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Adaptive Phage Therapy in the Treatment of Patients with Recurrent Pneumonia (Pilot Study)

Nataliya V. Beloborodova[1], Andrey V. Grechko[1], Marina M. Gurkova[2], Alexander Yu. Zurabov[2], Fedor M. Zurabov[2], Artem N. Kuzovlev[1]*, Anastasiya Yu. Megley[1], Marina V. Petrova[1,4], Valentina M. Popova[2], Ivan V. Redkin[1], Nicolay I. Sergeyev[3], Ekaterina A. Chernevskaya[1], Mikhail Yu. Yuriev[1], Alexey A. Yakovlev[1]

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Адаптивная фаготерапия пациентов с рецидивирующими пневмониями (пилотное исследование)

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Summary

Aim. To evaluate the safety and efficacy of the adaptive phage therapy technique in patients with recurrent pneumonia in neurological critical care.

Material and methods. The clinical study included 83 chronically critically ill patients with severe brain damage. The bacteriophage cocktail selected against specific hospital strains was administered by inhalation to 43 patients. The control group included 40 patients who received conventional antimicrobial therapy. The changes in clinical, laboratory and instrumental parameters, levels of biomarkers, microbiological and PCR tests of bronchoalveolar lavage fluid were assessed, including those in the «phage therapy with antibiotics» (*n*=29) and «phage therapy without antibiotics» (*n*=14) subgroups.

Results. The groups were comparable in terms of basic parameters (age, sex, diagnosis, organ dysfunction according to APACHE II, use of vasoactive drugs) and the level of airway colonization with antibiotic-resistant bacterial strains. Good tolerability and absence of clinically significant side effects were observed during inhalational administration of the bacteriophage cocktail. Computed tomography on day 21 showed a significant reduction in lung damage in patients who received bacteriophages. Patients treated with bacteriophages without antibiotics had significantly lower need for mechanical ventilation. The mortality rate on day 28 did not differ significantly and was 4.7% (2/43) in the bacteriophage-treated group vs 5% (2/40) in the control group.

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Conclusion. The first experience of using the adaptive phage therapy technique in chronically critically ill patients in neurological intensive care demonstrated the safety of inhalational administration of the bacteriophage cocktail. The efficacy of the technique was confirmed by the treatment results obtained in the phage therapy group, which were not inferior to those in the group with conventional antibiotic therapy, while several clinical and laboratory parameters tended to improve even in patients who received bacteriophages and did not receive antibiotics.

Keywords: antibiotics; resistance; pneumonia; bacteriophages; personalization; phage therapy

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

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Introduction

Chronically critically ill patients remain in intensive care units (ICU) for a long time and require comprehensive treatment, including life support. This creates conditions for the development of prolonged and recurrent pneumonia associated with hospital-acquired multidrug-resistant bacterial strains.

Currently, the antibiotic armamentarium for the treatment of patients in chronic critical illness has almost been exhausted. The treatment of infections caused by multidrug-resistant bacteria, including carbapenemase-producing pathogens, is extremely difficult due to the highly limited choice of effective drugs; their treatment is characterized by such negative sequelae as prolonged hospital stay, adverse treatment outcomes, and increased direct and indirect costs [1].

A potentially promising alternative to antibiotics could be the use of bacteriophages to treat and prevent nosocomial infections. Bacteriophages are intracellular obligate parasites of bacteria and play an important role in the natural regulation of bacterial populations. In the 1930s and 1940s, bacteriophages were actively used in the Soviet Union in various areas of medicine. However, the beginning of commercial production of penicillin and other antibiotics as well as the need for individual selection of bacteriophages for a particular infectious agent halted large-scale research and widespread use of bacteriophages for a long time. The development of molecular biological methods and genome sequencing technologies contributed to a more rational approach to the selection and use of therapeutic bacteriophages, which allowed scientific research in this area to continue [2, 3].

Accumulated clinical experience demonstrates high efficacy and safety of therapeutic and prophylactic preparations with bacteriophages in the treatment of infections in otorhinolaryngology, surgery, urology [4–6].

A systematic literature review published in 2019 summarizes the results of 13 studies conducted in Russia, the United States, Western Europe, and Asia, in which bacteriophages have been used to treat and prevent infections in humans. Concluding the review, the authors acknowledge that the beneficial effect of phage therapy is undeniable [7].

Traditionally, bacteriophages are used to treat infections caused by so-called «wild» strains with innate antibiotic sensitivity. In recent years, an increasing number of researchers and developers of antimicrobial drugs report the possibility of using bacteriophages active against antibiotic-resistant strains, in particular, a wide range of clinical isolates of *Staphylococcus aureus*. Experimental studies on laboratory animals confirm the effectiveness of bacteriophages against antibiotic-resistant strains of microorganisms causing pneumonia and sepsis [8–11]. In a clinical study by Australian researchers published in Nature Microbiology in 2020, the efficacy of a bacteriophage preparation was evaluated in 13 patients with severe staphylococcal infections, including endocarditis and septic shock [12]. The drug produced from three bacteriophages was administered intravenously twice a day for 14 days under careful monitoring of hematological and biochemical parameters; good tolerability, high safety, and no local and systemic adverse reactions were noted. However, the circulation of several «challenging» Gram-negative and Gram-positive strains simultaneously is characteristic of present-day ICU. Moreover, the continuous use of the latest generations of antibiotics with unpredictable frequency results in the selection of pan-resistant pathogens, which may cause outbreaks of hospital infections. In these circumstances, there is a need for a complex drug that will contain a set of bacteriophages active against the entire list of challenging pathogens in a particular ICU. In addition, periodic monitoring of this drug's efficacy is necessary, and, in case of resistant strain selection, new bacteriophages should be added to the preparation. In other words, the drug should be adapted to the changing microbial landscape.

This challenging issue is being addressed by the collaborative efforts of the Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology and the «MicroMir» research and production center. Based on a hospital bacteria collection of 66 antibiotic-resistant strains iso-

lated from 40 ICU patients of the Center of Intensive Care Medicine and Rehabilitology, «cocktail» of bacteriophages for inhalation was developed and proposed as an adaptive phage therapy method.

The preparation included about 50 bacteriophages active against bacterial respiratory pathogens, mainly hospital multidrug-resistant strains, such as *Acinetobacter baumannii, Citrobacter freundii, Enterobacter cloacae, Enterobacter kobei, Enterococcus faecium, Klebsiella pneumoniae* subsp. *ozaenae, Klebsiella pneumoniae, Cutibacterium acnes, Pseudomonas aeruginosa, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Stenotrophomonas maltophilia, Streptococcus pyogenes*. The preparation contains 3 to 4 virulent bacteriophages against each of the pathogens above.

The aim of the study was to evaluate the safety and efficacy of adaptive phage therapy technique in the treatment of patients with recurrent pneumonia in neurological critical care.

Material and Methods

Type of clinical study: prospective, nonrandomized, open-label parallel group study.

The site of the study: intensive care units (ICU) of the Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology, where patients with severe brain damage after acute stroke, traumatic brain injury (TBI), brain tumor surgery, anoxia, etc., are treated. This study included chronically critically ill patients transferred from intensive care units of other medical institutions for further intensive treatment.

The term «chronically critically ill» refers to those who have survived acute critical disease of any etiology, but remain long-term patients requiring intensive monitoring and temporary life support [13].

The study protocol was reviewed and approved by the Local Ethics Committee of the Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology No. 4/20 dated September 22, 2020.

Patient groups. According to the Protocol, adult patients admitted to the Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology were prospectively included in the study if they met the following inclusion criteria:

1. Patient age > 18 years.
2. Chronic critical illness, ICU stay for more than 2 weeks, previous treatment with antibiotics.
3. Previous pneumonia with the risk of recurrence, clinical indications for antimicrobial treatment (CT evidence, etc.).
4. Informed consent of the patients or their close relatives.

Exclusion criteria:

1. Low survival chance (SAPS II score > 65).
2. Treatment with immune suppressive drugs, including steroids.
3. Signs of acute infection/sepsis (according to the Sepsis-3 criteria).
4. Procalcitonin level > 2 ng/ml.
5. Candidemia.

Patients were enrolled gradually.

At the first stage of the study, consecutive enrollment of eligible patients was performed without intervention in the treatment process, with recording of clinical, laboratory and microbiological monitoring parameters at four time points (days 1, 7, 14, and 28 after admission).

At the second stage, the patients included in the study were prescribed a bacteriophage cocktail in addition to conventional antimicrobial therapy (safety assessment).

In the third stage, when the procalcitonin level was less than 0.5 ng/ml, only the bacteriophage cocktail without antibiotics was administered to selected patients.

Eighty-three patients were included in the study.

The main Group 1 consisted of 43 patients who received the bacteriophage cocktail. This group was divided into 2 subgroups: «phage therapy with antibiotics» (antibiotics + bacteriophage cocktail, Group 1A, n=29) and «phage therapy without antibiotics» (bacteriophage cocktail only, Group 1B, n=14).

Group 2 included patients who received conventional antibiotic therapy, n=40.

Patients received comprehensive treatment and rehabilitation including life support, drugs to improve consciousness level, nutritional and metabolic therapy, symptomatic care, etc. Therapeutic and rehabilitation measures were performed by specialists who were not aware of the inclusion of patients in this study.

The «Ground Glass» software for automatic assessment of the ground glass opacity lesions was used to analyze the chest CT scans. Segmentation of the right and left lungs along with trachea was performed with the threshold of -250 HU. The lesions with customized densities (from -785 HU to 150 HU as a default) were outlined inside the lungs. The small vessels which could be mislabeled as «lesions» were excluded from assessment using the morphological closing operation.

During the study, the patients were under continuous clinical and laboratory monitoring with assessment of cardiovascular, neurological, respiratory parameters, liver and kidney function, as well as the organ dysfunction using the SOFA score. Serial measurement of serum biomarkers (C-reactive protein, procalcitonin) was carried out. Levels of albumin, urea, creatinine, and CRP were determined

Table 1. Main characteristics of patients.

Parameter	Values in groups				*P*
	1, *n*=43			2, *n*=40	1A+1B vs. 2
	1A, *n*=29	1B, *n*=14	1A+1B		
Age, median	62 (39–71)	50 (32–74)	60 (38–72)	64 (54–72)	0.177
Sex, male/female, *n*	20/9	10/4	30/13	21/19	0.120
Diagnosis, *n* (%)					
Post:					
stroke	16 (55)	6 (43)	22 (51)	26 (65)	0.267
TBI	9 (31)	4 (29)	13 (30)	7 (18)	0.206
brain surgery	1 (4)	2 (14)	3 (7)	4 (10)	0.706
anoxia	3 (10)	2 (14)	5 (12)	3 (7)	0.714
APACHE II severity score, day 1, median	12 (8–15)	11 (10–16)	12 (10–15)	10 (8–14)	0.287
Lung ventilation required, Day 1, *n* (%)	14 (48)	5 (36)	19 (44)	24 (60)	0.189
Number of antibiotic-resistant bacteria in the initial BAL fluid sample, total (average per 1 patient)	46/29 (1.6)	25/14 (1.8)	71 (1.7)	72 (1.8)	—

Note. For tables 1–6, figures 1, 2: 1A — antibiotics + bacteriophage cocktail; 1B — bacteriophage cocktail alone; 2 — antibacterial therapy without bacteriophage cocktail.

on an automatic biochemical analyzer AU 480 (Beckman Coulter; USA) using original reagents. The procalcitonin concentration was measured on a VIDAS immunoanalyzer (bioMerieux SA, France).

Third-party laboratory physicians performed microbiological studies of bronchoalveolar lavage (BAL) fluid using culture and PCR methods. For microbiological examination a morning sputum sample was taken in sterile tubes in aseptic conditions. The time interval after the last administration of antibiotics and sputum collection was 8–12 hours. The native clinical specimens were immediately transported to the bacteriological laboratory. Microorganisms were identified and antibiotic sensitivity was determined using a BD Phoenix-100 automated system (USA).

To assess the taxonomic composition of BAL fluid a reagent kit for DNA isolation from clinical material «RIBO-prep» and reagent kits for the detection and quantification of *Pseudomonas aeruginosa* DNA, *Enterobacteriaceae* DNA, Staphylococci (*Staphylococcus* spp.) and Streptococci (*Streptococcus* spp.) were used. Qualitative assessment of antibiotic resistance genes was performed using reagent kits for the detection of acquired carbapenemase genes of KPC and OXA48-like groups (types OXA48 and OXA162), acquired carbapenemase genes VIM, IMP and NDM of MBL groups (Amplisens, Russia) by PCR with real-time hybridization-fluorescent detection of amplification products. Measurements were performed on a CFX 96 plate amplifier (BioRad; USA).

Statistical analysis was performed using Statistica 10.0 software. The generally accepted mathematical and statistical methods were used to calculate the main characteristics of sample groups. The Shapiro–Wilk test was used to assess the normality of variable distribution in the groups. Mann–Whitney test was used to analyze non-normally distributed variables. Wilcoxon test was used for comparative analysis of quantitative variables. Fisher's exact test was used to compare proportions (frequencies). To compare proportions at different time points, the McNimar test was used (Table 4). Data were presented as median ±25–75 percentiles (25–75 IQR). The critical level of significance was set at 0.05, and Bonferroni correction was used for multiple pairwise intergroup comparisons.

Results

The main characteristics of patients enrolled in the study are given in Table 1.

The groups were comparable in terms of sex, age, etiology of brain injury, severity of condition according to scales, and ventilation requirement.

The safety and efficacy of the bacteriophage cocktail were assessed using clinical and laboratory monitoring methods.

Assessment of clinical parameters. Neurological status of all chronically critically ill patients did not change over time. There were no differences between the groups in the severity of acute respiratory failure, also there were no significant changes in PaO_2/FiO_2 ratio in the groups. In Group 1A, there were significant positive changes in the severity of lung lesions according to CT (Table 2). No such improvement was observed in group 1B.

During the observation period 1 patient (6.7%) was weaned from mechanical ventilation in group 1B and 1 patient (3.1%) was weaned in group 1A. Organ dysfunction score according to the SOFA scale did not exceed 4–5 points in all groups during the study period. There were no significant differences between the groups in the frequency of vasoactive drug administration. The study did not reveal any clinically significant side effects of the bacteriophage cocktail administration. Mortality by day 28 was comparable in group 1 (2/43, 5%) and in group 2 (2/40, 5%) (*P*=1.0) with no fatal outcomes in subgroup 1B.

Table 2. Changes in lung lesion severity based on chest CT scans.

Parameter	Day	Values in subgroups		*P* (1A vs.1B) Mann–Whitney test for independent groups
		1A, *n*=22*	1B, *n*=12*	
Lung volume, ml[3]	1	3198 (2524–4221)	3125 (2580–3441)	0.510
	21	3844 (2341–4503)	2983 (2336–3705)	0.292
P (day 1 vs day 21) pairwise comparison using the Wilcoxon test		0,485	0,530	—
Lung lesion volume, %	1	33 (16–40)	30 (18–37)	0.683
	21	22 (10–38)	30 (4–56)	0.736
P (day 1 vs day 21) pairwise comparison using the Wilcoxon test		0.027	0.859	—

Note. * — lung CT data are shown only for 34 of 43 (80%) patients due to failure of automatic calculation of lung lesion volume in some scans.

