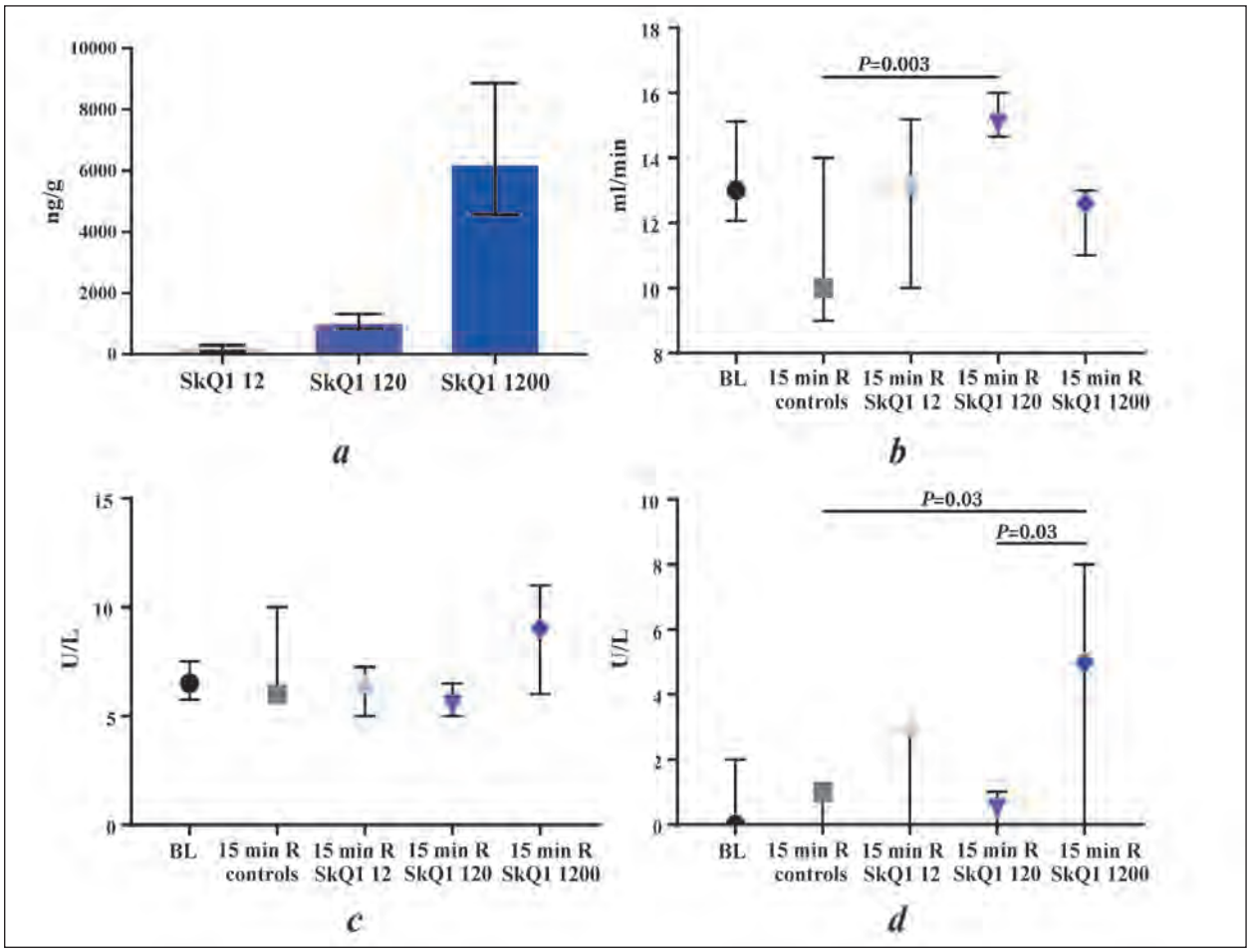

Fig. 2. Results of a pilot study of SkQ1 on an isolated rat heart model: *a* — SkQ1 concentration in myocardial tissue; *b* — coronary flow rate; *c* — creatine phosphokinase, MB fraction; *d* — lactate dehydrogenase level.
Note. For Fig. 2, 4–6: BL — baseline level; R — reperfusion.

an isolated rat heart model without aortic occlusion. Normothermic hypoperfusion with SkQ1 concentration of 12 ng/mL or 120 ng/mL had no effect on the baseline parameters of isolated hearts, in contrast to the 1200 ng/mL concentration, which provoked increased intracellular enzyme release with reduced CFR. Therefore, 12 ng/mL and 120 ng/mL SkQ1 concentrations were included in the main phase of the study.

Main phase of the experiment. The study of a new mitochondrial-directed antioxidant at the laboratory stage involved complication and bringing to clinical conditions of the experiment on the isolated heart, which included 240-minute cardioplegic total ischemia (anoxia) with a target myocardial temperature of +11°C. The range of studied parameters was expanded and grouped into 3 parts including oxidative stress, myocardial damage markers and cardiac parameters.

Oxidative stress. Antioxidant administration at a concentration of 12 ng/mL resulted in a significant decrease in stable NO metabolites compared with controls and the SkQ1-120 group: the total nitrate and nitrite concentration in the studied myocardial tissue homogenate was 36.2 [30.8; 39.8] μmol/mL (P=0.02), whereas in the SkQ1-120 group it was 52.3 [46.6; 55.0] μmol/mL (P=0.0006, Fig. 3, *a*).

NO is known to be a prooxidant and, together with peroxynitrite, directly damages DNA [18, 19]. However, our experiments did not reveal 8-OH-deoxyguanosine, a mitochondrial DNA oxidative stress product, in myocardial homogenate in either study group. The level of MDA, which reflects lipid peroxidation, was lowest in the SkQ1-12 group at 49.5 [41.1; 58.9] μmol/g and was significantly lower vs controls (P=0.02, Fig. 3, *b*) [20]. Normally, ROS are constantly formed in the cell at low concentrations. An antioxidant system that maintains the safe level of antioxidant molecules includes SOD-2 enzyme [21, 22]. However, there were no significant differences in mitochondrial SOD between the study groups; the average level of the enzyme was 14.4 ng/ml (Fig. 3, *c*). Therefore, we can assume that the decrease in oxidative stress in the SkQ1-12 group specifically relates to the antioxidant activity of SkQ1.

Markers of myocardial damage. When measuring the changes in CPK-MB and LDH release simultaneously before and after myocardial ischemia

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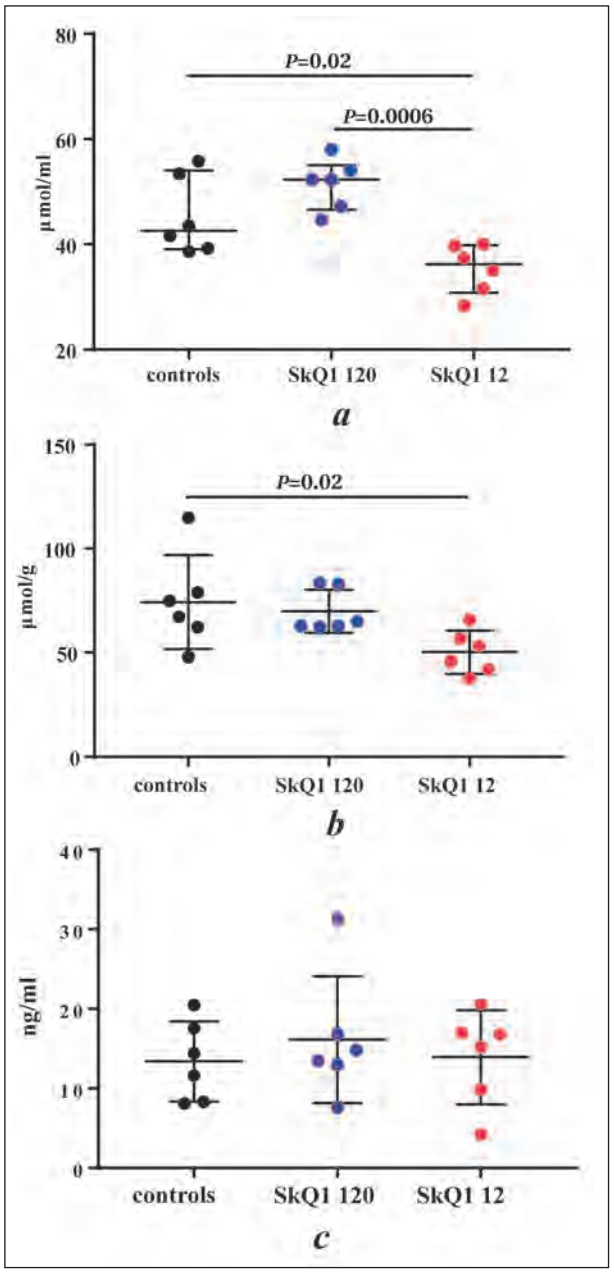

Fig. 3. Products of oxidative stress: *a* — total concentration of nitrites and nitrates; *b* — malondialdehyde; *c* — mitochondrial superoxide dismutase.