Table 3. Changes in clinical and laboratory parameters during the first two weeks of treatment in the study groups

Clinical and laboratory parameters	Values in the groups				*P*
	1, *n*=43			2, *n*=40	1A+1B vs. 2
	1A, *n*=29	1B, *n*=14	1A+1B		
On mechanical ventilation, day 1, *n* (%)	14/29 (48)	5/14 (36)	19/43 (44)	24/40 (60)	0.189
On mechanical ventilation, day 7, n (%)	18/29 (62)	3/14 (21)	21/43 (49)	25/40 (63)	0.270
On mechanical ventilation, day 14, n (%)	15/27 (56)	2/14 (14)	17/41 (41)	25/39 (64)	0.048
Albumin level, day 1, g/l	30 (27–33)	31 (25–35)	30 (26–32)	28 (24–35)	0.549
Albumin level, day 7, g/l	30 (28–32)	29 (27–37)	29 (27–31)	26 (24–29)	0.001
Albumin level, day 14, g/l	29 (27–31)	31 (25–34)	29 (26–32)	26 (24–30)	0.071

Table 4. Frequency of abnormal liver or renal function parameters by day 14 of treatment compared with the data on day 1 of follow-up.

Patients with abnormal clinical chemistry parameters	Number of patients, *n* (%)							
	Group 1					Group 2		
	1A		1Б		*P**	Day 1	Day 14	*P**
	Day 1	Day 14	Day 1	Day 14				
Bilirubin	0/29	0/27	0/14	0/14	—	1/40 (2)	1/39 (3)	0.900
ALT	7/29 (24)	8/27 (30)	6/14 (43)	2/14 (14)	0.804	10/40 (25)	14/39 (36)	0.424
AST	5/29 (17)	4/27 (15)	2/14 (14)	0/14	0.900	6/40 (15)	7/39 (18)	0.900
Urea	11/29 (38)	5/27 (18)	4/14 (29)	4/14 (29)	0.021	12/40 (30)	9/39 (23)	0.791
Creatinine	5/29 (17)	5/27 (18)	2/14 (14)	0/14	0.625	12/40 (30)	8/39 (20)	0.424

Note. * — McNimar test. The proportions of patients with elevated laboratory values on day 1 and day 14 in the pooled group 1 were compared (day 1 vs. day 14 over time); similarly, for group 2.

Table 3 shows that the need for lung ventilation tended to increase in patients who received antibiotics (group 2 and subgroup 1A) and, conversely, decreased in subgroup 1B, where only bacteriophages were used. Monitoring of biochemical parameters in group 2 also revealed a significant decrease in albumin level on day 7.

Table 4 compares the groups in terms of the number of cases of abnormal values of liver and kidney function parameters.

In group 2 and subgroup 1A, where antibiotics were used for 2 weeks, the proportion of patients with elevated enzyme levels persisted or even increased compared to the baseline. At the same time, in subgroup 1B, where patients were treated with bacteriophages alone without antibiotics, this pattern was not observed; on the contrary, there was a tendency for reduced number of cases with elevated clinical chemistry parameters, such as ALT, AST, and creatinine.

Changes in the levels of biomarkers. Procalcitonin is one of the markers which provides rationale for withholding antimicrobial therapy.

Most chronically critically ill patients had procalcitonin levels below the reference values (0.25–0.50 ng/ml) during the entire follow-up period, only less than a third of patients had minor elevations (0.51–0.80 ng/ml). No significant differences between the subgroups were observed according to the laboratory monitoring data during two weeks after the study initiation (Table 5).

The level of C-reactive protein was dozens of times higher than the reference value (5 mg/l) in all patients. The changes in CRP level were assessed by the percentage of reduction by thirty percent or more compared to the baseline values. In group 1, a decrease in CRP concentration on day 7 was observed in 40% of patients, while in group 2, this parameter was reduced only in 30% of cases (Fig. 1).

Table 5. Procalcitonin (PCT) concentration over time in subgroups 1A and 1B of patients treated with bacteriophages, median (interquartile range).

Day of study	PCT (ng/ml) in subgroups		*P* value for 1A vs. 1B
	1A	1B	
1	0.08 (0.05–0.36)	0.11 (0.05–0.35)	0.771
7	0.14 (0.08–0.56)	0.14 (0.05–0.51)	0.866
14	0.12 (0.05–0.80)	0.1 (0.05–0.43)	0.525

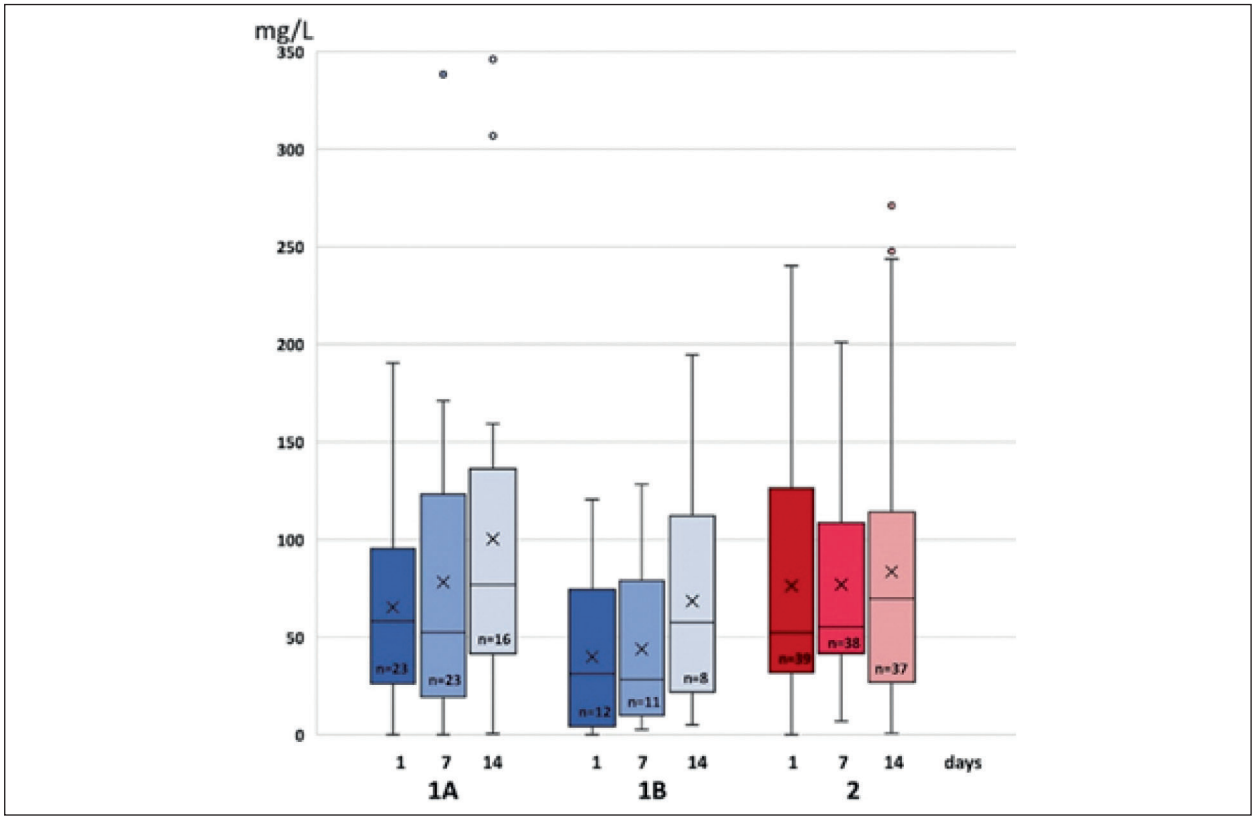

Fig. 1. Levels of C-reactive protein in the subgroups of patients treated with bacteriophages (median and interquartile range).
Note.

Day of study	*P*-values (after Bonferroni correction)		
	1A vs Group 2	1B vs Group 2	1A vs 1B
1	0.696	0.074	0.172
7	0.455	0.049	0.201
14	0.483	0.716	0.452

Results of microbiological monitoring.

The growth of hospital-acquired Gram-negative microorganisms in BAL fluid samples was observed in patients of different groups with approximately equal frequency at the time of inclusion in the study (Table 6).

By the end of the first week after inclusion, in Group 2 patients persistence of antibiotic-resistant strains such as *Klebsiella pneumoniae, Pseudomonas aeruginosa, Acinetobacter* spp., and *Escherichia coli* was observed. At the same time, in Group 1 patients who received the bacteriophage cocktail, a decrease in the main challenging Gram-negative microorganisms, such as *Acinetobacter* spp., *Escherichia coli* and *Klebsiella pneumoniae,* was observed. *Serratia* spp. strains were less common, but were less amenable to elimination, and their count even increased in the antibiotic therapy group (Table 6).

Molecular genetic typing by PCR was performed for individual strains of the challenging hospital microorganisms. The results of DNA testing for P*seudomonas aeruginosa* and *Enterobacteriaceae* family (including *Escherichia coli, Klebsiella* spp., *P. mirabilis*) in BAL fluid were comparable with the obtained microbiological data and confirmed the lack of a significant increase in bacterial identification by day 14 after the start of therapy. An increase in DNA content of the Enterobacteriaceae family was noted by day 7, which probably reflected bacterial lysis on airway mucosa (Fig. 2).

Table 6. Microorganisms isolated from BAL fluid samples in patients on days 1 and 7 from the start of treatment in the study groups.

Microorganism	Group					
	1, *n*=43		2, *n*=40	1, *n*=43		2, *n*=40
	1A, *n*=29	1B, *n*=14		1A, *n*=29	1B, *n*=14	
	Day 1			Day 7		
Pseudomonas aeruginosa	10	4	11	4	8	13
Klebsiella pneumoniae	15	10	26	16	6	25
Acinetobacter baumannii/calcoaceticus	8	3	13	3	2	10
Enterococcus faecalis	—	—	3	1	—	1
Staphylococcus aureus/haemolyticus	—	—	5	—	—	4
Escherichia coli	5	1	7	3	—	5
Serratia plymuthica/Serratia marcescens	2	3	3	5	4	6
Stenotrophomonas maltophilia	—	2	2	2	—	3
Proteus mirabilis/vulgaris	2	—	6	5	1	9
Providencia stuartii/alcalifaciens	2	—	4	2	2	2
Others:						
Chryseobacterium meningosepticum	1		—	—	—	
Alcaligenes faecalis		1				2
Morganella morganii		1				

Staphylococcus spp. DNA content exceeding 10^3 copies/ml was detected only in 2 patients on day 1 in group 1A, with subsequent reduction back to reference values by day 7.

DNA of metallobetalactamase (VIM and NDM types) and carbapenemase (KPC and OXA48) genes was detected in 60% of patients in both subgroups at the time of inclusion in the study. The upward trend in antibiotic resistance persisted in both subgroups; by day 14, the KPC gene was detected in 100% of patients in the 1A subgroup, while in patients who received only the bacteriophage combination alone it was found in 90% of cases. A detailed analysis in subgroup 1A showed that in patients treated with carbapenems (*n*=10) there was a relative increase in the acquired carbapenemase genes of KPC and OXA48 groups by 10 and 22%, respectively, by day 7. However, patients in the same group receiving other antibiotics (*n*=13) had a 22% decrease in the detection of OXA48 group acquired carbapenemase genes.

Clinical case 1. Patient P., 38 years old, was injured in a traffic accident driving a motorcycle. He has sustained combined brain and abdominal trauma, the following surgeries were performed: laparotomy, splenectomy, adbdominal drainage. Later, multiple organ failure (respiratory, cardiovascular, hepatic, renal, nutritional) developed. On day 49 after the accident the patient was transferred to the Institute of Rehabilitation of the Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology for further rehabilitation. On admission, the patient's general condition was extremely poor, he remained in a vegetative state.

During the stay in the Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology, the patient had 3 episodes of nosocomial pneumonia, the last one occurred on day 70 after the accident, he received repeated courses of antimicrobial therapy, including the antibiotics of latest generations, and the main pathogen of severe infectious complications was the antibiotic resistant strain of *Klebsiella pneumoniae*.

On day 80, to prevent nosocomial pneumonia recurrence, the bacteriophage cocktail active against antibiotic-resistant bacteria and customized for the Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology based on the microbiological data of the biomaterial from the ICU patients was administered. Due to the severity of patients' condition and high risk of pneumonia recurrence, a long-term course of the bacteriophage cocktail inhalation for 4 weeks was prescribed. During this period no recurrent pneumonia episodes were observed. The procalcitonin level remained below the reference values (less than 0.25 ng/ml). In a series of bronchoalveolar lavage examinations, *Klebsiella pneumoniae* titer decreased, furthermore, the initial antibiotic-resistant strain was eliminated, and the strain isolated after the treatment course was sensitive to a wide range of antibacterial agents.

Clinical case 2. An 82-year-old patient underwent brain surgery to remove a tumor in the deep parts of the left frontal and parietal lobes. The postoperative period was complicated by bilateral extensive pneumonia, sepsis, and septic shock. The patient received multiple courses of antibiotic therapy. On day 84 the patient was transferred to the Institute of Rehabilitation of the Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology for further rehabilitation. On admission, the patient's general condition was extremely poor, with minimal level of consciousness. Based on clinical assessment and CT scan findings, the patient was diagnosed with recurrent bilateral extensive pneumonia. The patient was prescribed a combination of vancomycin and meropenem. However, despite antibiotic therapy, the patient's

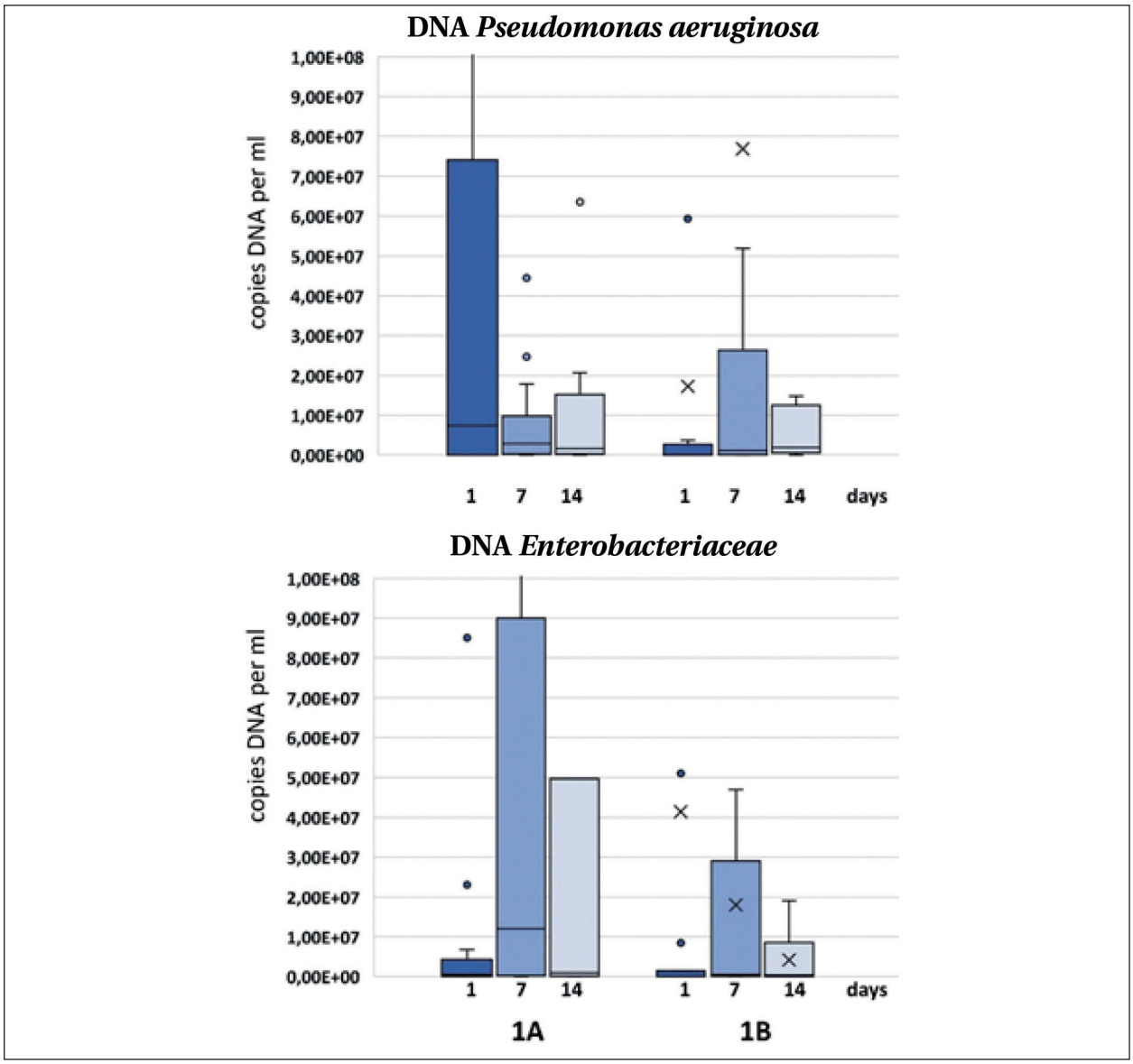

Fig. 2. The DNA content of *Pseudomonas aeruginosa* and *Enterobacteriaceae* in the group of patients receiving bacteriophages (subgroups 1A and 1B) (median, interquartile range).

Notes.

Day of study	*P*-value, Mann–Whitney test	
	1A vs 1B (*P. aeruginosa*)	1A vs 1B (*Enterobacteriaceae*)
1	0.122	0.118
7	0.542	0.309
14	0.837	0.595

condition deteriorated, respiratory failure progressed, and lung ventilation in BIPAP mode was initiated. Microbiological examination of BAL fluid revealed multiresistant strains of *Acinetobacter baumannii* and *Klebsiella pneumoniae*. On day 89, the bacteriophage cocktail active against antibiotic-resistant bacteria (including phage lysates of *Acinetobacter baumannii* and *Klebsiella pneumoniae* among others), customized for the Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology based on the patient's microbiological data was added. According to the results of microbiological tests on days 96 and 102 (that is, 7 and 14 days after the start of bacteriophage administration), *Klebsiella pneumoniae* was not found in bronchoalveolar lavage, while the multiresistant *Acinetobacter baumannii* strain was still present. In view of clinical improvement, on day 10 of the treatment with bacteriophages, vancomycin was discontinued, on day 14 meropenem was stopped.

Thus, starting on day 104, the patient received only the bacteriophage cocktail. According to CT scan results, improvement was

found. From day 107 (19th day after the initiation of bacteriophage combination) the patient was weaned from mechanical ventilation. On auscultation improvement was also found with reduction or disappearance of crackles. Fever subsided; the level of inflammatory markers returned to normal values. The change of sputum characteristics was registered: it became more mucous-like and its volume decreased. The procalcitonin level was normal (less than 0.25 ng/ml), which indicated the absence of bacterial infection. On day 109 (21 days after the start of the bacteriophage combination), microbiological test of the BAL fluid showed no bacterial growth, which confirmed the efficacy of the bacteriophage combination.

Discussion

In our study, a preparation for inhalation containing dozens of bacteriophages was administered, which had not been studied before. The data show that the bacteriophage cocktail is more effective than individual phages in broadening the lytic spectrum and significantly reducing the risk of phage-resistant forms generation [14]. During our study, careful clinical and laboratory monitoring revealed no adverse events when using the bacteriophage preparation for inhalation at a dose of 5 ml, 2–3 times per day, for at least 14 days.

There are few publications describing the use of inhaled [15] or intravenous [12] bacteriophages in patients with pneumonia, bronchitis, infectious endocarditis, etc. The authors also confirm safety and claim no adverse reactions when using bacteriophages for therapeutic purposes.

Our study was the first to evaluate the safety of bacteriophage use in a group of patients with chronical critical illness. Along with a good tolerability and an absence of local and general adverse events, an important aspect to note is that the adaptive phage therapy technique has demonstrated safety in terms of the risk of hospital bacterial strains selection. The main clinical outcomes in Group 1 using the bacteriophage cocktail were similar to those of conventional antibiotic therapy. Moreover, in the group of combined use of antibiotics and bacteriophages (1A) reduced severity of lung damage according to CT scan was revealed, which suggests efficacy of this drug combination in the treatment of nosocomial pneumonia. Hyperinflammation, characterized by levels of CRP more than 10 times higher than the reference values, is characteristic of chronic critical illness [13, 16]. Reduced intensity of the inflammatory response associated with bacterial infection, i. e., a decrease in the CRP level, may be one of the effects of bacteriophage use [17]. And our study did reveal a trend toward decreasing the level of CRP in the group receiving the bacteriophage cocktail.

The microbiological and molecular genetic monitoring showed that in some patients the use of the bacteriophage cocktail was associated with elimination of major multidrug-resistant Gram-negative bacteria. However, the recurrent detection of *Serratia* spp., *Acinetobacter baumanii, Stenotrophomonas maltophilia* indicates the need for control and regular adaptation of bacteriophage composition in the preparation.

Involvement of antibiotic-resistant bacteria significantly worsens the course of nosocomial infection and increases morbidity and mortality [18]. Currently, molecular methods are the «gold standard» for detecting carbapenemase producers [19]. Serine carbapenemases of molecular types OXA48 and KPC, as well as MBL of type NDM, are most prevalent in *Enterobacteriaceae. P. aeruginosa* is characterized by the production of MBL types VIM and, to a lesser extent, IMP [20]. Microbiological monitoring using PCR in our study showed that carbapenem resistance genes were detected in more than 60% of patients included in the study starting from the first day. This high prevalence of resistant strains can be explained by the severity of the patients' condition, prolonged hospital stay, and massive antibiotic therapy including several classes of antibiotics. The results of the study showed that the use of the bacteriophage preparation did not associate with increased antibiotic resistance, accumulation and proliferation of carbapenemase and metallobetalactamase genes.

In the human body antibiotics are known to bind to proteins, undergo conjugation, be metabolized and actively eliminated by the organs, which requires energy costs and creates additional burden on the body of a long-term sick person. When assessing the changes in blood clinical chemistry parameters we obtained interesting data: after antibiotic withdrawal in subgroup 1B there were no liver enzyme (ALT and AST) elevations over two weeks. An important advantage of bacteriophages over conventional antibiotic therapy is that when they are used instead of antibiotics, the antimicrobial effect is achieved «passively»: without the participation of cells of the macroorganism, the organism «recovers» that is very important for chronically critically ill patients requiring rehabilitation [21].

We used the adaptive phage therapy technique, which implies strict matching of the bacteriophage set to the needs of a particular ICU. Avoiding the need for individual selection of antibacterial agents based on microbiological testing of every specific patient, when implemented in practice, could reduce the decision time if treatment must be started immediately, thereby increasing the effectiveness of treatment of critically ill patients.

Conclusion

This clinical study presents the first experience in the use of adaptive phage therapy technique in the neurological critical care. Safety, absence of side effects and adverse events were demonstrated for the inhalational administration of the bacteriophage cocktail in the treatment of chronically critically ill patients with recurrent pneumonia. The effectiveness of the technique was confirmed by the treatment outcomes seen in the phage therapy group, which were not inferior to those in the group receiving conventional antibiotic therapy. Several clinical and laboratory parameters tended to improve even in cases of complete withdrawal of antibiotics in favor of bacteriophages.

The microbiological and molecular genetic monitoring showed that the use of the bacteriophage cocktail was not associated with increased antibiotic resistance, accumulation and proliferation of carbapenemase and metallo-beta-lactamase genes. In several patients using the bacteriophage preparation, elimination of the major multiresistant Gram-negative bacteria was observed, while at the same time persistent respiratory tract colonization with some challenging microorganisms indicates the need for control and regular adjustment of bacteriophage composition. Despite the relatively small sample size, the results obtained in this study indicate the feasibility of further study of the effects of adaptive phage therapy as a promising alternative to antibiotics in patients in neurological critical care.

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Effect of Intraoperative Propofol-Induced Sedation on the Neurotransmitter Levels (Pilot Study)

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Влияние интраоперационной седации пропофолом на концентрацию нейромедиаторов (пилотное исследование)

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Summary

The aim of the study was to determine the changes in the levels of various neurotransmitters depending on the depth of propofol-induced sedation.

Material and methods. Twenty-four patients were included in a prospective, simple blinded study. All patients underwent elective orthopedic intervention with subarachnoid anesthesia and moderate (group 1, *n*=12) or deep (group 2, *n*=12) propofol-induced sedation. Peripheral blood sampling for measurement of neurotransmitter levels was performed before regional blockade (Stage 1), 35–40 min after the start of sedation (Stage 2), and 10–15 min after sedation was terminated and consciousness was recovered (Stage 3).

Results. Deep propofol-induced sedation resulted in a decrease in norepinephrine level at stages 2 and 3. Under moderate sedation, its level decreased at Stage 2 and returned to baseline after restoration of consciousness. The initial concentration of norepinephrine (Stage 1) was higher in Group 2.

Conclusion. Propofol-induced sedation resulted in reduced level of the main stress hormone, which suggests its stabilizing effect on autonomic nervous system.

Keywords: propofol; sedation; neurotransmitter level; norepinephrine

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

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Introduction

Currently, the clinical effects of propofol are generally believed to be associated with a direct effect on GABA receptors in the brain, which accounts for their inhibitory effect on the central nervous system (CNS) with the development of drug-induced sleep [1–5]. At the same time, the limbic system structures, particularly the ventrolateral preoptic region of the hypothalamus responsible for natural sleep, are among the main targets for propofol [6, 7]. This area consists mostly of GABA neurons, 70% of which are norepinephrine (NE)-inhibitory and 30% are NE-activating [8]. Propofol, having agonist effect on GABA receptors, is perceived to inhibit NE-activating neurons, which activates NE-inhibit-

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ing neurons, reduces the NE level and, consequently, causes drug-induced sleep and anti-stress effect [9–12]. On the contrary, norepinephrine injection into hypothalamic area in animals accelerated recovery time from anesthesia [13].

Another target of propofol is the midbrain ventral tegmental area (VTA), which serves as an origin site for the mesocortical and mesolimbic dopamine pathways involved in behavioral responses and the maintenance of wakefulness [14]. For example, in experiments, the VTA damage or the use of dopamine receptor antagonists led to prolonged recovery time after propofol administration [15, 16].

However, the effects of intraoperative sedation with propofol on the changes in other CNS neurotransmitter systems (acetylcholine, serotonin) remain largely unclear [17]. At the same time, most of these systems are also responsible for the development of various human behavioral responses that accompany various psychotic conditions, such as anxiety and depression [18–21]. The origin of these conditions has not been sufficiently studied and may be directly related to the changes in brain neurotransmitter levels [22].

The aim of the study was to examine the changes in the level of various neurotransmitters depending on the depth of propofol-induced sedation.

Material and Methods

This study was approved by the Local Ethics Committee of the First Sechenov Moscow State Medical University and registered in ClinicalTrials.gov #NCT04695509.

A prospective simple blind pilot non-randomized clinical trial was performed in 24 patients who underwent surgery under spinal anesthesia. The laboratory specialist responsible for the measurement of neurotransmitter levels was not aware of group assignment and sedation levels.

Inclusion criteria for the study were patients aged 18 to 70 years, ASA (American Society of Anesthesiologists) class I–II, who underwent orthopedic interventions on the lower extremities under spinal anesthesia with intravenous sedation.

Exclusion criteria were patient's refusal to participate in the study and regional block anesthesia, age under 18 and over 70, allergic reactions to propofol, lidocaine, bupivacaine, pregnancy, history of epilepsy, ASA class III or higher, emergency surgery, ineffective spinal anesthesia, psychiatric disorders, anticoagulant or psychotropic therapy.

Patients were recruited at Moscow City Hospital No. 31 (affiliated with the First Sechenov Moscow State Medical University). The plasma levels of neurotransmitters were measured in the clinical laboratory of the B. V. Petrovsky Russian Surgery Research Center.

The patients were assigned to two groups depending on the depth of sedation: moderate (Group 1, *n*=12) and deep (Group 2, *n*=12). As shown in Table 1, the groups were comparable in age, sex, and body measurements.

Two intravenous peripheral 18 or 20 G catheters were inserted before regional anesthesia in the operating room for infusion therapy and blood sampling. Before spinal anesthesia, an infusion of Sterofundin® (isotonic balanced fluid) 6–8 ml/kg was given.

Aseptic lumbar puncture using a 27 G Pencil Point needle was performed under local anesthesia with lidocaine at the L2–L4 level. The cerebrospinal fluid return was used as a criterion for the proper procedure performance. After aspiration test, 10–15 mg of isobaric bupivacaine solution was injected.

The touch sensitivity (pinprick) test was used to evaluate the sensory block, the motor block was evaluated using the Bromage scale.

Intravenous infusion of propofol was performed with Perfusor Space (B. Braun, Germany) using the target-controlled infusion technique. For patients with moderate sedation, the target concentration of propofol was 1.5 mcg/ml, with deep sedation — 2.5 mcg/ml.

The Richmond Arousal and Sedation Scale (RASS) and bispectral index (BIS) (A-2000XP monitor by Medlekprom, Russia) were used to assess the depth of sedation. The RASS scale values of «-2» to «-3» (brief eye opening less than 10 seconds or voluntary movements without eye contact in response to voice) and BIS values of 70–90 were considered as moderate sedation. Deep sedation was diagnosed when RASS score was «-4» (eye opening or voluntary movements in response to physical stimulation) and BIS score was 60–70.

To ensure patient safety, the routine standard monitoring was used including assessment of BP, HR, ECG, SpO_2, and capnography (IntelliVue MP40

Table 1. Demographic parameters and body measurements in the study groups, *Me* [25, 75].

Parameters	Values in groups		
	1, *n*=12	**2, *n*=12**	***P-value***
Male, *n* (%)	6 (50)	3 (25)	0.4
Female, *n* (%)	6 (50)	9 (75)	
Age, years	51.5 [41.0; 60.5]	55.5 [33.0; 50.0]	0.91
Height, cm	169.0 [164.5; 182.5]	172.0 [167.5; 175.0]	0.73
Weight, kg	83.5 [63.0; 100.0]	72.5 [62.5; 81.5]	0.31

Table 2. Plasma neurotransmitter levels in the study groups, *Me* [25; 75].