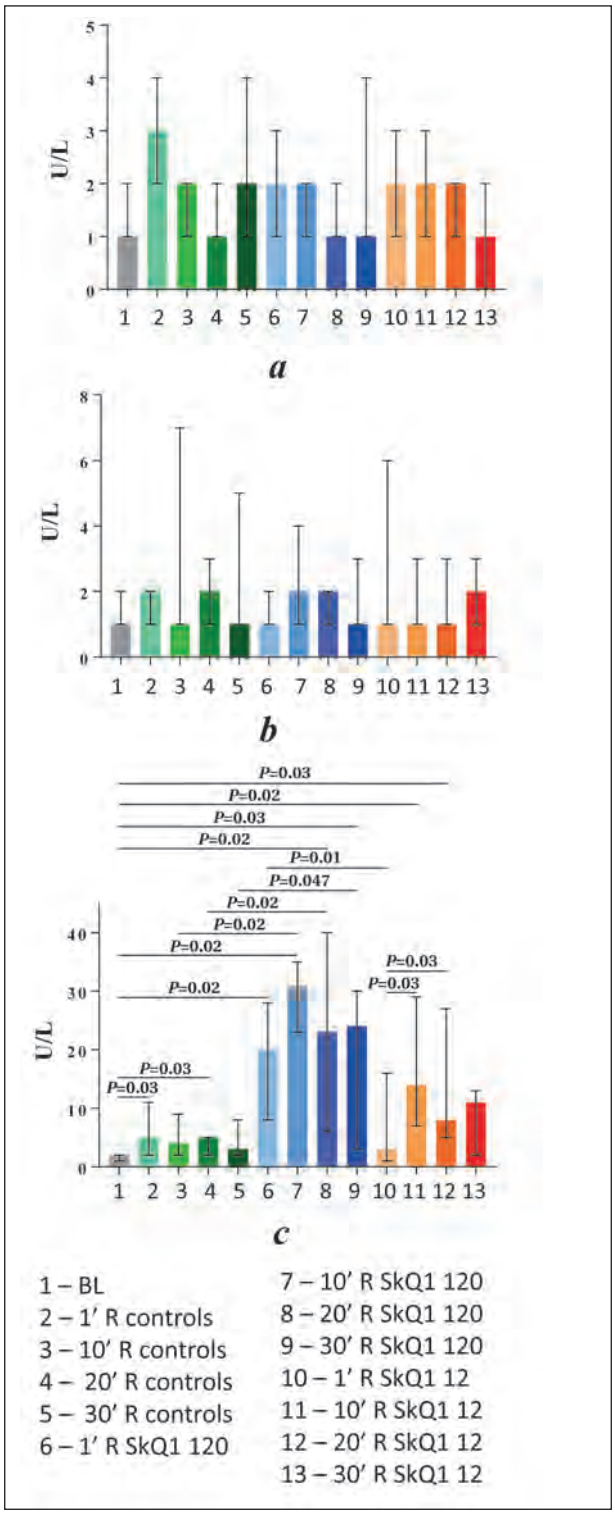

Fig. 4. Changes of the intracellular enzymes levels in the perfusate flowing from the isolated rat heart: *a* — creatine phosphokinase, MB fraction; *b* — lactate dehydrogenase; *c* — aspartate aminotransferase.

and reperfusion, we observed that the change in activity of both enzymes did not exceed 1–2 U/L (Fig. 4, *a*, *b*). However, addition of SkQ1 to the perfusion solution fostered a significant increase in AST release in myocardial outflow relative to baseline values and the control group ($0.01 \leqslant P \leqslant 0.047$, Fig. 4, *c*). The greatest increase in AST release was observed at ion concentration of 120 ng/ml: by the 30th minute, the enzyme activity exceeded the baseline one 12-fold. These changes can be regarded as a sign of cardiotoxicity of SkQ1 at a concentration of 120 ng/ml.

Lower SkQ1 concentration (12 ng/ml) resulted in delay of AST release at minute 1 (3.0 [1.0; 16.0] units/l). By the end of reperfusion, the median level of this enzyme was 5.5 times higher than the baseline one, but these changes were not significant and did not differ from the values at minute 30 of reperfusion in the control group (Fig. 4, *c*).

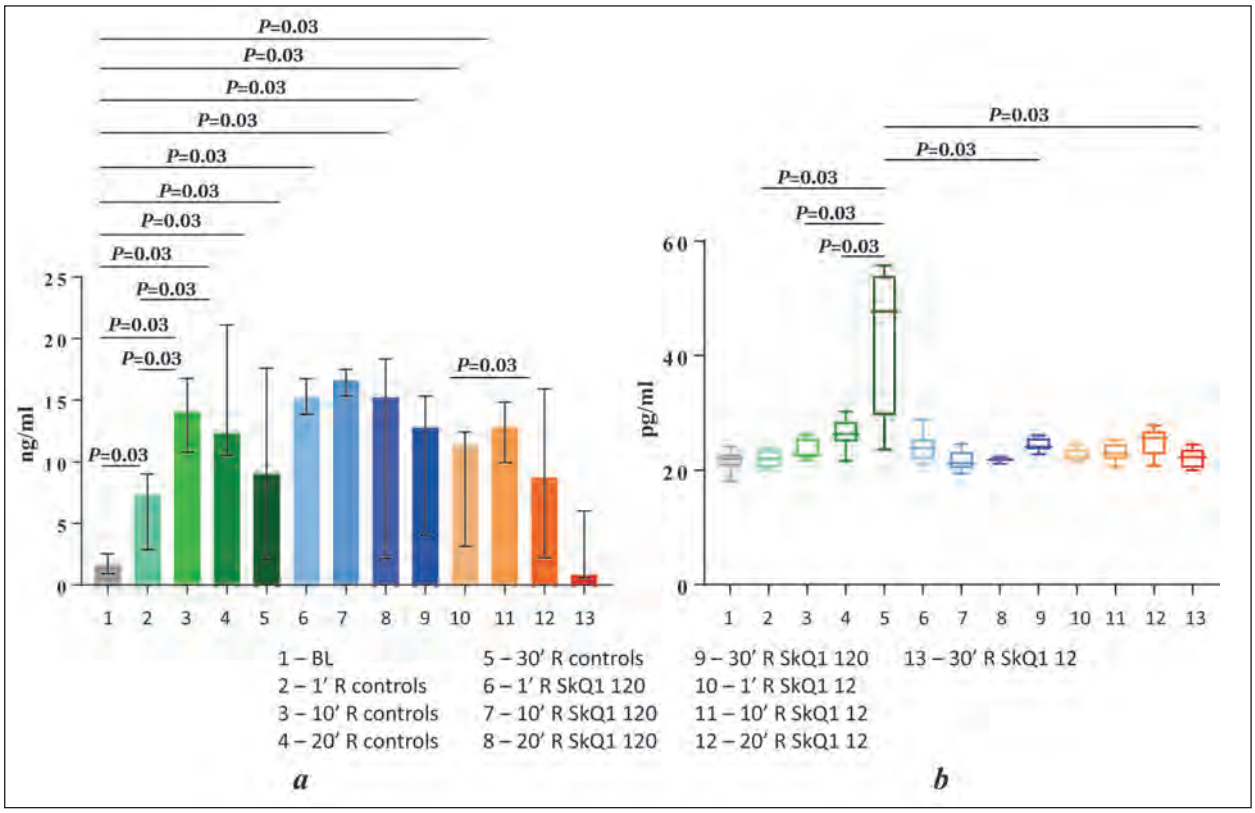

Fig. 5. Highly specific markers of myocardial damage: *a* — heart-type fatty acid binding protein; *b* — cardiac troponin I.

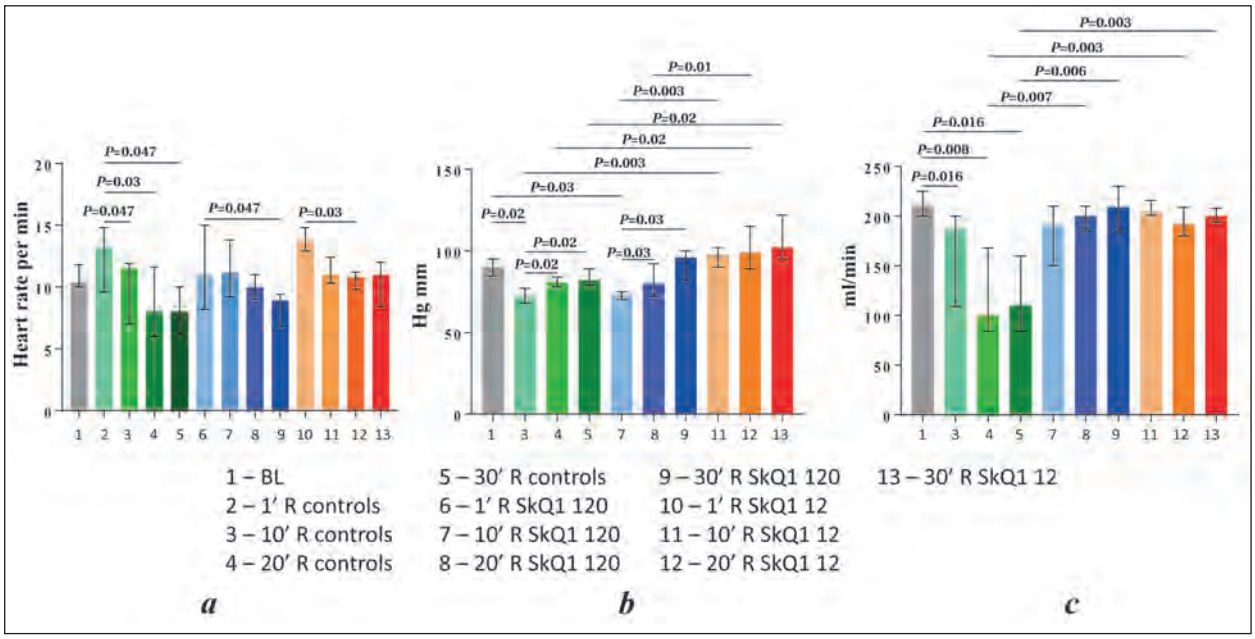

Fig. 6. Physiological parameters of isolated rat heart activity: *a* — heart rate; *b* — systolic blood pressure; *c* — coronary flow rate.

The most active release of H-FABP, a highly specific marker of myocardial damage, was observed in the SkQ1-120 group during the whole period of reperfusion at an average concentration of 14.6 ng/ml. In the SkQ1-12 group, there was an active decrease in H-FABP level in perfusate, which reached 0.8 [0.6; 6.0] ng/ml by minute 30 of reperfusion being significantly lower than that at minute 10 of reperfusion (P=0.03, Fig. 5, *a*)

Adding an antioxidant to the perfusion solution mediated protection of myocardial myofibrils throughout the reperfusion period: at drug concentrations of 12 ng/mL and 120 ng/mL, the intensity of cardiac contractile damage decreased vs the con-

trol group, where the cardiac troponin I level reached 47.4 [29.3; 54.15] pg/mL at 30 minutes after restoration of oxygenated flow of perfusion solution to the ischemic myocardium (Fig. 5, *b*).

Cardiac parameters. Addition of 12 ng/ml SkQ1 into the perfusion solution before the period of cold cardioplegia contributed to positive effects during reperfusion. The HR stabilized and reached the baseline level (211 [200; 225] beats/min) only on exposure to antioxidant, while in the control group there was a significant «fading» of HR by the end of the experiment down to to values that were only 52% of baseline (Fig. 6, *a*). In the SkQ1-12 group, a stable systolic pressure recovery to 98 [90; 102] mm Hg starting from the minute 10 of reperfusion was observed (Fig. 6, *b*).

The CFR recovery was observed on minute 10 of reperfusion only in the SkQ1-12 group and reached 11.0 [8.4; 12.0] ml/min by the end of the experiment. In the SkQ1-120 group, a 14.4% decrease in CFR vs the baseline of 10.4 [10.0; 11.8] mL/min was seen (Fig. 6c). The use of a lower concentration of antioxidant proved to be more effective with regard to cardiac parameters recovery. V. Kapelko et al. in *in vivo* experiments also showed the positive effects of SkQ1 on myocardial contractility [23]. Rhythm disturbances at minutes 1–2 in each study group were observed in 100% of cases. In the SkQ1-120 group, the frequency of short-term arrhythmia periods was 40% from minutes 15 to 30 of reperfusion, whereas in the SkQ1-12 group there was only 1 case of rhythm disturbance. The control group was characterized by maximal arrhythmia frequency, which was 50%, and in 1 case cardiac rhythm disturbances persisted during minutes 16 to 30 of reperfusion. These data correspond to those of V. Kapelko and V. Lakomkin, who succeeded in significant reduction of arrhythmia severity in the isolated heart using minimal doses of SkQ1 [24]. L.Bakeeva et al. also demonstrated that administration of extremely low doses of SkQ1 with food (0.02 nmol/kg/day for 3 weeks) was associated with elimination of cardiac arrhythmia in rats, while its increased dosage (125–250 nmol/kg/day for 3 weeks) resulted in reduced myocardial infarction area [25].

Conclusion

The model of cold cardiac ischemia/anoxia of isolated myocardium helps simulate heart condition under cardiopulmonary bypass. The cardioplegic solution in combination with low myocardial temperature (approximately 11°C) reduces the cardiac metabolic rate during anoxia but cannot completely and safely prevent the accumulation of oxidative stress products. Administration of an antioxidant SkQ1 at a concentration of 12 ng/ml prior to anoxia most effectively neutralized ROS, prevented the increase in the level of molecular markers of myocardial damage and restored its contractility during the reperfusion period. Minimal doses of SkQ1, a mitochondrial-directed antioxidant, possess cardioprotective action.

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Personalized Critical Care Medicine (Review)

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Персонализированная медицина критических состояний (обзор)

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Summary

Personalized medicine (PM) is a major trend in health care development in the 21st century. This area includes studying risk factors for disease development (prediction), interventions for preventing diseases (prophylaxis), individualization of diagnosis and treatment (personalization), informing the patient on disease prevention and treatment (participation). In the recent years, an intense research to introduce the personalized medicine principles into the management of critically ill patients, has been under way. This includes identification of patient groups based on genomic research, development of diagnostic tests using molecular markers, creation of novel classes of drugs based on individual patient characteristics.

The aim of the review is to summarize the available data on the implementation of the principles of PM in the routine practice of critical care institutions.

We analyzed more than 300 sources of literature from the Pubmed and Scopus databases, as well as the RSCI database. Eighty five most relevant sources were selected for the review. The paper reports data on the organization and results of implementation of PM principles and advanced technologies, such as Emergency Medicine Sample Bank (EMSB), in the daily activity of clinics providing emergency critical care. The formation of the novel PM concept focused on the treatment of critically ill patients has been discussed. The review contains detailed data on the patterns of development of specific critical illnesses such as acute cerebrovascular events, acute respiratory distress syndrome, traumatic brain injury, shock, myocardial infarction, cardiac rhythm and conduction disturbances. Medication efficacy in view of individual genetic patient characteristics has also been highlighted. No research limitations on the subject were identified.

Conclusion. The analysis of literature has demonstrated positive results of implementing PM principles in prevention, diagnosis and treatment of critically ill patients. Creation of Biobanks, development of training programs and regulatory documentation, advancing the scientific research, introduction of new methods of diagnosis and treatment will contribute to the implementation of PM principles in practical healthcare.

Keywords: personalized medicine; critical illness

Conflict of interest. The author declares no conflict of interest.

The full text version of the paper is available at www.reanimatology.com

Introduction

Individualized medical treatment strategy has been widely employed for centuries. Significant contribution to advancement of this approach was made by the founding fathers of Russian national medicine such as Matvey Mudrov, Sergey Botkin, Ivan Sechenov and others.

At the end of the twentieth century, Leo Holland (USA) formulated a trend called «Patient-Centered Diagnosis and Treatment», which marked the beginning of the era of personalized medicine (PM). In 1999, the term «personalized medicine» was proposed [1], reflecting the paradigm of 21st century healthcare [2]. The four cornerstones of PM (4P medicine) are prediction (ability to «predict» the disease), prevention (measures to prevent disease), personalization (individualized treatment), and participation (active role of the patient in the disease prevention and treatment) [3].

A paradigm shift from the «one size fits all» to individualized and targeted treatments has resulted in a greater focus on PM. Individual patient char-

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acteristics include genetic patterns and phenotype parameters (the latter include combination of physiological, biochemical, molecular, and morphological features). Unique personal characteristics are defined by such PM tools as personomics, which takes into account the human personality, preferences, values, goals, health beliefs, as well as available social support network, financial resources and individual life circumstances, which influence the response to treatment [4].

The need for the implementation of PM principles is driven by the lack of efficacy of existing treatment methods. According to Food and Drug Administration, the medications used are not effective in 75% of patients, which requires revision of the drug administration principles [5] and development of new drugs, devices and imaging technologies [6].

A survey of 153 institutions in the United States reveals considerable heterogeneity in the adoption of PM [7]. Relatively few health care providers in the United States offer PM as a part of the clinical workflow [8].

The development of PM requires elaboration of effective technologies for implementing the individualized patient care, formulating regulatory documentation, active involvement of educational institutions [9], and reducing health care costs through selection of effective therapies for the individual patient [10].

Public healthcare systems play a key role in the development of PM, as they guarantee new opportunities for patients in the implementation of individualized treatment approaches [11]. In the Russian Federation, the development of PM is regulated by the Presidential Decree of June 6, 2019 N254 «On the Strategy for the development of healthcare in the Russian Federation for the period until 2025», Orders of the Ministry of Health of the Russian Federation from April 24, 2018 N186 (the Concept of personalized medicine), from February 01, 2019 N42 (targeted program: «Development of fundamental, translational and personalized medicine»).

The aim of this review is to summarize the available evidence on the implementation of PM principles in the practice of medical institutions that treat critically ill patients.

The Role of Genetic Research in The Development of PM

The impact of PM on medical practice is largely attributed to genomic research. In this regard, expanding genetic curriculum in medical education could be the first key step to ensuring the widespread adoption of PM [12].

In a survey of individuals 18 years of age and older, many respondents cited educational resources as critical to successful implementation of PM [13]. A survey of 559 medical, pharmacy, genetics, and bioengineering students indicated positive student attitudes toward genetic testing and PM. The importance of pharmacogenomic education for more effective implementation of PM in clinical practice is emphasized [14]. Results of a population and healthcare providers survey revealed serious concerns about the protection of genetic privacy and the lack of support for a common genetic database [15]. Unprecedented opportunities are offered by population-based biobanks storing large amounts of genetic information and stimulating the development of PM [16] using the advantages of digital medicine [17]. The integration of electronic medical records and genomic research is an important aspect of PM development. The consortium network of electronic medical records and genomics data established in 2007 is funded by the National Institutes of Health (NIH) [18].

Based on a literature review of PM-related problems, the range of diagnostic methods and individual biological information, including genetic data and biomarkers, evaluation of the effectiveness of new drugs has been determined [19]. Due to advances in genetic knowledge, the patterns of clinical phenotype and individual response to drugs have gained better understanding [20].

Several national and international PM-based genomic projects have been realized based on big data analytics (complete and targeted sequencing, use of artificial intelligence), aimed at solving complex issues and developing new PM implementation programs [21].

The forecast of PM development by 2025 includes widespread genome sequencing, which will become affordable and commonly used in molecular diagnostics [22]. The Partners Health Care Personalized Medicine (introduction of genetics and genomics into research and clinical practice) program has developed the Whole Genome Sequencing (WGS) process, which is used to study both healthy individuals and patients with various diseases [23].

Both genomic and epigenomic changes, including methylation, acetylation, phosphorylation and ubiquitination of DNA and histone proteins (nucleosomes) as well as chromatin remodeling, significantly contribute to disease development. In this regard, both genetic and epigenetic diagnostic testing is required to implement the principles of PM [24].

Some urgent care centers employ various molecular assays based on genomics, transcriptomics, proteomics, and metabolomics to unravel disease mechanisms at the molecular level. However, the results of such approaches in emergency care have not been sufficiently addressed in the scientific literature [25].

Introducing PM Principles Into Critical Care Medicine

Despite certain obstacles to the implementation of PM principles in critical care medicine, there are several cases of successful implementation of measures in this direction.

The creation of the «Emergency Medicine Sample Bank» (EMSB) is an obvious success. The EMSB is a biobank of clinical data and biological samples collected from adult patients who were treated in the emergency department of a Colorado hospital, USA. EMSB is the first acute care biobank that seeks to cover all patients presenting to the emergency department. The EMSB has been integrated into the clinical workflow and serves as a powerful tool for researchers identifying new biomarkers of acute conditions, determining drug response mechanisms, and elucidating mechanisms of critical illness. Matching patient samples with data from the electronic medical record more accurately assists in identifying patient phenotypes. Combining these data with individual patient genomics allows determining the genetic basis of clinical manifestations and variability of treatment response. The authors believe that biobanks will be an important resource in emergency medicine [26].