Neurotransmitters	Values in groups at study stages					
	1, *n*=12			2, *n*=12		
	Stage 1	Stage 2	Stage 3	Stage 1	Stage 2	Stage 3
Norepinephrine, pg/ml	130.3 [24.7; 151.0]##	3.3 [0.2; 17.6]*	73.7 [13.4; 142.2]	189.9 [143.3; 223.7] **	18.4 [1.0; 142.8]#	77.4 [8.5; 161.8]
Acetylcholine, pg/ml	36.2 [28.7; 49.4]	49.2 [33.5; 62.6]	35.6 [27.7; 61.1]	53.6 [42.9; 67.7]	51.6 [41.8; 74.3]	47.1 [37.0; 78.9]
GABA, μmol/l	0.02 [0.005; 0.025]	0.04 [0.02; 0.06]	0.035 [0.02; 0.06]	0.015 [0.005; 0.04]	0.04 [0.025; 0.055]	0.003 [0.015; 0.045]
Serotonin, ng/ml	7.5 [3.5; 12.5]	6.2 [5.1; 9.6]	5.0 [4.3; 7.6]	5.0 [4.3; 7.6]	7.7 [5.4; 11.5]	8.3 [6.1; 9.4]
Dopamine, ng/ml	7.3 [0.92; 1478.1]	1.7 [0.66; 98.4]	3.7 [0.4; 10.2]	0.81 [0.17; 4.0]	3.5 [1.5; 11.2]	1.0 [0.27; 3.9]

Note. * — *P*=0.007 vs Stage 1 in group 1; ** — *P*<0.002 vs Stage 3 in Group 2; # — *P*<0.001 vs Stage 1 Group 2; ## — *P*=0.007 vs Stage 1 in Group 2.

monitor, Philips Medizin Systeme Boblingen GmbH, Germany).

The levels of neurotransmitters were measured at the following stages of the study: stage 1 — before regional block, stage 2 — 35–40 minutes after the start of sedation, stage 3 — 10–15 minutes after the end of sedation and restoration of consciousness (RASS «0», BIS 90-100).

Blood samples were centrifuged in 367525 BD (Becton Dickinson) Vacutainer 10 ml tubes with K2 ethylenediaminetetraacetate (EDTA) at 4000 rpm for 8 min, and the separated plasma was aliquoted into 363706 BD (Becton Dickinson) Microtainer 0.5 ml tubes with K2-EDTA and frozen at -20°C until analysis. Subsequently, dopamine, serotonin, gamma-aminobutyric acid (GABA), acetylcholine (ACh), and norepinephrine (NE) levels were measured by enzyme-linked immunosorbent assay (ELISA).

Statistical analysis of the data was performed using MS Excel and Statistica 12. Quantitative variables were presented as medians (*Me*) and 25–75% percentiles [25; 75]. The Shapiro–Wilk's test was used to check the normality of data distribution.

Analysis of categorical variables was performed using Fisher's exact test. Mann–Whitney *U*-test was used to compare quantitative variables between groups. A nonparametric Friedman test was used for comparisons between three stages of the study. Nonparametric Wilcoxon's test for dependent samples with Bonferroni correction was used for multiple pairwise comparison of neurotransmitter concentrations at different stages of the study in each group. For pairwise comparisons, the differences were considered significant at $P<0.017$; for intergroup comparisons, at $P<0.05$.

Results

Data analysis showed that the changes in plasma serotonin, ACh, dopamine, and GABA levels depending on propofol dose and associated anesthetic suppression of consciousness were not significant (Table 2).

However, the changes in dopamine levels at all stages were highly variable. Most likely, the study of larger samples of patients will lead to a clearer understanding of patterns of dopamine concentration changes and their possible causes.

At the same time, in both groups a decrease in plasma NE concentration was noted when the sedative effect developed (stage 2). The decrease in NE level was not affected by the drug dose or the depth of sedation (no differences between the groups at stages 2 and 3).

Upon awakening, patients' plasma NE levels rose and did not differ from baseline values in group 1 ($P=0.62$). In the group with deep sedation, when the dose of propofol was accordingly higher, the NE level on awakening was significantly lower than the baseline values ($P<0.002$).

Interestingly, differences between the groups in the baseline NE levels were found ($P=0.007$). The differences were not related to body measurements, age, or sex.

Discussion

Our data demonstrate the stabilizing effect of propofol on the autonomous nervous system regardless of the depth of medical sedation. Norepinephrine is a stress hormone produced mainly in the postganglionic fibers of the sympathetic nervous system and, to a lesser degree, in the adrenal medulla [23-26].

The lack of changes in the levels of other brain-derived neurotransmitters (ACh, etc.) may indicate that they cannot be studied in the blood plasma due to their low concentrations. However, this conclusion requires additional studies due to the fact that these mediators are almost not metabolized in the brain and can enter the circulation with delay. In general surgical practice, it is impossible to perform a study with microdialysis fluid sampling from human brain structures during sedation [27].

The findings indicating the lack of changes in plasma dopamine concentration during sedation in the groups contradict several animal studies, which,

on the contrary, describe its reduced level during propofol infusion [28]. At the same time, the authors note that after discontinuation of propofol infusion and awakening, dopamine level returned to the baseline values [29].

Surprisingly, the baseline plasma NE levels differed between the groups, which could be related to the predominance of women in the second group and probable more intense stress response [30]. Although the groups did not differ significantly in gender, this requires further and thorough research to identify possible gender differences in the development of preoperative stress.

Different patterns of change of NE level on recovery from sedation among the groups are most likely related to the residual effect of propofol and a longer recovery of autonomic response to perioperative stress in the group with deep sedation.

This is a pilot study that cannot fully explain the patterns of neurotransmitter level changes following the use of anesthetics, which warrants randomized clinical trials.

Conclusion

Sedation with propofol reduces the blood level of norepinephrine, which indicates its stabilizing effect on the autonomic nervous system.

This stabilizing effect is independent of the drug dose and the depth of sedation.

The recovery rate of blood norepinephrine concentration depends on the dose of propofol.

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Risk Assessment of Hemodynamically Significant Arrhythmias after Elective Cardiac Operations with Cardiopulmonary Bypass Using the Modified Nomogram (Retrospective Study)

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Оценка риска развития гемодинамически значимых аритмий после плановых кардиальных операций в условиях искусственного кровообращения с использованием номограммы М (ретроспективное исследование)

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Summary

Aim of the study was to evaluate the feasibility of using a modified nomogram (the M nomogram) to predict the occurrence of new postoperative hemodynamically significant arrhythmias after elective cardiac surgery with cardiopulmonary bypass within 30 days post operation.

Materials and methods. This was a retrospective cohort study. The prognostic value of the model using ROC-analysis of the modified nomogram was estimated based on the medical records of 144 patients who underwent elective cardiac surgery with cardiopulmonary bypass.

Results. The incidence of new postoperative hemodynamically significant arrhythmias was 13.9% (20 of 144 patients). For the modified nomogram, the AUC was 0.777 [95% CI: 0.661–0.892] (P<0.001); at a cutoff of 12 points, the sensitivity was 60.0% and specificity was 89.52%. The odds ratio was 10.26 (95% CI: 3.63–29.06) (P<0.001).

Conclusion. The modified nomogram has an acceptable prognostic value for the occurrence of new hemodynamically significant arrhythmias after elective cardiac operations with cardiopulmonary bypass based on AUC 0.777 [0.661–0.892] (P<0.001), and is currently the best model for predicting the outcome.

Keywords: cardiac surgery; bypass; nomograms; arrhythmias; mortality.

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

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Introduction

Currently, there are a lot of studies concerning new-onset postoperative rhythm disturbances, both in cardiac [1–7], and in noncardiac surgery [1, 6, 8–11]. Atrial fibrillation (AF) occurs in 15–40% of patients after coronary artery bypass grafting, 37–50% of patients after heart valve surgery and

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60% of patients after combined valve and coronary surgery [12–14]. Hospital mortality in patients with sustained postoperative ventricular arrhythmias is 50% [1] vs 3.4% in the general population of cardiac surgery patients [15].

There are several prognostic models and scales allowing to estimate the risk of AF in the postoperative period [16–20]. However, these scales do not always provide definitive information on the hemodynamic significance of predicted AF, which reduces their value for intensive care unit doctors. Moreover, these prognostic models rely only on preoperative risk factors, ignoring important intraoperative predictors of AF such as myocardial ischemia, duration of bypass, hemodynamic support, etc. [21, 22]. The above disadvantages hamper targeted identification of patients at risk of new-onset hemodynamically significant AF.

Earlier we proposed a modified nomogram (the M nomogram) [23], which has demonstrated some advantages in predicting 30-day mortality, compared to the original version [24] and Euroscore 2. This nomogram includes assessment of age, sex, body mass index, glomerular filtration rate, recent use of antiplatelet agents, low mobility, resting angina, left ventricular ejection fraction, preoperative critical illness, vasoactive inotropic score (VIS) on admission to ICU after operating room.

The aim of the study was to evaluate the feasibility of using a modified nomogram (the M nomogram) to predict the occurrence of new-onset postoperative hemodynamically significant arrhythmias after elective cardiac surgery with cardiopulmonary bypass within 30 days after surgery.

Материал и методы

Design of the study. We performed a single-center retrospective cohort study.

We analyzed the medical records of the cardiac surgery patients of M. F. Vladimirsky Moscow Region Research and Clinical Hospital, who underwent cardiac surgery with cardiopulmonary bypass between June 2014 and September 2017.

The inclusion criteria were age older than 18 years and elective cardiac surgery with cardiopulmonary bypass. The exclusion criteria were congenital heart defects and preoperative cardiac rhythm disturbances.

The following data were summarized and analyzed: age, sex, height, body weight, glomerular filtration rate, left ventricular ejection fraction, recent use of antiplatelet agents [25], low mobility and severity of preoperative patients (according to E-CABG criteria [26] and Euroscore 2 [27]), presence of angina at rest, congestive heart failure, myocardial infarction, peripheral artery disease, hypertension, diabetes mellitus, stroke, transient ischemic attacks, chronic use of beta-blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, diuretics, nitrates, statins, antiplatelet agents and anticoagulants, proteinuria, and VIS on admission to ICU after operating room.

The primary end point was new-onset postoperative hemodynamically significant arrhythmia. This term included any rhythm disturbances requiring either drug therapy, or cardioversion, or pacemaker implantation.

Statistical analysis.

For each patient, the values of the modified nomogram (Table 1), as well as POAF [17], CHA_2DS_2-VASc [18], ATRIA [20] and HATCH [16] scores were calculated. Then ROC analysis of the M nomogram and the above scales was performed to predict the occurrence of postoperative hemodynamically significant arrhythmias. After that, we determined the cutoff point for the M nomogram, which was used to form two groups of patients. Group 1 included patients who scored less than the

Table 1. The modified (M) nomogram.

Parameter	Points
VIS on admission to ICU (points)	
<8	0
8–15	2
>15	4
Critical illness prior to surgery	4.5
Left ventricular ejection fraction (%)	
>50	0
31–50	1
21–30	5
⩽20	6.5
Angina at rest	2
Low mobility	3
Recent administration of antiplatelet agents	2
eGFR MDRD (class)	
1	0
2	0
3a	1
3b	4.5
4	7
5	8
Body mass index (kg/m²)	
15	2
20	2.5
25	3
30	4
35	4.5
40	5
50	6.5
Female	0.5
Age (years)	
20	2
30	3
40	4
50	5
60	6
70	7
80	8

Note. eGFR MDRD — glomerular filtration rate estimated using the MDRD equation; VIS — vasoactive inotropic score; ICU — intensive care unit.

Table 2. Preoperative patients' characteristics.

Parameter	Value
Mean age, years	59.8 ± 8.1
Men (%)	112 (77.8%)
Mean body mass index, kg/m^2	28.2 ± 3.9
Blood creatinine, μmol/l	93.5 [85.3; 104.0]
Glomerular filtration rate, ml/min	82.9 [67.1; 96.1]
Left ventricular ejection fraction (%)	59.0 [52.0; 66.8]
Vasoactive inotropic score on admission to ICU after the operating room, points	1.5 [0; 5.0]
CHA_2DS_2-VASc, points	3.0 [2.0; 3.8]
POAF, points	1.0 [0; 1.0]
ATRIA, points	2.0 [1.0; 4.0]
HATCH, points	3.0 [1.0; 3.0]

Note. ICU — intensive care unit; for table 2 and figure 2: CHA_2DS_2-VASc — risk assessment scale for stroke and systemic thromboembolism in patients with atrial fibrillation; POAF — risk assessment scale for postoperative atrial fibrillation; ATRIA — stroke risk assessment scale for patients with atrial fibrillation; HATCH — scale for assessing the likelihood of progression of atrial fibrillation from paroxysmal to permanent.

Table 3. Types of surgery.

Type of surgery	Number of patients (%)
Coronary artery bypass grafting	118 (81.95)
Cardiac valve surgery	11 (7.63)
Coronary artery bypass grafting and aneurysmectomy	7 (4.85)
Single valve surgery and aneurysmectomy	4 (2.77)
Coronary artery bypass grafting and single valve surgery	1 (0.7)
Coronary artery bypass grafting, single valve surgery and aneurysmectomy	1 (0.7)
Double valve surgery and aneurysmectomy	2 (1.4)

Table 4. Types of new-onset arrhythmias.

Type of arrhythmia	Number of patients (%)
New-onset postoperative atrial fibrillation	13 (9.0)
New-onset postoperative atrial fibrillation with atrioventricular block	1 (0.7)
New-onset postoperative atrial fibrillation with ventricular extrasystole	1 (0.7)
Atrioventricular junction rhythm with the rate <60 beats per minute	1 (0.7)
Ventricular extrasystole	2 (1.4)
Ventricular tachycardia	1 (0.7)
Ventricular fibrillation	1 (0.7)

cutoff point value; Group 2 consisted of patients who scored more or equal to the cutoff point value.

Normality of distribution was tested for the following parameters: age, body mass index, plasma creatinine before surgery, glomerular filtration rate, left ventricular ejection fraction, VIS value on admission to ICU after operating room, M nomogram, POAF, CHA_2DS_2-VASc, ATRIA and HATCH scores. Normally distributed data were presented as mean and standard deviation. Data with non-normal distributions were reported as median and quartiles.

Statistical data analysis was performed using the IBM SPSS Statistics 25.0 and MedCalc Statistical Software version 20.008 (MedCalc Software bv, Ostend, Belgium) software packages. Normality of the distribution was assessed using the Shapiro–Wilk test. Critical *P*-value was considered as 0.05. To assess the predictive ability of various parameters we used ROC-analysis with assessment of the AUC parameters (area under the ROC-curve and 95% confidence interval). The threshold value was chosen based on the optimal sensitivity/specificity ratio in accordance with the results of ROC-analysis (Yuden's statistics). Sensitivity, specificity, accuracy, and odds ratio (OR) were calculated for predictors.

Participants. In this study, 520 case records were studied. 158 patients met the inclusion criteria. Among the patients not included in the study, 169 were younger than 18 years, 193 patients underwent surgery without cardiopulmonary bypass. Of the 158 patients who met the inclusion criteria, 14 patients had exclusion criteria, i.e., preoperative cardiac rhythm disturbances. As a result, 144 patients were included in the analysis (Fig. 1).

Descriptive statistics. The preoperative characteristics of patients are shown in Table 2.

The types of surgical interventions are shown in Table 3.

The types of new-onset postoperative arrhythmias are summarized in Table 4.

Medications taken prior to surgery by patients with/without postoperative hemodynamically significant rhythm disturbances are listed in Table 5.