The identification of patients with genotypic and phenotypic patterns influencing the success of diagnostic and therapeutic measures is an important principle of PM. In particular, stratification techniques based on the matching characteristics which serve as a tool for personalization of patients at risk of developing acute circulatory disorders [27] and cancer [28] have been proposed.

A new concept of PM, focused on the treatment of critically ill patients, based on four pillars, which include patient fitness and frailty assessment to determine their physiological reserve, monitoring of key physiological variables in disease and therapy, evaluation of the success of resuscitation, and integration of physiological and clinical data into an adaptive model of the patient was proposed [29].

To realize the benefits of PM it is necessary to resolve several organizational challenges such as determining the regulations for clinical trials, developing criteria for collaborative development and diagnostic standards, eliminating the incompatibility of information systems [30] by engaging the advantages of artificial intelligence [31].

An increasing number of publications covering the development, treatment and outcomes of critical conditions from the PM perspective is available. The study of acute cerebrovascular events seems promising. Cerebrovascular diseases, in particular stroke, are a major challenge for the public health. The genetic research has not yet been widely used in daily practice for stroke prevention. Currently, personalized aspects of stroke prevention are applied in an institutional care and patient education models [32]. The effective use of biomarkers allows to characterize more precisely a phenotype of patients, to trace progression of disease and response to the treatment methods.

A scheme for using biomarkers to diagnose aneurysmal subarachnoid hemorrhage has been proposed [33]. Cerebral hemodynamics is an important diagnostic biomarker in stroke. The authors have developed a simulation-based method that allows assessing cerebral hemodynamics based on the patient's vascular configuration and has high specificity and sensitivity in detecting changes in cerebral vascular perfusion [34].

The use of PM for prevention of cardiovascular diseases in women is crucial for the gender-specific medicine [35]. Based on the study of angiogenesis and neuroplasticity, modern biomarkers of post-stroke recovery have been proposed and recommended for use in clinical practice [36].

Acute respiratory distress syndrome (ARDS) is one of the life-threatening critical conditions, characterized by 40% mortality in patients of intensive care units and diagnosed based on acute hypoxemia, bilateral pulmonary infiltration and noncardiogenic pulmonary edema. ARDS has multiple clinical risk factors and mechanisms of lung damage, which in most cases can explain the lack of efficacy of pharmacological treatment. Identifying ORDS phenotypes and using this information for patient selection for clinical trials increases the chances of novel therapies being effective. Procollagen alveolar type III peptide (PCP-III) is a robust candidate biomarker among bronchoalveolar fluid proteins whose levels are associated with ARDS development and outcomes. In an observational study of 32 patients, PCP-III was highly sensitive (0.90) and specific (0.92) for the diagnosis of fibroproliferation in ARDS [37]. Its potential is used for the development of new therapeutic agents based on the mechanisms of ARDS and identification of ARDS subpopulations which can benefit from patient-specific treatment approach [38].

Identification of genetic biomarkers offers hope for the creation of effective methods of stratification, prognosis, and development of novel treatments for ARDS [39]. ARDS associated with sepsis is characterized by significant mortality. If subtypes of both sepsis and ARDS are taken into account, the prospect of a personalized approach for effective treatment of patients with these critical conditions seems promising [40].

Based on the study of blood biomarkers such as interleukins (IL-6 and IL-8), interferon gamma (IFN-γ), surfactant proteins (SPD and SPB), von Willebrand factor antigen, angiopoietin 1/2 and plasminogen activator inhibitor-1 (PAI-1), two subgroups of ARDS phenotypes (hypo- and hyperinflammatory) were identified. Patients with these

phenotypes have significantly different clinical outcomes and response to mechanical ventilation, infusion therapy and simvastatin treatment [41]. The hyperinflammatory subgroup is associated with shock, metabolic acidosis and poor clinical outcome [42–44].

Hemodynamic disturbances often are associated with adverse outcome in critical conditions. Therefore, prediction of acute hypotension development in patients is necessary for improving the intensive care performance [45].

Traumatic brain injury (TBI) is commonly associated with critical illness being one of the leading causes of mortality in young adults. In TBI, patients with similar injuries, age, and health status often show differences in recovery from trauma.

Currently, emphasis is placed on the development of a personalized approach to the treatment of TBI. Studies in model systems and the use of candidate genes in human studies have allowed to identify factors influencing the outcome in TBI. Functional outcomes after TBI vary widely among patients with «apparently similar» injuries. The presence/absence of a single nucleotide polymorphism (SNP) has been found to affect outcome after TBI. One of the well-characterized SNPs, Val66Met, is associated with the brain-derived neurotrophic factor (BDNF) gene. This SNP affects neurological function in both healthy subjects and patients with TBI [46]. The use of neuroimaging techniques has resulted in the development of tailored methods of studying brain atrophy associated with TBI [47].

The data on endocannabinoid metabolism and its therapeutic effects in traumatic brain injury have been summarized from the PM perspective [48]. The development of neuronal system models for the study of human trauma evolution using chips is under way. Three classes of chips have been identified including microfluidic, compartmentalized and hydrogel. The methods of using 3D-printing to design and produce next-generation chips created on the base of stem cells and their application in «personalized neuroscience» have been developed [49].

Shock is one of the essential issues of critical care medicine. Personalized medicine has identified subclasses of septic shock based on gene expression with phenotypic differences. Gene expression data for 100 genes with identifiable subclasses were obtained using a multiplex information RNA quantification platform and visualized using gene expression mosaics. Based on this technology, two subclasses (one of which showing decreased gene expression) characterized by different course of septic shock were reproduced. The above-mentioned subclass was independently associated with mortality, and the use of corticosteroids in such patients was also independently associated with lethal outcome [50].

The role of steroids in survival in septic shock remains controversial. Thus, the individual treatment effect of corticosteroids in adults with septic shock in intensive care units has been evaluated [51]. The data suggest that an individualized treatment strategy allowing to choose the patient for steroid therapy was successful irrespective of the potential side effects of the drugs [52].

Myocardial infarction is one of the common life-threatening critical conditions. Research based on personalized medicine is underway to unravel the pathogenesis of circulatory disorders in the coronary artery system and to identify the diagnostic molecular markers. Epigenome changes have been shown to elucidate some mechanisms of coronary heart disease (CHD) pathogenesis. The «network medicine» combines standard clinical signs and noninvasive cardiac imaging tools with epigenetics for in-depth molecular phenotyping of CHD. In particular, this approach is used to develop new drugs based on natural components.

Several clinical trials have focused on the evaluation of circulating miRNAs (e.g., miR-8059 and miR-320a) in the blood in combination with imaging parameters such as the coronary calcifications and the degree of coronary artery stenosis [53].

Rhythm and conduction abnormalities can also be life-threatening. Atrial fibrillation (AF) is the most common cardiac arrhythmia. Despite advances in surgical technologies, antiarrhythmic drugs remain the mainstay of treatment of symptomatic AF. However, the response varies considerably among patients: more than half of patients who received rhythm control therapy have recurrent AF within a year.

The limited success of rhythm control strategy could be partially due to individual differences in disease mechanisms and the inability to predict response to medications in individual patients. Studies of AF over the past decade have shown that susceptibility to AF therapy could be due to genetic regulation. Increased predisposition to AF has been found to be associated with the chromosome 4q25 locus. Screening of candidate genes regulating cardiac potassium and ion channel function in probands and families with early-onset AF revealed several rare variants. Screening of DNA isolated from cardiac atria has identified a mutation of the GJA5 gene underlying abnormal electrical connections between cardiac cells. Based on meta-analysis, more than 10 loci relevant to the development of AF were identified [54].

A study of 6,567 Caucasian patients found an association between the incidence of atrial fibrillation and greater height in women [55].

Potassium channel genes have been shown to be associated with the risk of AF. Their enhanced function leads to a faster repolarization current

and a shorter effective refractory period which increases cellular excitability and susceptibility to arrhythmias. Mutations in sodium channel subunit genes have also been associated with AF. A single-nucleotide polymorphism in SCN10A has been found to be associated with the early-onset AF [56].

Possible interactions between obstructive sleep apnea (OSA), atrial fibrillation (AF) and connexins have also been revealed. Epidemiological studies show that OSA is associated with increased incidence and progression of coronary heart disease, heart failure, stroke, and arrhythmias, especially AF. The role of connexins in AF is now relatively well established. Understanding the biology and regulatory mechanisms of connexins in OSA at the transcriptional, translational, and posttranslational levels will allow to elucidate the role of connexins in the development of OSA-induced AF [57]. Increased susceptibility to AF can be explained by various risk factors modifying left atrial tissue [58].

Atrial fibrillation is characterized by structural and electrical remodeling of the heart. Atrial fibrosis, a hallmark of structural atrial remodeling, is a complex multi-factorial process involved in the occurrence and maintenance of AF [59]. Atrial models have been developed that include detailed atrial anatomy, tissue ultrastructure, and the pattern of fibrosis distribution. Use of atrial models has given important insights into the mechanisms underlying AF by demonstrating significance of atrial fibrosis and altered atrial electrophysiology in the initiation and maintenance of AF [60]. Recent data demonstrate a hereditary component underlying AF [61].

Critical conditions are often accompanied by deadly infectious complications. Advances in diagnostics have minimized the frequency of «blind» antibiotic prescription without proper laboratory evaluation. Molecular diagnostics, in turn, have been improved by nanobiotechnology and are coupled with improved delivery of antimicrobial agents. Sequencing the microbial and viral genomes and studying the genetic susceptibility of patients makes it possible to develop individualized approaches to their treatment [62].

Critically ill patients are often prescribed with enteral or parenteral feeding. Personalized nutrition in general may be a more effective way of changing lifestyle than other measures. A study [63] evaluated the effects of a 10-week personalized nutrition system on lifestyle and health outcomes. The intervention reduced calorie, carbohydrate, sugar, total and saturated fat intake. A reduction in body weight, fat content, and hip circumference was registered in the studied cohort. Health improvements were most pronounced in the altered phenotype subgroup, indicating that a personalized nutrition program may be particularly effective for behavior change in target groups with impaired health.