The median M nomogram score was 10.0 points [IQR, 9.0–11.4].

Table 5. Medications taken preoperatively by study participants.

Drug class	Postoperative patients		*P*-value
	Without arrhythmia (*n*=124)	With arrythmia (*n*=20)	
Beta-blockers	84 (67.7%)	16(80%)	0.310
Calcium channel blockers	24 (19.4%)	2 (10%)	0.530
ACE inhibitors	37 (29.8%)	8 (40%)	0.437
Angiotensin receptor blockers	13 (10.5%)	1 (5%)	0.693
Diuretics	62 (50%)	11(55%)	0.811
Nitrates	19 (15.3%)	2(10%)	0.738
Statins	60 (48.4%)	10 (50%)	0.999
Antiplatelet agents	44(35.5%)	7 (35%)	0.999
Anticoagulants	50 (40.3%)	9 (45%)	0.807

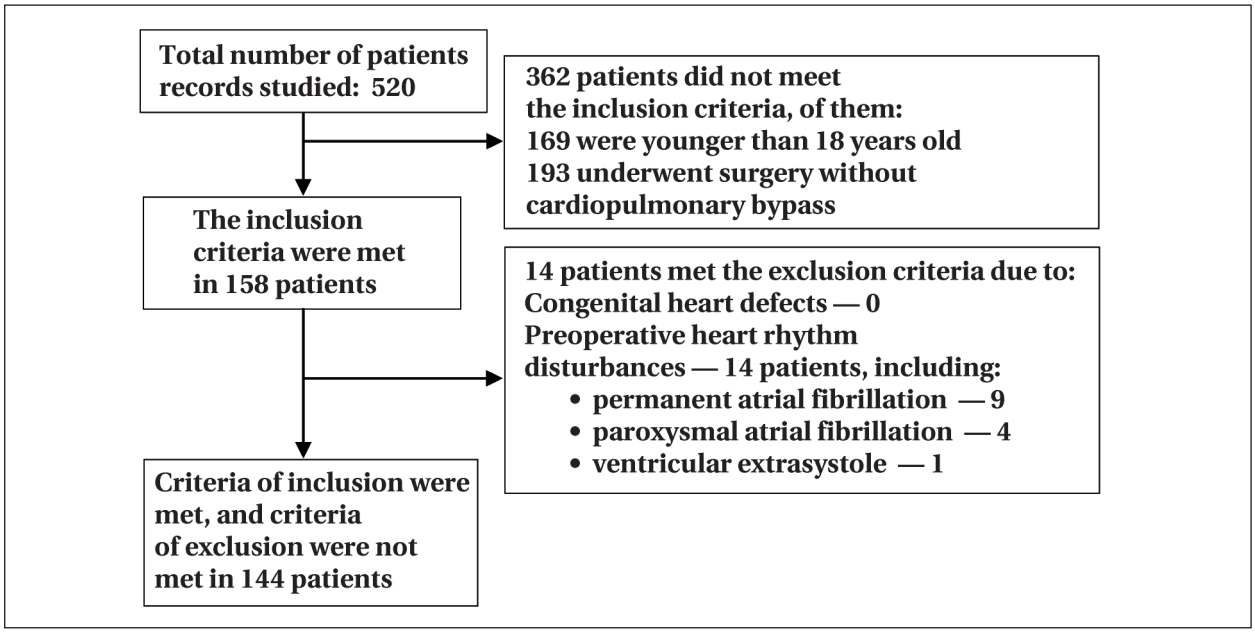

Fig. 1. Study flowchart.

Results

The overall mortality in the study group was 5.56%, the median ICU stay was 19.0 hours [17.1; 40.0] ranging from 12.5 to 334.0 hours.

The incidence of new-onset postoperative hemodynamically significant arrhythmias was 13.9% (20 of 144 patients). The mortality in the group of patients who developed postoperative hemodynamically significant arrhythmias was 35.0% (7 of 20 patients), whereas in the group of patients without postoperative hemodynamically significant arrhythmias it was 0.8% (1 of 124 patients) (P<0.001). For the M nomogram, the AUC parameter was 0.777 [0.661; 0.892] (P<0.001) (Fig. 2). The cutoff point was 12 points (sensitivity, 60.00% [95%CI, 36.05–80.90], specificity, 89.52% [95%CI, 82.74–94.30]). The accuracy of the prognostic model was 85.42% [95%CI, 78.58–90.74%]. The positive and negative predictive values were 48.0% [95%CI, 33.0–63.3] and 93.3% [95%CI, 89.0–96.0], respectively. The absolute risk of developing postoperative hemodynamically significant arrhythmias during hospital stay in group 1 was 6.25% (7 of 112 patients) and 40.63% (13 of 32 patients) in group 2. The odds ratio of group 2 versus group 1 was 10.26 [95% CI, 3.63–29.06] (P<0.001).

Of the «competitors», only ATRIA showed a significant result with AUC = 0.656 [0.539; 0.773] (P=0.026).

When assessing the prognostic value of POAF, CHA_2DS_2-VASc, and HATCH scales regarding the development of new-onset hemodynamically significant arrhythmias after cardiac surgery with cardiopulmonary bypass, no significant predictors were found with P=0.091, P=0.092, and P=0.525, respectively.

Discussion

Our data suggest that the M nomogram has an acceptable prognostic power regarding the new-onset hemodynamically significant arrhythmias with AUC = 0.777 [0.661; 0.892] (P<0.001) and could also be the best available model for predicting this outcome.

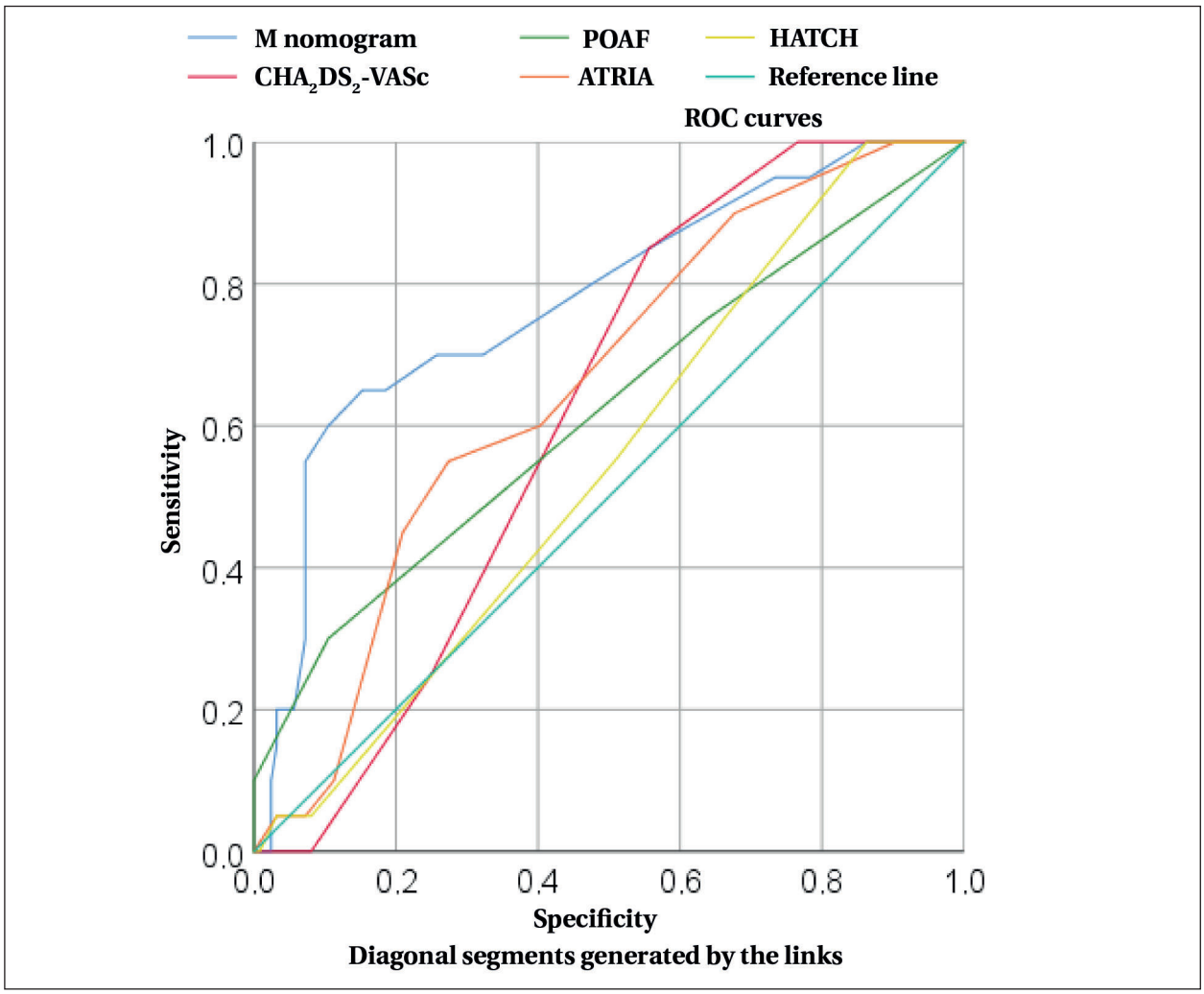

Fig. 2. The validity of different predictive models for the new-onset postoperative hemodynamically significant arrhythmias.

Importantly, the odds ratio of developing new hemodynamically significant arrhythmias in patients who scored 12 or more on the M nomogram versus patients who scored less than 12 is 10.26 [95% CI, 3.63–29.06] (P<0.001). Moreover, the lower limit of the 95% confidence interval of the odds ratio is 3.63, indicating truly significant differences in the odds of new hemodynamically significant arrhythmias after elective cardiac surgery with cardiopulmonary bypass between these two groups.

The presence of the lower limit of the 95% confidence interval for sensitivity below 50%, as well as the positive prognostic value less than 50%, indicates that only a one-sided interpretation of the results is possible based on the M nomogram. The M nomogram allows to identify with a high degree of probability a group of patients with a low risk of hemodynamically significant arrhythmias in the postoperative period (patients who scored less than 12 points). At the same time, when the M nomogram score is 12 or more, one cannot be sure about the likelihood of hemodynamically significant arrhythmias. Nevertheless, it allows identifying a group of patients who require more careful postoperative monitoring.

Also, the rate of arrhythmias was 13.9%, while in the studies of other authors who validated the above-mentioned scales, it varies from 21.0% [16] to 33.8% [19]. Probably, it is related to the prevalence of CABG in our study which is rather specific cardiac surgery.

The mortality of patients with hemodynamically significant arrhythmias was 35.0%, whereas in the studies of other authors it varies from 3.6% [20] to 9.0% [16]. This difference is probably due to the fact that close, but not identical phenomena were evaluated: in the present study the «new-onset hemodynamically significant arrhythmias», in the cited publications the «new-onset atrial fibrillation» were in the spotlight. Thus, here we can speak only about a comparison «by analogy», and not about a comparison of the frequency of identical phenomena.

In our comparison of the prognostic significance of the M nomogram with the POAF, CHA_2DS_2-

VASc, HATCH and ATRIA scales widely used for this purpose, all but the latter were not reliable.

Earlier reports suggested a sufficient significance of the discussed scales in predicting AF [16, 17, 19, 20]. A possible explanation for the discrepancy between the results of this study and the literature has already been suggested above. The following considerations are also important.

1. New hemodynamically significant arrhythmias were evaluated, whereas in the cited papers atrial fibrillation was an inclusion criterion. Obviously, not all episodes of AF are hemodynamically significant.

2. Hemodynamically significant ventricular rhythm disturbances were to be included in the present study and were not considered in the cited papers.

3. We studied patients who underwent surgery with cardiopulmonary bypass.

It is difficult to define what is more important to assess from the practical point of view, AF or hemodynamically significant arrhythmias. Given the higher risk of mortality, the broader concept should prevail. In terms of specificity of effect, AF should probably be preferred. In any case, the M nomogram appears to be a reliable tool for predicting adverse events after cardiac surgery performed with cardiopulmonary bypass.

External validity. We evaluated the medical records, not the experimental models, which indicates a high external validity of the study. At the same time, limitation of the sample patients to those who underwent cardiopulmonary bypass, had no congenital heart defects and preoperative rhythm disturbances actually reduces the external validity of this study by hampering extrapolation of its results to other groups of patients.

Limitations. This single-center retrospective cohort study was probably less valid compared to prospective studies in the context of evidence-based medicine. The significance of this study could also be reduced by the fact that 81.95% of the patients underwent CABG which decreases the reliability of extrapolation of the results to other types of surgery. The unidirectional interpretation of the nomogram results reduces the prognostic potential of this model regarding the occurrence of hemodynamically significant arrhythmias.

Conclusion

The modified (M) nomogram has an acceptable prognostic value for predicting new-onset hemodynamically significant arrhythmias after elective cardiac surgery with cardiopulmonary bypass with AUC = 0.777 [0.661; 0.892] (P<0.001). It could also be the best available model for predicting this complication in the postoperative period.

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Efficacy of Nasogastric and Nasojejunal Enteral Feeding in the Early Phase of Acute Pancreatitis

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Эффективность назогастрального и назоеюнального энтерального питания в раннюю фазу острого пакреатита

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Summary

Enteral nutrition in the early phase of predicted severe acute pancreatitis can be administered via a nasogastric or nasojejunal tube. Finding the most effective method in terms of daily balance, the volume of feeding and residual gastric volume in the early period of moderate and severe acute pancreatitis is a current challenge.

The aim of the study was to estimate the efficacy of nasogastric and nasojejunal early enteral feeding during the early phase of predicted severe acute pancreatitis.

Material and methods. The study was prospective, single-center, and randomized. The data were collected from November 2012 to October 2018. The study included 64 ICU patients in the early period of acute pancreatitis exhibiting predictors of severity. During randomization, the patients were assigned to either nasogastric (group 1) or nasojejunal (group 2) feeding for the next four days. The volume of enteral feeding on Day 1 was 250 ml/day, and on each successive day it was increased by 250 ml/day. During group allocation, the disease severity and the way of nutrient administration were taken into account. Daily balance was calculated using the difference between enterally administered and residual gastric volume. Statistical analysis was performed using SPSS v.23 software package. The null hypothesis was rejected at $P<0.05$.

Results. The volume of enteral nutrition administered over 4 days did not differ between the study groups. Patients with severe acute pancreatitis had significantly better nutrient absorption over 4 days when the postpyloric route was used (1.63±0.98 l/d) vs the nasogastric one (0.55±0.29 l/d) ($P=0.001$). In moderate pancreatitis, the enteral nutrition absorption over 4 days did not differ ($P=0.107$) between the groups with nasogastric (2.06±0.87 l/day) and nasojejunal (2.6±0.45 l/day) feeding.

Conclusion. Nasojejunal route is the preferred way to start enteral feeding in patients with severe acute pancreatitis. In moderate acute pancreatitis, feeding can be initiated via the gastric route and only in case of intolerance it should be switched to the nasojejunal one.