To develop personalized nutrition, the concept of «system flexibility» has been introduced, involving real-time assessment of metabolism and other processes. Genetic variants and performance measures were integrated into this systemic approach to provide a strategy for a balanced assessment of individual nutrition [64].

The treatment based on personalized medicine also takes gender differences into account. The terms «sex» and «gender» are often misused as synonyms. Sex implies anatomical and physiological differences, while gender includes mental, cultural and social differences. Consideration of sex and gender differences is important for effective disease prevention, identification of clinical signs, outcome prediction and therapy optimization [65].

Pharmacogenomics of critical conditions. Pharmacogenomics is the most important element in dealing with PM issues. Difficulties in implementing the principles of pharmacogenomics are related to gene variability. For example, CYP2D6 has several alleles that determine different rates of drug metabolism, which can change the therapeutic effect [66] and influence individual treatment response and drug toxicity manifestations [67]. Clinical implementation of personalized therapy based on pharmacogenomics is still limited. In Korea, an assessment of physicians' knowledge of personalized therapy based on pharmacogenomics was conducted. Fifty-three percent of physicians reported insufficient knowledge of pharmacogenomics. The main obstacle to its clinical implementation was the high cost of genetic testing and the lack of education of medical professionals and clinical experts in pharmacogenomics [68].

It is unclear whether pharmacogenomics data can be used to predict emergency department hospitalization. A cohort study has shown that traditional risk factors, such as age and self-perceived health, are much more likely to predict emergency department hospitalization and treatment than pharmacogenomic information (69). At the same time, pharmacogenetic testing can help identify patients at increased risk for drug toxicity. A step-by-step approach to pharmacogenetic testing in primary care has been developed, involving identification and education of patients, ordering of pharmacogenetic tests, and interpretation of their results [70].

Clopidogrel and CYP2C19 variants are the first example of a drug-gene interaction. Clopidogrel is an antiplatelet agent used in acute coronary syndrome (ACS). Studies have shown that certain variants of the CYP2C19 gene are associated with altered function of enzymes involved in clopidogrel metabolism, which puts patients with acute coronary syndrome at risk for thrombotic complications [71].

Pharmacogenetics is used to develop individualized treatments specific to people from different

ethnic or racial groups with varying degrees of genetic diversity. Genetic differences can alter the therapeutic efficacy of drugs. Pharmacogenetic studies in mixed ethnic groups have identified candidate genes, the best of which is the gene encoding the ARDB2, the target receptor for beta-agonist therapy [72].

In 2015, the IGNITE (Introducing Genomics into Practice) network created an online resource toolkit on genomic medicine implementation, allowing users to create targeted guidelines for introducing genomic medicine, including pharmacogenomics [73].

Multiple driver genes can cause «resistance» to individual drugs. New personalized driver genes and combinatorial drug identification algorithm (CPGD) have been developed. The results showed that the new technology is more efficient compared to existing synergistic combinatorial strategies [74].

Adverse drug reactions (ADRs) are an important and frequent cause of ineffective treatment. Genetic predisposition to adverse reactions is an emerging challenge in various areas of medicine. Improved genotype-phenotype correlation using novel laboratory methods and the introduction of artificial intelligence can contribute to personalized prediction of adverse reactions, selection of the optimal drug and its dose for each patient [75].

Drug candidates demonstrating well-defined pharmacokinetic and pharmacodynamic profiles often fail to confirm their efficacy in phase II and III clinical trials. A system (QSP platform) based on a drug development strategy has been proposed and implemented at the University of Pittsburgh Drug Discovery Institute. This platform addresses the issues of biological heterogeneity and the evolution of resistance mechanisms, which present a major obstacle in drug development, and involves a paradigm shift from conventional medicine to personalized medicine [76].

Studies of individualized efficacy of pharmacological drugs in critical conditions, such as asthma [77], thrombotic complications [78], COVID-19 infection involving in silico analysis (computer models) [79], are being conducted.

The personalized medicine is a constantly evolving area. One of the novel directions is theranostics which includes the creation of pharmacological preparations that can be used to resolve diagnostic and medical problems in an integrated manner. In particular, several preparations for tailored diagnosis and treatment of central nervous system diseases have been developed from the theranostics position [80]. Our studies of molecular markers in ischemic and hemorrhagic strokes have revealed individualized changes in their serum level during the disease course [81, 82].

Conclusion

Literature data analysis demonstrates the positive results of implementing personalized medicine principles in the prevention, diagnosis and treatment of critically ill patients. Creation of biobanks, development of training programs and regulatory documentation, intensification of scientific research, introduction of new diagnostic and therapeutic methods will promote the implementation of personalized medicine principles in practical health care.

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Paroxysmal Sympathetic Hyperactivity Syndrome (Review)

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Summary

Paroxysmal sympathetic hyperactivity (PSH) is one of the complications of acute severe brain injuries (traumatic brain injury, intracranial hemorrhage, ischemia, and posthypoxic conditions) in both adults and children. Its high incidence and severe sequelae including organ dysfunction, infectious complications, impaired blood supply to organs and tissues associate with increased disability and mortality. The choice of effective therapy can be challenging because of multifaceted manifestations, diagnostic difficulties, and lack of a clear understanding of the pathophysiology of PSH. Currently, there are various local and international treatment strategies for PSH.

The aim of the review is to summarize clinical and scientific research data on diagnosis and treatment of PSH to aid in the selection of an effective therapy.

Material and methods. Web of Science, Scopus and RSCI databases were employed to select 80 sources containing relevant clinical and research data on the subject of this review.

Results. The key principles of diagnosis and treatment of paroxysmal sympathetic hyperactivity have been reviewed. The current views on etiology and pathogenesis of paroxysmal sympathetic hyperactivity development were outlined. The clinical data concerning complications and sequelae of paroxysmal sympathetic hyperactivity were analyzed. We conclude the review with a discussion of current methods of the syndrome prevention.

Conclusion. Preventing PSH and its adequate and prompt treatment could help avoid the abnormal pathway development following a severe brain injury, reduce its negative consequences and rate of complications, along with the duration of mechanical lung ventilation, patient's stay in ICU, disability and mortality rates. Careful selection of pathogenetic, symptomatic and supportive therapy significantly improves the rehabilitation potential of patients.

Keywords: sympathetic hyperactivity; traumatic brain injury; intracranial hemorrhage; neurovegetative stabilization

Conflict of interest. The authors declare no conflict of interest. The illustrations were taken from open sources and are used under a CC BY license (free use with credit to the authors).

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Introduction

The first observation of paroxysmal sympathetic hyperactivity (PSH) published in 1929 was the report of Canadian neurosurgeon Wilder Penfield on the treatment of a 41-year-old woman with cholesteatoma of third ventricle [1]. Later, multiple observations reporting PSH in traumatic brain injury (TBI), intracranial hemorrhage (ICH), ischemic, infectious, posthypoxic, and dysmetabolic brain injuries appeared. Various terms have been used to describe this condition including diencephalic seizures, central autonomic dysregulation, hyperadrenergic state, midbrain syndrome, autonomic dysfunction syndrome, dysautonomia, autonomic storm, sympathetic storm, diencephalic catabolic syndrome (DCS), etc. [2–7]. The study of PSH in the A. L. Polenov Russian Neurosurgical Institute started as early as in the 1950s. The scientists from this institute coined the term «diencephalic catabolic syndrome» and elaborated its pathophysiology, clinical, laboratory and pathological criteria as well as the management strategy [2, 8, 9]. The widely accepted term «paroxysmal sympathetic hyperactivity» was first recommended in 2010 [10, 11].

The International Consensus (2014) developed diagnostic criteria and finally approved the term «paroxysmal sympathetic hyperactivity», which was defined as a syndrome, recognised in a subgroup of survivors of severe acquired brain injury, by simultaneous, paroxysmal transient increases in sympathetic [elevated heart rate, blood pressure, respiratory rate, temperature, sweating] and motor [posturing] activity» [12]. The panel of experts selected 11 of 16 previously considered signs as pathognomonic for PSH. The scales assessing the probability of a PSH diagnosis and its severity were developed (Tables 2 and 3) [12]. Pediatric scales have also been proposed (Table 4) [13].

The aim of this review is to summarize clinical and scientific research data on the diagnosis and treatment of PSH to aid in selecting an effective therapy.

Etiology. Hyperactivity of the sympathetic nervous system may develop following the severe brain injury of any etiology. This illness is probably due to the adaptive «fight or flight» response, universal for mammals and developed during evolution, where the sympathetic nervous system plays the pivotal role. The sympathetic hyperactivity manifestations, initially adaptive, become abnormal after having persisted for a long time.

The risk of PSH is higher in patients with severe TBI (up to 80% of all cases of PSH) [14, 15], intracranial hemorrhages (ICH), hypoxic, dysmetabolic (in particular, hypoglycemic) brain injuries, intracranial hypertension, including those due to hydrocephalus. Less commonly, PSH develops in patients with a brain tumor, acute ischemic cerebrovascular events, meningitis, and encephalitis [16–18]. A review of 349 published cases of PSH showed that about 80% of them developed after TBI, 10% in patients with postanoxic encephalopathy, 5% after cerebrovascular event, while the remaining 5% were associated with hydrocephalus, tumor, hypoglycemia, infections or unspecified causes [10].

The frequency of PSH after traumatic brain injury ranges from 8 to 33% [4, 11, 19]. Retrospective reviews show that PSH most often develops in diffuse axonal damage [20].

The etiology and incidence of PSH in children are comparable to those in adults [21]. The main causes of this syndrome are traumatic brain injury and posthypoxic encephalopathy. Many researchers note that in children the severity of sympathetic hyperactivity is usually higher than in adults, which is associated with age-specific characteristics of the autonomic nervous system [22, 23].

The frequency of PSH decreases over time [10, 24, 25]. A survey of 333 patients in a vegetative state in Italy [25] showed a decrease in the incidence of PSH over time, from 32% (for TBI) and 16% (for other etiologies of vegetative state) between 1998-2005 to 18% and 7% between 2006–2010. There are papers indicating an increase in the incidence of PSH over time [10]. This is mainly due to the increased pain syndrome and autonomic instability caused by discontinuation of opioid analgesics and alpha2-agonists after the patient's transfer from intensive care unit (ICU) to a specialized department or rehabilitation facility. Preparation of the patient for transfer (timely withdrawal of potent drugs, selection of oral medications, adequate nutritional support, and control of infections) allows to reduce the rate of PSH and prevent its increase.

The wide range of reported morbidity makes diagnosing PSH even more difficult. Factors explaining the differences between studies may include variations in design, assessment of underlying disease severity and differential diagnoses, timing, and frequency of PSH evaluation.

Pathogenesis. There are many theories concerning the pathophysiology of paroxysmal sympathetic hyperactivity. None of them is comprehensive. It is still unclear which factors underlie the paroxysms, why they may stop on their own and what affects their frequency and duration.

W. Penfield suggested the epileptogenic theory of PSH origin [1, 26]. In the 1970–80s, the Polenov Neurosurgery Institute considered the syndrome as a nonspecific response of diencephalic structures triggered by brain injury and persisting long after elimination of the damaging factor. This response included impaired consciousness, central hyperthermia, hypothalamic-type respiratory disorders, severe vascular pressure reactions, and widespread neurodystrophy [2, 8]. Particular attention focused

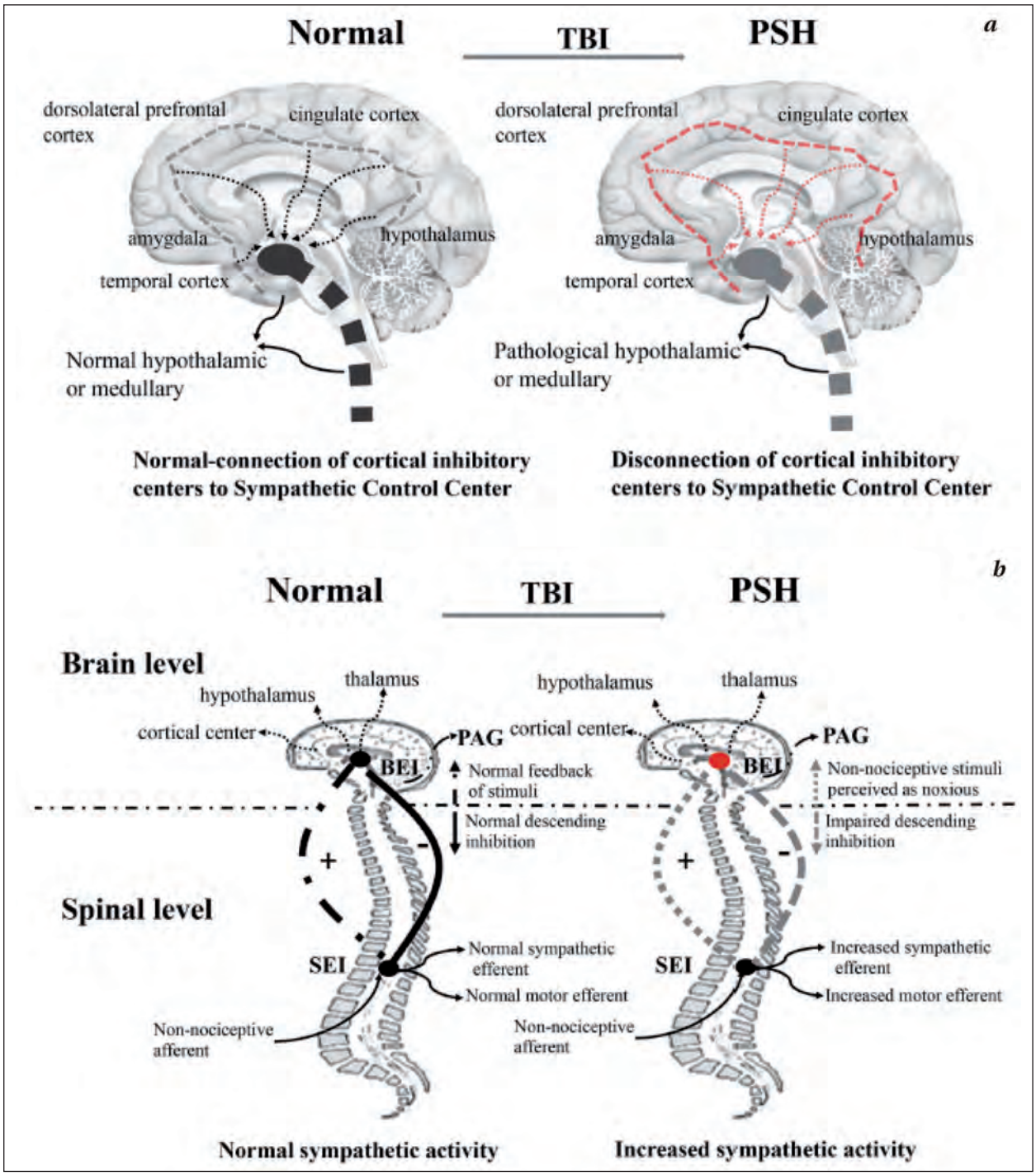

Fig. 1. Disconnection theory and EIR model of the pathogenesis of PSH, by Zheng R-Z, Lei Z-Q, Yang R-Z et al., 2020 [33].
Note. EIR — excitatory/inhibitory ratio; BEI — brain excitatory/inhibitory centers; PAG — periaqueductal gray matter; PSH — paroxysmal sympathetic hyperactivity syndrome; SEI — spinal excitatory/inhibitory centers; TBI — traumatic brain injury.

on changes in the bioelectrical activity of the diencephalic structures, the appearance of delta and theta wave activity [2, 8, 9]. In our opinion, these mechanisms may underlie the pathophysiology of PSH in many cases.

According to one of the current hypotheses, the combination of diffuse and/or focal injury «disconnects» one or several cortical inhibitory centers (such as islet and cingulate cortex) with hypothalamic, diencephalic and brain stem centers responsible for supraspinal control of sympathetic tone (disconnection theory) [27, 28]. The existing disconnection theory (Fig. 1, *a*) is based on the fact that severe paroxysmal activity is associated with impaired regulatory and integrative functions, including those of the brainstem [10, 28]. Sympathetic activity originates in the brainstem, hypothalamus, and spinal cord. The anterior hypothalamus and medulla ob-

longata are considered to be the main regions involved in central sympathetic nervous system activation [20, 28, 29]. Sympathetic activity inhibition occurs in cortical structures such as hippocampus, amygdala, insular, cingulate, medial temporal, and dorsolateral prefrontal cortex [30]. Subsequently, a more detailed study showed that disconnection of one or more brain centers or cortical and subcortical abnormalities caused by focal lesions or diffuse injuries lead to autonomic dysfunction [28]. Despite the existing evidence supporting the theory of disconnection of cerebral inhibitory pathways from excitatory centers, it is still insufficient to explain all the symptoms observed in patients with PSH.

Normally, various cortical, hypothalamic, thalamic, and other subcortical areas modulate activity in brainstem centers with the periaqueductal gray matter considered a key center that inhibits excitation [30]. The periaqueductal gray matter has an inhibitory effect on spinal reflex arcs, thus maintaining the balance between inhibitory and excitatory inter-neuronal influences on motor and sympathetic efferents and allowing adequate perception of normal sensory stimuli as non-threatening. In the excitatory/inhibitory ratio model (EIR), disabling the descending inhibition causes maladaptive dendritic arborization and spinal circuit excitation, and even minor stimuli (temperature change, tactile stimulation, and others) can be perceived as strong and cause increased motor and sympathetic activity [27, 28]. This is complicated by a relative decrease in functional dopaminergic activity. As a result, activation of the sympathetic nervous system and increased levels of circulating catecholamines develop [27] (Fig. 1, *b*). The presented model describes PSH as a two-stage pathological process. First, excitation occurs due to the disabling of descending inhibitory pathways, and second, the paroxysm stops when inhibitory factors are restored [10, 27, 28, 31]. This theory explains the abnormally enhanced and prolonged response to stimuli that are either not nociceptive or are only minimally nociceptive (e. g., tracheal lavage) as an allodynamic adaptation, resembling the phenomena observed in chronic pain syndromes. The paroxysm triggers include vascular spasm and increased intracranial pressure with a reported case of paroxysm development after abrupt termination of hypothermia procedure [32]. The proposed theory explains why patients with lesser injury of the brain stem have shorter duration of paroxysms and much faster onset of inhibition in the upper parts of the spinal cord. It also suggests that paroxysmal sympathetic symptoms may be a response to structural or functional disturbances of the midbrain in patients with TBI [10].

Figure 1, *a* presents the disconnection theory. On the left, normal connection of the cortical inhibitory center (islet and cingulate cortex) with the sympathetic centers (hypothalamic, diencephalic, and stem) is shown. On the right, disconnection of the cortical inhibitory centers from the sympathetic center during TBI is depicted.

A part of Figure 1, *b* presents the model of impaired excitation-inhibition relationship. On the left, normal variant is shown as cortical and subcortical, hypothalamic and thalamic centers modulate activity of incoming signals and then exert inhibitory effect on the spinal reflex activity. At the spinal cord level, spinal centers normally provide afferent feedback (afferent) from sensory receptors perceiving various stimuli (pain, temperature, tactile etc.) and exert efferent action (sympathetic and motor). On the right, disabling descending inhibition leads to excitation of the feedback loop, with a minor stimulus potentially perceived as a strong one.

It has been suggested that an imbalance between the sympathetic and parasympathetic nervous system underlies PSH [27, 28, 33].

Neuroinflammation is considered to be one of the causes of PSH. Elevated levels of interleukins stimulate the sympathetic activity [34]. In severe brain injury, neuroinflammation can become chronic and trigger sympathetic overactivity.

Recently, increasing attention has been paid to disorders of neuroendocrine regulation [35]. In the neurotransmitter system, paroxysms occur due to uncontrolled activity of the adrenergic system, leading to increased circulation of catecholamines [10, 33, 36, 37]. Studies show that the blood levels of adrenocorticotropic hormone, adrenaline, noradrenaline, and dopamine significantly increase during paroxysms, while the levels of noradrenaline and dopamine decrease during the interictal period [19, 33, 36].