Keywords: acute pancreatitis; nasogastric feeding; nasojejunal feeding; nutrition; residual gastric volume

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

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Introduction

Acute pancreatitis (AP) can be associated with abnormal motility, secretion, digestion, and intestinal barrier function, which are grouped under the term «acute gut injury». These changes can cause feeding intolerance (FI) syndrome, when adequate enteral nutrition is impossible due to some clinical reason (vomiting, high gastric residual volume (GRV), diarrhea, gastrointestinal bleeding, entero-

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cutaneous fistula, etc.) [1]. Currently, there is no single, clearly formulated set of signs and symptoms, as well as quantitative characteristics that can confirm the diagnosis of FI and its severity. Administration of enteral nutrition (EN) in severe acute pancreatitis (SAP) associates with a significant reduction in mortality [2, 3]. Enteral feeding can be delivered via nasogastric (NG) or nasoejunal (NJ) tube. Several small prospective randomized studies have shown that NG feeding is not inferior to the NJ one in terms of infectious complications, changes in inflammatory marker levels, and frequency of analgesic use [4, 5]. To date, there is no convincing evidence on the superiority, disadvantages, or equivalence of nasogastric or nasojunal enteral tube feeding regimens in SAP [6], so both routes are acceptable. After the initiation of enteral feeding, the issue of gradual increase of its volume to achieve the target volumes becomes relevant. The main goal is a proper increase in EN volume, rather than strict adherence to the protocol with an inappropriate increase in volumē with no regard to its tolerability. In modern clinical practice, the GRV measurement remains the easiest and most accessible way to assess the feasibility of enteral feeding, despite the fact that this test is not considered mandatory for making a decision to start or stop enteral feeding, especially if the residual volume is less than 500 ml [7]. Most studies on early enteral feeding in AP were done before a new type of AP, moderately severe acute pancreatitis (MSAP), was recognized in 2012 [8]. The lack of information on the absorption of early enteral nutrition in patients with predicted severe acute pancreatitis, depending on the type of disease and routes of nutrient delivery with a gradual «as-per-protocol» increase of nutrition volumes, makes our study relevant.

The aim of the study was to evaluate the efficacy of nasogastric and nasojejunal early enteral feeding in the early severe predicted phase of acute pancreatitis.

Material and Methods

We performed a randomized single-center study in the intensive care unit (ICU) of the «Neftyanik» medical unit in Tyumen during the period from November 2012 to October 2018. The inclusion criteria were diagnosed acute pancreatitis and at least one predictor of severe course. The exclusion criteria were age more than 80 years and terminal chronic diseases. The diagnosis of acute pancreatitis was made according to typical manifestations, confirmed by laboratory and instrumental tests [8]. C-reactive protein (CRP) > 150 mg/l, Acute Physiology And Chronic Health Evaluation (APACHE) II score >8, and Sepsis-related Organ Failure (SOFA) score >2 were considered predictors associated with severe acute pancreatitis [9]. The patient assignment to 2 groups was done using the randomization envelope method. The first group consisted of 33 patients who received early (first 12–24 h after admission) EN via the nasogastric tube. The second group included 31 patients with early EN solely via a nasogastric tube placed endoscopically. Table 1 shows that the groups are comparable in terms of age, severity of multiple organ dysfunction (MOD), plasma CRP concentration on day 1 and 48 h after admission.

Subsequently, the type of the disease according to the classification adopted in 2012 was documented [8]. In the study groups, patients with SPAP were assigned the «S» letter, and those with MSAP — with the «M» letter (Table 1). Pairwise comparison of the study groups was performed.

The standard isocaloric formula enriched with dietary fiber (BBraun Nutricomp Standard Fiber, country of origin Germany) was used for enteral feeding. The duration of study was four days. In the second group the nasojejunal route was supplemented with the nasogastric one. The nutrition formula was administered into the tube as a continuous drip. Gastric decompression was performed

Table 1. Clinical and laboratory parameters of patients in the early period of predicted severe acute pancreatitis.

Parameter	Values in groups								
	1, *n*=33	**2, *n*=31**	**S, *n*=31**	**M, *n*=33**	**S1, *n*=16**	**M1, *n*=17**	**S2, *n*=15**	**M2, *n*=16**	***P***
Sex, male/female	20/13	19/12	21/10	18/15	11/5	9/8	10/5	9/7	—
Age, years	43±11	46(34;58)	41(35;57)	42±12	42±13	42±10	47±13	45±15	0.667
Shapiro–Wilk's test	0.86	0.04	0.032	0.062	0.094	0.264	0.122	0.132	—
APACHE-II, points	5.1±2.8	6(4;10)	7.3±4.0	4(2;5)	6.5±2.9	3.6±2.1	5.5±4.9	5.4±3.6	0.002
Shapiro–Wilk's test	0.169	0.027	0.301	0.001	0.239	0.333	0.575	0.11	—
SOFA, points	2(1;2)	2(1;3)	2(1;3)	2(1;2)	2(1;2)	2(1;2)	3(1;4)	1(1;2)	0.369
Shapiro–Wilk's test	0.02	0.01	0.001	0.001	0.007	0.013	0.007	0.002	—
CRP24, mg/l	80.1±58.5	89.7±57.8	87.6±51.8	78(23;136)	72.8±54.8	85.6±64.7	101.2±47.8	77.2±67.6	0.934
Shapiro–Wilk's test	0.057	0.173	0.334	0.015	0.225	0.171	0.144	0.055	—
CRP48, mg/l	183 (146; 203)	181 (155; 203)	181 (160; 200)	181 (141; 203)	182.4±50.2	195 (130; 207)	175 (155; 203)	181 (152; 189)	1.0
Shapiro–Wilk's test	0.001	0.003	0.011	0.001	0.434	0.002	0.043	0.033	—

Note. For tables. 1–4, 1 — group 1, nasogastric tube feeding; 2 — group 2, nasojejunal tube feeding; S/M — number of patients with severe/moderately severe acute pancreatitis. Subscripts represent group numbers. APACHE — Acute Physiology And Chronic Health Evaluation; SOFA — Sepsis-related Organ Failure; CRP — C-reactive protein. CRP24 — CRP level 24 hours after admission, CRP48 — CRP level 48 hours after admission. *P*-values were derived from Kraskel–Wallis test.

every 6 hours in nasogastric feeding. In the second group, gastric decompression was continuous. The initial rate of feeding was 15 ml/h, and then every subsequent day it was increased by 15 ml/h. The required volume of enteral nutrition for the first day was 250 ml/day, and every subsequent day it was increased by 250 ml/day depending on tolerance. If nausea, vomiting, increased pain or nasogastric tube discharge >500 ml/hour appeared, the rate was reduced by half, and if the above symptoms persisted, the feeding was discontinued. Later, after symptoms of food intolerance subsided, the rate was gradually increased to the previous values. The daily volume of enteral nutrition and GRV were used to calculate the balance of absorbed nutrition.

Statistical analysis was performed using the SPSS-23 software package. After checking for distribution normality using the Shapiro–Wilk's test, the results were presented as means with standard deviation $M \pm \sigma$ or medians with quartiles *Me*, (Q25; Q75). Parametric and nonparametric criteria were used for group comparison. The null hypothesis was rejected at $P<0.05$.

Results

The results obtained during 4 days of treatment in ICU are shown in Tables 2–4: Table 2 describes the daily volume of enteral feeding, Table 3 presents the daily GRV, and Table 4 displays the balance between the enteral nutrition administered and the GRV.

Discussion

The volume of delivered nutrition did not differ significantly between patients fed via nasogastric (group 1) or nasojejunal (group 2) tubes (Table 2). Nasogastric tube spillage was significantly greater in the NG group than in NJ (Table 3). This was reflected in the 4-day absorbed nutrition balance, which was significantly greater in the group with the postpyloric nutrient delivery (Table 4).

Thus, due to lower GRV, the volume of absorbed nutrition was greater with postpyloric feeding than with the NG route. Based on the results presented in Table 4, starting from day 3 and altogether over the entire follow-up period, patients with MSAP absorbed significantly more nutrition than those with SAP. The volume of nasogastric nutrition did not differ between the SAP and MSAP groups (Table 2), but in the MSAP group, starting from day 3 and over the whole follow-up period, the daily GRV was significantly lower (Table 3) resulting in a higher volume of nutrition absorbed by the MSAP patients (Table 4). Thus, with nasogastric feeding, patients with MSAP, starting from day 3, absorbed more nutrition (Table 4) than patients with SAP due to lower

Table 2. The volume of enteral feeding in patients with predicted severe acute pancreatitis.

Parameter	Values in groups											
	1, *n*=33	**2, *n*=31**	***P***	**S, *n*=31**	**M, *n*=33**	***P***	**S1, *n*=16**	**M2, *n*=17**	***P***	**S2, *n*=15**	**M2, *n*=16**	***P***
Day 1	0.25 (0.25; 0.30)	0.25 (0.25; 0.27)	0.775	0.25 (0.25; 0.30)	0.25 (0.25; 0.25)	0.656	0.25 (0.25; 0.30)	0.25 (0.25; 0.25)	0.557*	0.25 (0.25; 0.25)	0.25 (0.25; 0.30)	0.984
Shapiro–Wilk's test	0.001	0.001	—	0.001	0.001	—	0.005	0.001	—	0.001	0.001	—
Day 2	0.5 (0.5; 0.5)	0.5 (0.5; 0.5)	0.260	0.5 (0.5; 0.5)	0.5 (0.5; 0.6)	0.691	0.5 (0.5; 0.5)	0.5 (0.5; 0.5)	0.986	0.5 (0.5; 0.5)	0.5 (0.5; 0.6)	0.599
Shapiro–Wilk's test	0.001	0.001	—	0.001	0.001	—	0.001	0.004	—	0.001	0.018	—
Day 3	1.0(0.8; 1.0)	1.0 (0.8; 1.0)	0.811*	0.8 (0.5; 1.0)	1.0 (1.0; 1.0)	0.002*	0.8 (0.6; 1.0)	1.0 (0.8; 1.0)	0.309	0.8 (0.5; 1.0)	1.0 (1.0; 1.0)	0.004
Shapiro–Wilk's test	0.001	0.001	—	0.001	0.001	—	0.002	0.003	—	0.028	0.001	—
Day 4	1.0 (1.0; 1.0)	1.0 (1.0; 1.3)	0.376*	1.0 (0.95; 1.3)	1.3 (1.0; 1.5)	0.019*	1.0 (1.0; 1.5)	1.3 (1.0; 1.5)	0.444*	1.0±0.3	1.2 (0.1; 1.5)	0.037*
Shapiro–Wilk's test	0.001	0.012	—	0.017	0.001	—	0.023	0.002	—	0.552	0.001	—
Total	2.8±0.6	2.8±0.5	0.766#	2.6±0.5	3.0±0.5	0.014**	2.7±0.6	2.9±0.6	0.399**	2.5±0.5	2.9±0.6	0.002**
Shapiro–Wilk's test	0.284	0.281	—	0.236	0.262	—	0.76	0.646	0.001	0.487	0.577	—

Note. For Tables 2–4: * — Mann–Whitney test; ** — Student's *t*-test; # — given that the Levene's test for the equality of variances is less than 0.05, Mann–Whitney test is used.

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Table 3. Daily residual gastric volume in early enteral feeding in patients with predicted severe acute pancreatitis.

Parameter	Values in groups										
	1, *n*=33	2, *n*=31	*P*	S, *n*=31	M, *n*=33	*P*	S1, *n*=16	M2, *n*=17	*P*	S2, *n*=15	M2, *n*=16	*P*
Day 1	0.1 (0.1; 0.4)	0.1 (0.0; 0.2)	0.035*	0.2 (0.1; 0.4)	0.0 (0.0; 0.1)	0.001*	0.4 (0.8; 0.5)	0.1 (0.0; 0.2)	0.014*	0.1 (0.1; 0.2)	0 (0.0; 0.0)	0.019*
Shapiro–Wilk's test	0.001	0.001	—	0.001	0.001	—	0.001	0.001	—	0.035	0.001	—
Day 2	0.3 (0.2; 0.5)	0.2 (0.0; 0.3)	0.034*	0.3 (0.2; 0.5)	0.2 (0.1; 0.5)	0.234*	0.3 (0.2; 0.5)	0.2 (0.1; 0.5)	0.168*	0.3 (0.0; 0.4)	0.2 (0.1 (0.3)	0.711*
Shapiro–Wilk's test	0.001	0.001	—	0.039	0.001	—	0.007	0.001	—	0.04	0.008	—
Day 3	0.5 (0.15; 0.8)	0.1 (0; 0.5)	0.004*	0.5 (0.2; 0.8)	0.1 (0; 0.4)	0.001*	0.8 (0.5; 1.0)	0.2 (0.05; 0.5)	0.001*	0.2 (0.1; 0.6)	0.0 (0.0; 0.2)	0.049*
Shapiro–Wilk's test	0.001	0.001	—	0.001	0.001	—	0.001	0.001	—	0.008	0.001	—
Day 4	0.1 (0.0; 0.3)	0.0 (0.0; 0.1)	0.062*	0.2 (0.0; 0.3)	0.0 (0.0; 0.0)	0.001*	0.4±0.4	0.0 (0.0; 0.1)	0.001*	0.1 (0.0; 0.2)	0.0 (0.0; 0.0)	0.119*
Shapiro–Wilk's test	0.001	0.001	—	0.002	0.001	—	0.073	0.001	—	0.004	0.001	—
Total	1.3 (0.7; 1.9)	0.6 (0.25; 1.1)	0.001*	1.4 (0.8; 2.0)	0.6 (0.3; 1.1)	0.001*	2.2±1.3	0.8±0.6	0.001**	0.9±0.2	0.3 (0.1; 0.7)	0.119*
Shapiro–Wilk's test	0.003	0.001	—	0.01	0.005	—	0.169	0.263	—	0.435	0.01	—

Table 4. Daily balance between enterally administered nutrition and residual gastric volume in patients with predicted severe acute pancreatitis.

Parameter	Values in groups										
	1, *n*=33	2, *n*=31	*P*	S, *n*=31	M, *n*=33	*P*	S1, *n*=16	M2, *n*=17	*P*	S2, *n*=15	M2, *n*=16	*P*
Day 1	0.2 (–0.1; 0.3)	0.2 (0.1; 0.3)	0.13*	0.2 (–0.2; 0.3)	0.2 (0.2; 0.3)	0.012*	0.0 (–0.2; 0.3)	0.2 (0.1; 0.3)	0.074*	0.1±0.2	0.3 (0.2; 0.3)	0.232*
Shapiro–Wilk's test	0.001	0.007	—	0.001	0.001	—	0.001	0.022	—	0.267	0.04	—
Day 2	0.2 (–0.1; 0.3)	0.3±0.3	0.032*	0.2 (0.1; 0.3)	0.3 (0.1; 0.4)	0.155*	0.0±0.4	0.3 (0.0; 0.4)	0.231*	0.3±0.3	0.3±0.3	0.704**
Shapiro–Wilk's test	0.01	0.379	—	0.038	0.001	—	0.126	0.02	—	0.361	0.226	—
Day 3	0.5 (0.0; 0.7)	0.8 (0.3; 0.1)	0.023*	0.3 (–0.1; 0.5)	0.9 (0.6; 1.0)	0.001*	0.2 (–0.2; 0.4)	0.6 (0.5; 0.9)	0.001*	0.4±0.5	1.0 (0.8; 1.0)	0.004*
Shapiro–Wilk's test	0.001	0.001	—	0.001	0.001	—	0.001	0.018	—	0.544	0.001	—
Day 4	1.0±0.4	1.0±0.3	0.434**	0.8±0.4	1.2 (1.0; 1.5)	0.001*	0.7±0.4	1.2 (1.0; 1.5)	0.001*	0.9±0.3	1.1 (1.0; 1.4)	0.001*
Shapiro–Wilk's test	0.069	0.123	—	0.777	0.001	—	0.909	0.022	—	0.776	0.041	—
Total	1.3±1.3	2.1±0.9	0.007**	1.1±1.2	2.3±0.8	0.001**	0.56; 0.3	2.1±0.9	0.001**	1.63; 1.0	2.6±0.4	0.009**
Shapiro–Wilk's test	0.376	0.133	—	0.829	0.306	—	0.335	0.768	—	0.814	0.554	—

GRV (Tables 3, 4). With NJ nutrition in the group of patients with MSAP, on the contrary, starting from day 3, it was possible to deliver more nutrition (Table 2), and GRV in postpyloric feeding did not differ significantly between the groups with MSAP and SAP (Table 3).