Although the anatomy of PSH pathogenesis is still uncertain, several studies have shown that focal brain parenchymal lesions increase its likelihood [33, 38]. A more detailed characterization of structural lesions has been obtained using neuroimaging techniques [33]. Patients with deeper brain lesions in the periventricular white matter, the corpus callosum or stem were more likely to develop PSH than those with lesions in the cortex and subcortical structures [33, 39].

Symptoms. PSH is characterized by impaired consciousness (depression or agitation), hyperhidrosis, fever, increased heart rate, respiratory rate, hypertension, mydriasis, increased muscle tone, dystonia, hyperkinesis and myoclonus [10, 33, 40, 41] (Table 1).

Sympathetic crises can develop from 1 to 15 times per day and last from 10 to 30–40 minutes [4]. Symptoms are thought to persist for several months to several years, with one study showing a mean duration of 5 years after trauma [4].

Table 1. The symptoms of PSH.

Organs and systems	The symptoms
Cardiovascular system	Tachycardia
	Increased myocardial contractility
	Increased cardiac output
	Hypertension
Bronchopulmonary system	Tachypnea
	Bronchial dilation
	Pulmonary edema
Eyes	Pupillary dilation
Gastrointestinal tract	Decreased motility
	Malabsorption
	Ileus
Musculoskeletal system	Muscle tone increase
	Dystonia
	Contractures
	Spasticity
	Myoclonus
Skin	Increased redness
	Sweating

Table 2. Diagnostic criteria of PSH (Clinical Feature Scale, CFS)

Criteria	Points			
	0	1	2	3
Heart rate (per min)	< 100	100–119	120–139	⩾140
Respiratory rate (per min)	< 18	18–23	24–29	⩾30
Systolic blood pressure (mmHg)	<140	140–159	160–179	⩾180
Temperature (°C)	<37,0	37,0–37,9	38,0–38,9	⩾39
Sweating	Absent	+	++	+++
Posturing during episodes	Absent	+	++	+++

Table 3. Additional criteria for PSH (Diagnosis Likelihood Tool, DLT).

Criteria	Points
Clinical features occur simultaneously	1
Episodes are paroxysmal in nature	1
Sympathetic over-reactivity to normally non-painful stimuli	1
Features persist ⩾3 consecutive days	1
Features persist ⩾2 weeks post-brain injury	1
Features persist despite treatment of alternative differential diagnoses	1
Medication administered to decrease sympathetic features	1
⩾2 episodes daily	1
Absence of parasympathetic features during episodes	1
Absence of other presumed causes of features	1
Antecedent acquired brain injury	1

Table 4. Pediatric score for the diagnosis of PSH.

Parameter	Points							
	0		1		2		3	
Years	1–4	5–15	1–4	5–15	1–4	5–15	1–4	5–15
Heart rate (per min)	<110	<100	110–124	100–119	125–139	120–139	⩾140	
Respiratory rate (per min)	<30	<25	30–34	25–29	35–39	30–34	⩾40	⩾35
Systolic blood pressure (mmHg)	<100	<120	100–109	120–129	110–119	130–139	⩾120	⩾140
Diastolic blood pressure (mmHg)	<65	<75	65–72	75–82	73–79	83–89	⩾80	⩾90
Temperature, °C	<37		37–37,9		38–38,9		⩾39	
Sweating	Normal		Increased		Localized diaphoresis		Generalized diaphoresis	
Muscle tone increase	Absent		Mild increase		Neat increase		Generalized spasticity or opisthotonus	

Diagnosis. Diagnostic criteria for PSH were defined by an international consensus in 2014 (Tables 2, 3) [12]. In the same year, diagnostic scales for children were proposed [13] (Table 4).

Additional criteria (Diagnosis Likelihood Tool) were defined for the confirmation of the diagnosis (Table 3).

Based on the total score of CFS and DLT, a decision on the diagnosis of PSH is made: unlikely < 8 points, possible 8–16 points, probable > 17 points.

The researchers at Polenov Neurosurgical Institute developed original criteria for the diagnosis of PSH in 2019 [3, 42] (Tables 5, 6).

Table 5. Diagnostic criteria for PSH.

Parameter	Points			
	0	1	2	3
Main criteria				
Heart rate (per min)	< 100	100–119	120–139	⩾140
Systolic blood pressure (mmHg)	< 140	140–159	160–179	⩾180
Respiratory rate (per min)	< 18	18–23	24–29	⩾30
Kerdö Autonomic Index	0	+1–+10	+11–+20	>+21
Body temperature, °C	< 37,0	37,0–37,9	38,0–38,9	⩾39,0
Muscle tone increase (Ashworth Scale)	0	1–2	3	4–5
Sympathetic over-reactivity (24 h)	Absent	1–3	4–6	>6
Additional criteria				
Glasgow coma scale	15	14–13	12–10	<10
Sweating	Absent	+	++	+++
Skin redness	Absent	+	++	+++
Albumin (g/l)	34–48	28–33	22–27	<22
EEG signs of diencephalic abnormalities	Absent	+	++	+++

Table 6. Differential diagnostic criteria.

Parameters	Points		
	1	2	3
Difference in body temperature, °C	0,5–0,6	0,7–0,9	⩾1
Serum procalcitonin (ng/ml)	>0,5	>2	>10
The presence of pain syndrome	+	++	+++
Heart rate (per min)	80–99	60–79	<60
Systolic blood pressure (mmHg)	90–100	80–89	<80
Body temperature, °C	<36,0	<35,5	<35,0

Score interpretation Table 5:

0 — condition absent

1–7 points (main criteria) and not more than 5 points (additional criteria) — mild PSH

8–14 points (main criteria) and not more than 10 points (additional criteria) — moderate PSH

15–21 points (main criteria) and 10–15 points (additional criteria) — severe PSH

Score interpretation Table 6:

1–5 points — likely association with other conditions requiring additional diagnosis and treatment

5–11 points — PSH is questionable or does not play a major role

11–18 points — PSH is ruled out

Extras:

- Assessment is done only with normovolemia, pO_2>60 mmHg or SpO_2>90%, pCO_2<45 mmHg, and blood glucose >3.5 mmol/l.
- Difference in body temperature implies that between the rectal and axillary values
- Kerdö Autonomic Index = 100×(1-DBP/HR) (DBP — diastolic blood pressure, HR — heart rate)
- + mild
- ++ moderate
- +++ severe
- The level of consciousness is assessed using the Glasgow Coma Scale
- The muscle tone is assessed using the Ashworth Scale.
- Assessment of pain syndrome in conscious patients can be made using a 5-point verbal pain rating scale (Frank A. J. et al., 1982) [50], where 1 point equals +; 2–3 points, ++, and 4 points, +++.
- The level of sympathetic overactivity is assessed at least once a day
- The use of differential diagnostic criteria in the initial and each subsequent evaluation is mandatory.

Some researchers believe that PSH develops in a stepwise manner [33]. The first stage is often asymptomatic because the patient in the early acute phase of brain injury receives various sedatives, narcotic analgesics and myorelaxants. The second stage is characterized by tachycardia, hypertension, tachypnoea, hyperhidrosis, while the third one manifests with muscle tone disorders and dystonia [4].

The diagnosis of PSH is based on clinical signs and symptoms being largely a diagnosis of exclusion. The differential diagnostic list includes sepsis, hypoxemia, hypercapnia, hypoglycemia, seizures, pulmonary embolism, thyrotoxic crisis, acute myocardial infarction, alcohol or drug withdrawal, malignant neuroleptic syndrome, serotonergic syndrome, malignant hyperthermia, and intracranial hypertension [3, 4, 33, 43, 44].

Complications of PSH. Numerous studies have shown that PSH associates with unfavorable long-term outcomes such as impaired consciousness, late recovery of consciousness, impaired motor functions, multiple organ failure, malnutrition, infectious complications, prolonged mechanical ventilation, longer ICU stay, low scores on Glasgow Outcome Scale, increased disability and mortality (Table 7) [3, 4, 33, 45, 46]. Patients with prolonged unconsciousness and PSH have less rehabilitation potential than those with stable autonomic status [25, 33, 46, 47].

Meanwhile, several studies have shown that PSH is not associated with serious complications and has no effect on the outcome [4, 21].

Table 7. Complications of PSH.

Organs and Systems	Complications
Nervous system	Decrease in the level of consciousness
	Abnormal circadian rhythms
	Excitation
	Convulsions
Skin and mucous membranes	Trophic disorders
	Sweating
	Skin redness
	Increased skin grease
Musculoskeletal system	Polyneuropathy
	Polymyopathy
	Muscular dystrophy
	Spasticity
	Dystonia
	Myoclonus
	Contractures
Cardiovascular system	Arterial hypertension
	Myocardial infarction
	Acute coronary syndrome
	Arrhythmias
	Myocardial dystrophy
Bronchopulmonary system	Bronchorrhea
	Pulmonary edema
Gastrointestinal tract	Motility disorders (nausea, vomiting, constipation, diarrhea)
	Malabsorption
	Erosions and ulceration of the mucous membrane
Endocrine system	Increased activity of the hypothalamic-pituitary-adrenal and the renin-angiotensin-aldosterone systems
	Hypogonadism
	Temperature regulation disorders
Immune system	Decreased immunity, chronic infections
Other organs	Neurogenic dystrophy
	Multiple organ dysfunction

Such discrepancies in the results of studies can be related both to their design and methodology. The choice of the control group is essential because the severity of brain injury in this group should be comparable with that of the main group. The occurrence and severity of PSH sequelae largely depend on its severity and duration. Based on our own observations and literature data, we can argue that the PSH significantly aggravates the underlying disease and its outcome, reducing the rehabilitation potential [3, 4, 46–48].

Prevention. Prevention of PSH in critically ill patients can significantly decrease the rate of complications, increase survival rate and reduce the duration of ICU stay [3, 33].