Thus, we can say that patients with MSAP absorbed a larger volume of nutrition in postpyloric delivery due to a better tolerance of its «per-protocol» volume increase. The main function of the stomach is known to be mixing and propelling food into the small intestine at a rate optimal for nutrient absorption through increasing contact time with the mucosa. The mechanisms leading to impaired gut motility in the critical illness are complex [10]. The activity of gastric smooth muscles is regulated by internal myogenic activity, signals from parasympathetic and sympathetic enteric nervous system, and also by some hormones [11]. The main pathophysiological mechanism leading to these disorders is primary gastric motor dysfunction with impaired coordination between its proximal and distal parts [12, 13] as a result of imbalance of hormones secreted by gut, such as ghrelin [14], cholecystokinin, peptide YY [15], and motilin [16]. In critically ill patients, delayed gastric emptying increases as the severity of the disease progresses [17].

Thus, the reduced ability to absorb enteral nutrition in SAP is probably related to the severity of disease in this patient group in the first week of illness [18] due to a longer period of multiple organ failure [19]. The survival of a critically ill patient is affected by the amount of energy and protein he receives with food [20]. Therefore, it is very important to know whether a particular route of nutrient delivery will be more beneficial in a specific type of disease. In the group with SAP, the balance of absorbed nutrition with its postpyloric delivery was significantly

(*P*=0.001) three times greater than with nasogastric route. The results we obtained are consistent with the ones of earlier study proving that the more severe the condition, the more preferable is postpyloric route of feeding compared to nasogastric, due to the greater amount of digested nutrients [21]. In patients with MSAP, the balance of digested nutrition over four days did not differ significantly (*P*=0.107) between NJ (2.6±0.5 L/day) and NG (2.1±0.9 L/day) routes.

Conclusion

Enteral feeding in patients with severe acute pancreatitis should preferably be initiated via nasojejunal tube due to better absorption of nutrients compared to the nasogastric route. In moderately severe acute pancreatitis starting with the gastric route of feeding is appropriate; however, if intolerant, the nutrient delivery should be switched to the nasojejunal route.

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The Effects of Different Pressure Pneumoperitoneum on the Pulmonary Mechanics and Surgical Satisfaction in the Laparoscopic Cholecystectomy

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Влияние пневмоперитонеума под различным давлением на показатели легочной механики и удовлетворенность хирурга при лапароскопической холецистэктомии

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Summary

Objectives. Inspiratory, hemodynamic and metabolic changes occur in laparoscopic surgery depending on pneumoperitoneum and patient position. This study aims to evaluate the effects of intra-abdominal pressure increase based on CO_2 pneumoperitoneum in laparoscopic operations on hemodynamic parameters and respiratory dynamics and satisfaction of surgeon and operative view.

Materials and Methods. A total of 116 consecutive, prospective, ASA class I–III cases aged 18–70 years undergoing laparoscopic cholecystectomy were enrolled in this study. Data of 104 patients were analysed. Patients were divided into two groups as the group Low Pressure (<12 mmHg) (Group LP) (*n*=53) and the group Standard Pressure (>13 mmHg) (Group SP) (*n*=51). In this study administration of general anesthesia used total intravenous anaesthesia in both groups. All groups had standard and TOF monitorization applied. The anaesthesia methods used in both groups were recorded. Before, during and after peritoneal insufflation, the peroperative ventilation parameters and hemodynamic parameters were recorded. The adequacy of pneumoperitoneum, gastric and the operative view were evaluated by the operating surgeon and recorded.

Results. The peripheral oxygen saturation showed no significant difference between the low and standard pressure pneumoperitoneum in view of tidal volume, respiratory rate, end tidal CO_2, mean and peak inspiratory pressure, and minute ventilation values. In terms of hemodynamics, when values just after intubation and before extubation were compared, it was observed that in the LP group systolic, diastolic and mean blood pressure values were higher. In terms of heart rate, no significant difference was observed in determined periods between groups. There was no significant difference between the groups in terms of surgical satisfaction and vision.

Conclusion. Low pressure pneumoperitoneum provides effective respiratory mechanics and stable hemodynamics for laparoscopic cholecystectomy. It also provides the surgeon with sufficient space for hand manipulations. Anaesthetic method, TIVA and neuromuscular blockage provided good surgery vision with low pressure pneumoperitoneum.

Keywords: laparoscopic cholecystectomy; pneumoperitoneum; surgical vision; surgery satisfaction; low pressure; deep neuromuscular blockage

Conflict of Interest. The authors declare no conflict of interest. Abstract of this study was presented partly at the Euroanaesthesia Congress 2016, London.

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Introduction

Cholelithiasis is a common disease of the digestive system treated with surgical methods. With the development of laparoscopy, laparoscopic cholecystectomy has become an accepted surgical intervention. Due to many advantages such as less pain in the postoperative period, small incisions, shorter hospital stay and more rapid return to daily life, it is accepted as the gold standard globally. This minimally invasive technique reduces mortality and morbidity and is a very reliable and effective method [1–3].

Of those with gallstones, each year 2–4% become symptomatic with biliary colic, acute cholecystitis, obstructive jaundice and gallstone pancreatitis [4, 5]. Each year in America more than 1.5 millon cholecystectomies are performed [6]. The incidence of gallstones in the adult population in the West is about 10–15% [5–8].

The insufflation pressure for laparoscopic cholecystectomy is generally 12–15 mmHg. In a review of the Cochrane database. Grusamy et al. [7] defined standard pressure as varying between 12 and 16 mmHg, with low pressure as less than 12 mmHg and high pressure more than 17 mmHg. Volume and pressure studies have been performed and it was found that pressures greater than 15 mmHg did not further expand the operation field [8]. Pneumoperitoneum ensures sufficient visualisation of the abdominal cavity and allows manipulation of the laparoscope. There is some evidence that low pressure pneumoperitoneum is associated with decreased pain for laparoscopic cholecystectomy; however, these results are still open to debate as varies of the clinical studies detailing the benefits were found to be at a high risk of bias and inadequate blinding [2].

Randomised clinical studies using low pressure pneumoperitoneum have shown reduced cardiac changes [9], shoulder pain complaints [10], pain severity and analgesic requirements [10, 11]. The important critical point is that low pressure pneumoperitoneum ensures sufficient surgical view and is safe.

In this study, we have compared various factors like respiratory dynamics and hemodynamic parameters in patients undergoing laparoscopic cholecystectomy under standard pressure versus low pressure. In addition we have aimed to research and discuss the effects in terms of surgeon satisfaction and vision quality.

Materials and Methods

This study was performed after receiving permission from «Dokuz Eylül University, Faculty of Medicine, Non-interventional Research Ethics Committee» (date 29.05.2014, Protocol No. 1538-GOA, Decision No. 2014/21-07) and informed patient consent. The study included patients in ASA classification I–III, from 18–70 years, undergoing elective laparoscopic cholecystectomy surgery and was completed as a prospective observational study.

The records of laparoscopic cholecystectomy patients in 3 months examined. According to these records, we found that low pneumoperitoneum pressure was applied to 53 patients and standard pneumoperitoneum pressure was applied to 51 patients. Then, we continued our evaluations under 2 groups. The study was performed on 116 consecutive patients and data from a total of 104 patients were analysed. Patients were divided into two group as low pressure (< 12 mmHg) (LP) (n=53) and standard pressure (> 13 mmHg) (SP) (n=51). Four patients in LP group and 8 patients in SP group underwent open laparotomy and were excluded from the study.

Exclusion Criteria:

1. Acute cholecystitis
2. Cases with low pulmonary compliance or high airway resistance (chronic pulmonary diseases)
3. Morbidly obese patients (BMI > 35)
4. Malignancy or chronic inflammatory disease
5. Renal or liver disorders
6. Endocrine or immune system disorders
7. Patients receiving immunosuppressive treatment
8. Cases with open laparotomy
9. Any surgical intervention in addition to cholecystectomy
10. Previous abdominal surgery

The demographic characteristics of the patients are shown in Table 1.

Patients in LP and SP groups had standard monitoring (non-invasive blood pressure, electrocardiogram, peripheral oxygen saturation measurements) and neuromuscular junction monitoring with TOF Guard (TOF Guard (TOF-GUARD, Biometer International A.S. DENMARK) applied before anaesthesia induction.

In both groups, for anaesthesia induction 0.2–0.5 mcg/kg/min remifentanil infusion was administered over two minutes followed by intravenous (IV) 1–2 mg/kg propofol and IV 0.5 mg/kg rocuronium. After induction patients had 6 L/min 100% oxygen administered with a face mask for ventilation.

For the anaesthesia maintenance 50% O_2/air mixture and 0.1–0.4 mcg/kg/min remifentanil and 50–150 mcg/ kg/min (3–9 mg/kg/hr) propofol IV infusion was administered. During the surgical procedure when TOF>1 twitch response occurred 0.1–0.15 mg/kg dose of the neuromuscular blocker agent rocuronium was administered. To reverse neuromuscular block, when post-tetanic count (PTC) reached 1–2, 4.0 mg/kg sugammadex IV was administered.

Table 1. Demographic data of patients.

Parameters	Values in groups		*P*-value
	LP, *n*=53	SP, *n*=51	
*Age, year	53.00 (38.50–61.00)	50.00 (37.00–62.00)	0.543
Gender Female/Male, *n*	40/13	32/19	0.160
*Body mass index, kg/m^2	27.80 (25.50–30.55)	26.90 (23.40–31.20)	0.390
ASA 1/2/3, *n*	14/29/10	19/28/4	0.191
*Anaesthesia time, min	95.00 (80.00–117.50)	100.00 (90.00–120.00)	0.351
*Insufflation time, min	60.00 (45.00–70.00)	60.00 (45.00–80.00)	0.181

Note. For Tables 1, 2: * — values are median (25–75 percentiles), mean (range) or number (proportion).

Table 2. Surgical and insufflation data.

Parameters	Values in groups		*P*-value
	LP, *n*=53	SP, *n*=51	
Attempts to insert Veress needle (1/2/3), *n*	52/0/3	50/1/0	1.00
*Initial intra-abdominal pressure, mmHg	12.0 (11.0–12.0)	14.0 (13.0–15.0)	0.297
*Volume of insufflation CO_2, L	3.2 (2.5–5.1)	3.6 (2.5–5.8)	0.388
Grade of quality of view			
1	1	0	0.781
2	8	8	
3	23	24	
4	21	19	

Positive pressure respiration was begun with 2–4 L/min fresh gas flow and FiO_2 0.5 volume control for 6–8 ml/kg tidal volume and 10–12 respirations/min frequency. PEEP was not used and inspiration:expiration (I:E) ratio was set at 1:2. Mechanical ventilation was performed with the anaesthesia machine (Dräger, Zeus Infinity Empowered; Dräger Medical AG&Co. KG, Germany).

In the peroperative period the ventilation parameters (airway peak pressure, mean airway pressure, tidal end carbon dioxide, tidal volume, minute ventilation volume) and hemodynamic parameters (systolic, diastolic and mean arterial pressure, heart rate) were measured at 4 different times; 2 minutes after intubation (T1), 10 min after peritoneal insufflation (T2), before desufflation (T3) and before extubation (T4).

Pneumoperitoneum pressure values were determined by the surgical team with values of 12 mmHg and below in the low pressure group and 13 mmHg and above included in the standard pressure group [7]. Immediately after intra-abdominal laparoscopic intervention and immediately before the end of peritoneal insufflation, gastric distension was evaluated on a scale of 0–10 (0=empty stomach, 10=distension obstructing the surgical field) by a surgeon blind to the airway device [12].

For surgical satisfaction, surgical view quality was evaluated. To evaluate surgical view quality, the surgeon provided a point value from 1 to 4 (1: bad, 2: acceptable, 3: good, 4: perfect) [13]. All surgical procedures were performed by the same surgical team and view quality was evaluated with points by the same team.

The anaesthesia duration, operation duration and hospital stay of the patients were recorded. In the postoperative period the time when patients returned to physical activities or to work was learned by telephone and recorded.

Statistical Analysis. The data obtained in the research was entered into a database in the SPSS (Statistical Package For Social Sciences) 15.0 program and statistical analyses were performed with this program. Continuous variables and sub groups are presented as mean, standard deviation, median, values, while categorical variables are presented as frequency and percentage. Calculation of sample size has performed by «OpenEpi» program. Margin of error was 5%, safety margin was 95% and frequency was accepted as 50% what unknown frequency of situation. Minimum 73 cases would have included to study: but we have included 104 patients.

The variables specified by the measurement was analyzed after the analysis of conformity to normal distribution for comparison. For comparison of independent groups the «Mann–Whitney *U*» test was used. Paired multiple groups were analysed with the «Friedman Test» method. Categorical variables are presented in diagonal tables as frequency and percentage, and distribution was compared with the chi-square method. Significance value was at $P<0.05$.

Results

There was no significant difference between the groups in terms of surgical satisfaction and vision (Table 2). Results of surgical and insufflation data are showed in Table 2. Stomach distension val-

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ues medians (25–75 percentiles) are 3.00 (2.00–5.00) in LP Group and 3.00 (2.00–4.00) in SP Group for 10 minutes after insufflation (T2). Stomach distension values medians (25–75 percentiles) are 3.00 (2.00–4.00) in Group LP and 3.00 (2.00–4.00) in Group SP for before desufflation (T3). In both group, 10 minutes after insufflation (T2) (P=0.546) and before desufflation (T3) (P=0.855) there were no statistically significant difference in stomach distension identified.

This study did not observe any significant differences between patients undergoing laparoscopic cholecystectomy with low and standard pressure pneumoperitoneum in terms of peripheral oxygen saturation , tidal volume, respiratory count, end tidal carbon dioxide, mean and peak airway pressure and minute ventilation values. Comparison of ventilation parameters between groups are showed in Table 3.

When hemodynamics are evaluated, when values immediately after intubation (T1) and before extubation (T4) are compared, the systolic, diastolic and mean blood pressure values in the low pressure group were observed to be higher. When these values are examined after insufflation and before desufflation, there was no significant difference between the two groups. There was no significant difference observed in terms of heart rate in the stated periods. Comparison of hemodynamics parameters between groups are presented in figure.