International researchers report that currently there are no effective measures for PSH prevention [4, 10, 33]. There are several drugs recommended to reduce the frequency of paroxysms, which are commonly referred to as prophylactic. These include clonazepam, bromocriptine, propranololol, oxycodone, gabapentin, clonidine, baclofen. Clinical experience shows that prolonged sympathetic overactivity is less susceptible to correction [3, 43, 49]. In our opinion, the therapeutic anesthesia technique according to Professor Kondratyev (described in detail in the next section) and therapeutic hypothermia, in particular craniocerebral hypothermia (CCH), could be considered preventive for PSH.

Treatment. PSH therapy methods is usually classified into non-pharmacological, pharmacological, and prophylactic ones. The treatment of PSH should be primarily based on general ICU principles (adequate correction of hemodynamics, gas exchange, fluid volume, nutritional support, electrolyte balance, blood glucose level, and body temperature) [3, 4, 10, 33, 49–51]. Prior to treatment, the identification of leading signs and symptoms requiring therapy is mandatory [2, 33]. Careful daily calculation of volumetric balance with consideration of abnormal fluid and electrolyte loss through respiration, sweat, vomiting or diarrhea is also essential. Thus, in patients with hyperhidrosis, fluid replacement is sometimes sufficient to increase the level of consciousness and reduce the frequency of paroxysms [10, 33].

Nutritional support with calculation of caloric intake, basic nutrient and mineral requirements, has a pivotal role. Energy expenditure during a paroxysm increases threefold compared to the interictal period [33, 53]. In addition, problems with digestion of administered food are common in PSH, which is due to both sympathetic overactivity effect on gastrointestinal functions and prolonged antibiotic therapy. Therefore, it is often necessary to prescribe enzyme preparations, pre- and probiotics. Adequate selection of an optimal caloric intake, nutritional volume, and types of nutritional support can reduce the frequency and severity of paroxysms,

as well as their negative sequelae [33, 53]. Maintenance of normal body weight is one of the priority tasks.

Proper care, including maintaining a comfortable temperature and humidity, preventing bedsores pain, and contractures, is another important aspect [4, 33, 54].

Hyperbaric oxygenation could be another nonpharmacological treatment method to increase oxygen availability and improve aerobic metabolism in damaged tissues [33].

Physical therapy and therapeutic exercise can reduce the severity of spasticity, prevent contractures, muscular dystrophy, trophic skin disorders, and pain syndrome and increase their treatment efficacy [10].

The choice of drug therapy depends on the severity of the underlying disease, a comprehensive analysis of clinical manifestations and the individual characteristics of the patient [10, 54, 55]. Thus, in the acute phase of the disease parenteral medications are preferable, while at the time of patient transfer from ICU and the start of rehabilitation oral therapy could be more efficient. Transcutaneous drug delivery (patches) is increasingly common and convenient to use [33].

According to international authors, drug treatment usually begins with symptomatic therapy including β-blockers, gabapentin, benzodiazepines, valproate [10, 19, 33, 54–61]. When the treatment is not effective, continuous administration of opioids and propofol is suggested. During last 10–15 years after dexmedetomidine was introduced in practice, alpha2-agonists have been successfully used for PSH [33, 62, 63, 65–70]. The issue of duration of administration of opioids, hypnotics, and alpha2-agonists is still unresolved. Premature drug discontinuation can lead to recurrence of PSH, however their prolonged use could delay rehabilitation and result in multiple side effects. Using the «diagnostic window» approach, reducing the number of drugs administered and a smooth transition to oral drug ingestion allows to avoid many treatment complications [3, 50].

The use of neuroleptic drugs should be avoided because of the risk of malignant neuroleptic syndrome [3, 4, 50, 51].

Interestingly, some differences exist in the action of the same drugs depending on the etiology of brain injury, in particular, traumatic and nontraumatic. Thus, fentanyl and propofol effectively reduce blood pressure and heart rate in traumatic PSH, whereas they are not effective in nontraumatic lesions [64]. This is probably due to the polymorphic character of brain damage in TBI.

In clinical practice, most patients require treatment with multiple potentially synergistic drugs useful for both for symptomatic treatment and paroxysm prevention [3, 10, 33, 54, 55, 64].

Our long-term observations have shown that the therapeutic anesthesia developed in the 1990s by Professor A. N. Kondratyev can be considered as a pathogenetic therapy for PSH [3, 43, 50, 51, 71].

The main objectives of therapeutic anesthesia include creation of neurovegetative stability, a comprehensive protective reaction in response to brain damage, and ensuring an adequate functional level without abnormal components, which is sufficient for maintenance of compensatory reactions and integrative activity necessary for recovery [43, 50]. Anesthesia technique includes intravenous continuous injection of the opioid analgesic fentanyl 0.5–1 μg/kg/h, an alpha2-agonist (such as clonidine 0.2–0.7 μg/kg/h or dexmedetomidine 0.2–0.5 μg/kg/h), propofol 2–5 mg/kg/h (not longer than 24 hours due to a risk of «propofol infusion syndrome»), and sodium thiopental 2–4 mg/kg/h. Duration of therapy ranges from 12 hours to 7–10 days [3, 43, 50, 51].

Hypothermia sessions are an obligatory component of acute severe brain injury therapy and prevention of PSH [3, 42]. Severe brain injury causes focal hyperthermia caused by neuronal excitation, glutamate and aspartate release, activation of free radical reactions and neuroinflammation. The difference between the temperatures of individual brain regions can reach 2–4°C [72]. A decrease in neuronal temperature results in reduced metabolism and decreased oxygen and glucose requirements of brain cells. Hypothermia helps to reduce neuroinflammation and limit ROS formation and pro-apoptotic reactions [73–76]. Craniocerebral hypothermia (CCH) is one of the effective cooling methods. The technique consists in lowering the scalp temperature to 5–8°C using helmets with circulating fluid, maintaining the skin temperature at a constant level during the entire session. The duration of cooling ranges from 12 hours to 7 days, if the temperature rises after the cooling cessation, the procedure is repeated until stable normothermia is achieved. Smooth withdrawal from a hypothermia session is crucial [3, 42, 75, 76]. Abrupt withdrawal, as mentioned above, can become a trigger for new paroxysms of PSH.

Once the symptoms and signs of PSH appear after the withdrawal of therapeutic anesthesia, continuous intravenous clonidine or dexmedetomidine, β-blockers, antiepileptic drugs (phenytoin, clonazepam), nonsteroidal anti-inflammatory drugs and other symptomatic agents are commonly used [3, 42].

In the Polenov Russian Neurosurgical Institute, the management strategy is based on the assessment according to original scales (Tables 5, 6) (Fig. 2).

The duration of therapy is individual. The patient is regularly assessed using the «diagnostic window» approach [3, 42].

Despite the considerable interest of experts in the study of PSH, many aspects remain unclear.

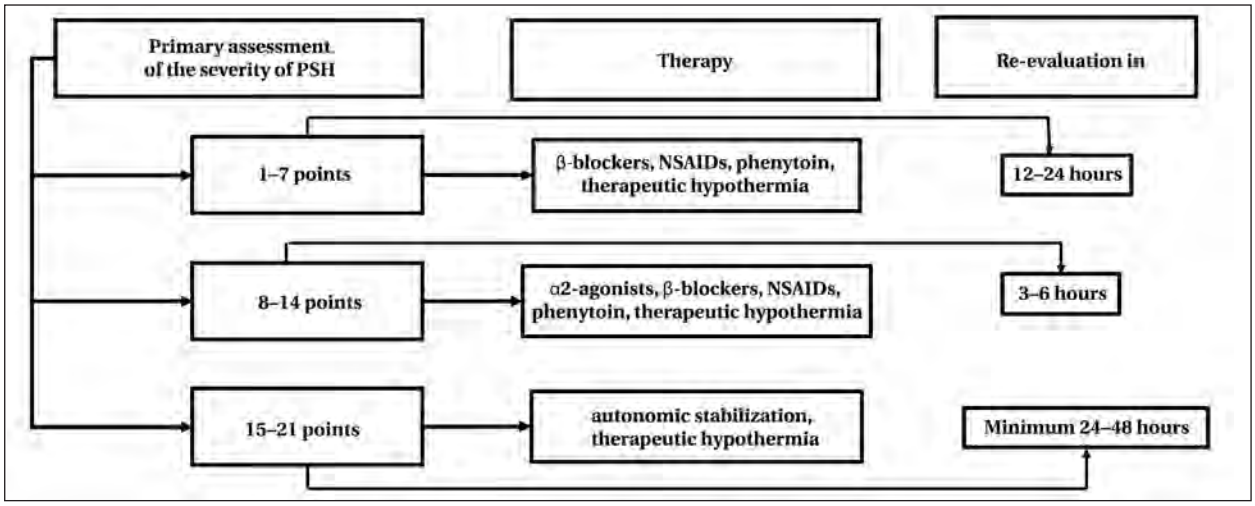

Fig. 2. Algorithm of management of PSH.
Note. NSAIDs — non-steroidal anti-inflammatory drugs.

They include triggering and maintaining mechanisms, optimal diagnostic criteria, efficient differential diagnosis strategy, severity assessment, as well as the most appropriate preventive and therapeutic modalities [10, 33, 77–79]. Although severe brain injury is frequently complicated by PSH, it is still difficult to aggregate and manage all the available data due to the lack of generally accepted diagnostic and treatment strategies [10, 33, 79, 80].

Conclusion

Prevention of PSH and its adequate and timely treatment could preclude the pathological pathway development in severe brain injury, allowing to reduce the negative sequelae and associated complications, as well as the duration of mechanical ventilation, patient's stay in ICU, morbidity, and mortality. The selection of pathogenetic, symptomatic and supportive therapy significantly improves the rehabilitation potential of patients. In addition to drug treatment, ensuring comfortable environment (temperature, humidity, protection from harsh sounds, strong smells, and other stimuli), proper care and nutritional support is equally important for patients with PSH. Rehabilitation measures conducted in patients with autonomic instability are both ineffective and harmful since they can provoke PSH paroxysms and increase their frequency.

Further study of this challenging syndrome will help intensivists, neurologists, and rehabilitation specialists to timely provide symptomatic and pathogenetic therapy.

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