Hospital stay time are 1.51±0.80 days in Group LP and 1.47±1.00 days in Group SP. Beginning daily activities for patients are 3.13±1.09 days in Group LP and 3.25±1.07 in Group SP. Beginning work in the postoperative period for patients are 7.06±4.17 days in Group LP and 6.19±1.67 days in Group SP. When patients are investigated in terms of hospital stay, beginning daily activities and beginning work in the postoperative period, there was no statistically significant difference identified between the low pressure and standard pressure groups (P=0.389, P=0.518, P=0.847, respectively).

This study found no significant difference in respiratory dynamics between patients undergoing laparoscopic cholecystectomy with low and standard pressure pneumoperitoneum. However, in terms of hemodynamic parameters, in the low pressure group immediately after intubation and before extubation the SBP, DBP and MAP values were found to be higher. There was no significant difference between the groups in terms of surgeon satisfaction and vision quality.

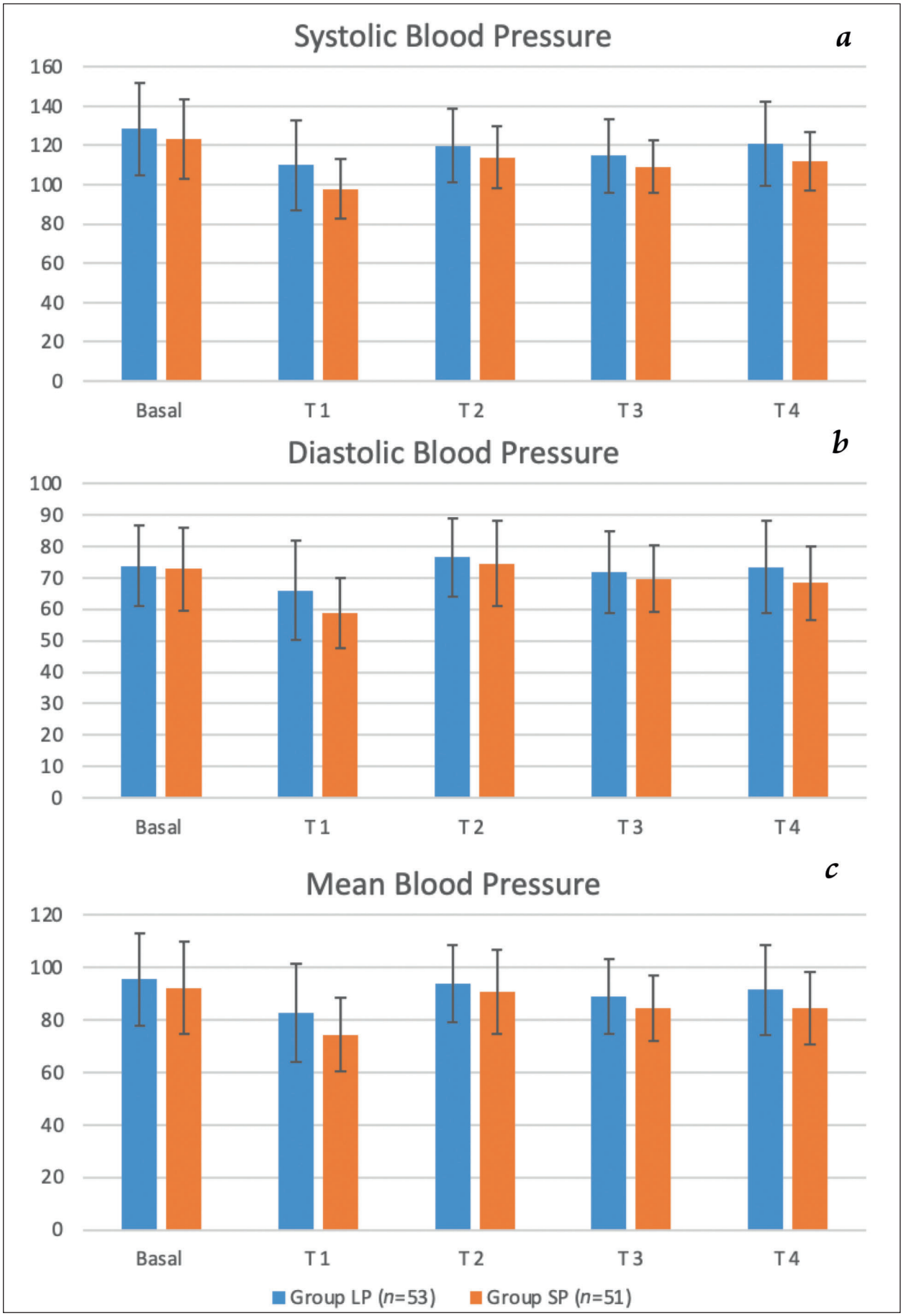
Table 3. Comparison of ventilation parameters between groups at the study stages, median (25–75 persentiles).

Parameters	Values in groups							
	2 minutes after airway device insertion T1		10 minutes after insufflation T2		Before desufflation T3		Before removal airway device T4	
	LP	SP	LP	SP	LP	SP	LP	SP
Tidal volume, ml	465.0 (422.5–500.0)	460.0 (425.0–550.0)	480.0 (415.0–540.0)	480.0 (430.0–550.0)	480.0 (402.0–540.0)	490.0 (430.0–580.0)	480.0 (415.0–535.0)	490.0 (430.0–560.0)
Expiratory volume, L.min^{-1}	5.76 (4.82–6.42)	5.72 (5.04–6.72)	6.00 (5.05–6.84)	5.94 (5.20–6.72)	6.00 (5.22–7.00)	6.30 (5.40.7.50)	6.00 (5.18–6.88)	6.00 (5.04–7.20)
Respiratory rate/min	12.0 (12.0–12.0)	12.0 (12.0–13.0)	12.0 (12.0–13.5)	12.0 (12.0–13.0)	13.0 (12.0–14.0)	13.0 (12.0–14.0)	12.0 (12.0–14.0)	12.0 (12.0–14.0)
$ETCO_2$, mmHg	31.0 (28.00–33.00)	31.0 (29.0–34.0)	32.0 (28.5–34.5)	32.0 (30.0–34.0)	33.0 (31.0–36.0)	34.0 (32.0–36.0)	31.00 (30.00–32.50)	32.0 (31.0–34.0)
Peak airway pressure, cmH_2O	20.0 (16.0–22.0)	18.0 (15.0–22.0)	23.0 (19.0–25.0)	21.0 (19.0–24.0)	22.0 (19.0–25.0)	21.0 (18.0–24.0)	20.00 (17.00–22.50)	18.0 (16.0–22.0)
Mean airway pressure, cmH_2O	8.0 (7.0–9.0)	8.0 (7.0–9.0)	9.0 (8.0–10.0)	9.0 (8.0–10.0)	9.0 (8.0–10.0)	9.0 (8.0–10.0)	8.00 (7.00–9.00)	8.0 (7.0–9.0)
SpO_2	100.0 (99.0–100.0)	100.0 (100.0–100.0)	100.0 (100.0–100.0)	100.0 (100.0–100.0)	100.0 (100.0–100.0)	100.0 (100.0–100.0)	100.0 (100.0–100.0)	100.0 (100.0–100.0)

Note. P>0,05; SpO_2 — peripheral oxygen saturation; $ETCO_2$ — end tidal carbon dioxide.

Discussion

Grusamy et al. [7] in a review of the Cochrane database found a total of 15 clinical studies and presented the effects of low and standard pressure



Systolic blood pressure (*a*), diastolic blood pressure (*b*) and mean blood pressure (*c*) in groups.

pneumoperitoneum. This study defined standard pressure as between 12 and 16 mmHg, with low pressure below 12 mmHg and high pressure 17 mmHg. There was no difference between the two groups in terms of postoperative complications, mortality, morbidity and changing to open cholecystectomy [7].

In situations where significant anatomic structures cannot be defined, if the intervention does not advance within a certain time, if there is uncontrolled hemorrhage and bile duct problems that cannot be resolved laparoscopically, the operation should be changed to open surgery. The rate of change from laparoscopic cholecystectomy to open operations is 5% [13–15]. In our study the rate of change to open operations was found to be 10.34%.

In the review by Grusamy et al. [7] the operation duration was found to be mean 2 minutes longer in the low pressure group. Different to this result, the study by Sarli et al. [10] found that low pressure pneumoperitoneum did not increase the operation duration and did not cause peroperative and postoperative complications. They determined that low pressure pneumoperitoneum technique was sufficient. However, these results may vary linked to surgeon experience. At the same time, they may be linked to patient factors like obesity and previous surgery. In a study researching the effects of low (7–8 mmHg) and standard (12–14 mmHg) pressure pneumoperitoneum by Singla et al. [16] they found the surgical durations were similar in both groups. They showed that this result indicated low pressure pneumoperitoneum did not negatively affect surgical success, and that laparoscopic cholecystectomy can be completed in the same duration. In our study, we excluded patient linked factors like obesity and previous surgery and did not observe a significant difference statistically between anaesthesia duration and insufflation duration; similar to the results of the previous study. In our study there was no statistically significant difference in terms of anaesthesia and insufflation durations between the low pressure and standard pressure groups.

Grusamy et al. [7] reported no significant difference between the mean hospital stay and patient satisfaction between the low and standard pressure groups. In our study there was no significant difference observed between the groups in terms of hospital stay. There is no clinical study reporting the duration to return to normal activity or work and surgeon satisfaction. In our study, the return to normal activity and work was investigated and there was no significant difference found between the two groups.

When the literature is examined in terms of additional port requirements, it was reported that there was no requirement for an additional port during surgery in both groups, and that in the low pressure group the requirements for intra abdominal pressure increase was higher to ensure sufficient surgical view [17–19]. In our study in both groups there was no need for additional port in either group. However, in the LP group there was a need for intra abdominal pressure increase. This situation is similar to previous studies [17–19]. In our study initially due to insufficient surgical view in those included in the LP group, a total of 7 patients required increased intra abdominal pressure.

During pneumoperitoneum, reaching high intra abdominal pressures may negatively affect respiratory parameters [20–22]. Makinen et al. [23] stated that 12 mmHg CO_2 pneumoperitoneum reduced respiratory compliance by 30%, while Luis et al. [24] reported a reduction of 40%. Kendal et al. [25] showed that 15 mmHg pneumoperitoneum reduced respiratory compliance by 49%. Another study by Makinen et al. [26] reported a reduction in pulmonary dynamic compliance of 50% with increases in Ppeak and Pplateau. After pneumoperitoneum desufflation they identified a fall in basal values of pulmonary compliance and airway pressures. In our study, in both the low pressure and standard pressure groups, there was an increase observed in Ppeak and Pmean values in the insufflation period and after desufflation there was no significant difference between the basal values of both identified. When low pressure and standard pressue groups are compared, there was no statistically significant difference observed between the groups in terms of Ppeak and Pmean.

The potential benefit of low pressure pneumoperitoneum is a reduction in cardiopulmonary complications. When the literature is examined, many studies assessing the effects of different pressure pneumoperitoneum have reported no cardiopulmonary morbidity. It was observed that the patient population included in these studies were classified as ASA I and II [7, 17, 19]. In a case series comprising 400 patients, the cardiopulmonary complication rate was found to be 0.5% and they reported that 70% of patients were in the low risk group for anaesthesia [9]. The difference in our study is that we included patients in ASA III class. In our study when the groups are compared after intubation and before extubation, the SBP, DBP and MAP values were higher in the low pressure group. These results may be linked to our inclusion of ASA III patients.

Rishimani et al. [27] in a study of laparoscopic cholecystectomy including 30 patients with low (6 mmHg) and high (14 mmHg) intra abdominal pressure values found that in the high pressure group 10 patients had 8–20/min increase in heart rate, 7

patients had 6–12/min decrease and 13 patients had no change. They identified a 15–30% fall in cardiac index. Mean arterial pressure increased by mean 41.15% after insufflation compared to before insufflation. After desufflation there was a 24.94% increase compared to before insufflation. There was no change in heart rate. In our study for hemodynamic data only blood pressure and heart rate were recorded, cardiac index measurements were not performed. Joris et al. [28] reported a reduction in cardiac index of 20% corresponding to an increase of 35% in MAP. The same study found that SCR increased by 65% and pulmonary vascular resistance (PVR) increased by 90%, with no change in HR observed. Marshall et al. [29] reported that hemodynamics varied linked to intra abdominal pressure increase, with CO_2 insufflation causing an increase in HR, MAP and total peripheral resistance, a reduction in beat volume and sympathetic stimulation.

Pneumoperitoneum may cause a variety of arrhythmia like A–V dissociation, nodal rhythm, sinus bradycardia and asystole. This response is a vagal cardiovascular reflex linked to peritonal strain. Hypercarbia may increase these types of effects. In our study when heart rates are compared, there was no difference between the groups. This result may be linked to CO_2 insufflation rate being held constant for all patients.

In our study there was no difference when the groups were compared in terms of surgeon satisfaction. This result may be related to the lack of difference between the groups when stomach distension is assessed. Distended stomach negatively affects the surgical field of view and manipulation of the trochars. Stomach distension was assessed on a scale of 1–10 10 minutes after insufflation and before desufflation by a surgeon blind to the groups. There was no statistical difference between the groups.

A study by Dubois et al. [30] researched the effects of deep neuromuscular blockage on surgical conditions for patients undergoing laparoscopic hysterectomy. With fixed pneumoperitoneum pressure (13 mmHg), surgical view quality was assessed by the surgeon and it was concluded that patients with deep neuromuscular block had better surgical view scores [31, 32]. Staehr-Rye et al. [33] in a study of laparoscopic cholecystectomy with low pressure pneumoperitoneum (8 mmHg) compared the effects of deep neuromuscular block and moderate neuromuscular block on surgical view quality and concluded that deep neuromuscular block provided better surgical view conditions. Martini et al. [31] in a study evaluating the effects of deep neuromuscular blockage on surgical conditions for laparoscopic surgeries found that the significance of the deep neuromuscular blockage effect was large and that it provided sufficient working area in the surgical field and increased view quality.

In our study in spite of low insufflation pressure, the surgical duration, surgical field conditions and complication risks were not greater and this may be linked to standardisation of neuromuscular blockage with TOF monitoring during induction and maintenance.

The study has some limitations; our defined low pressure value of 12 mmHg is higher than in previous studies [10, 16, 34, 35]. This value (12 mmHg) was determined linked to the experience of the clinical surgery team at our hospital. Additionally invasive cardiac monitoring with cardiac index, continuous arterial pressure monitoring and blood gas monitoring were not performed. There was no comorbidities analysis for these patients.

Conclusion

In conclusion, during laparoscopic cholecystectomy surgery, low pressure pneumoperitoneum ensures effective respiratory mechanics and stable hemodynamics. Additionally it provides sufficient surgical area for hand manipulations by the surgeon.

When these results are considered, with TIVA anaesthesia method and deep neuromuscular blockage administration, we believe low pressure pneumperitoneum ensures better surgical view quality and surgeon satisfaction.

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Delirium in Acute Poisoning with 1,4-Butandiol and Its Correction

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Делирий при острых отравлениях 1,4-бутандиолом и его коррекция

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Summary

Delirium complicating regular use of psychoactive substances remains one of the major issues of critical care, toxicology, and psychiatry. However, the pathogenetic mechanisms of delirium development in patients with 1,4-butanediol poisoning have been poorly studied until now.

The aim of the study was to reveal specific patterns of delirium in patients with 1,4-butanediol poisoning as well as to study the changes in systemic hemodynamic parameters, respiratory function, and body fluid compartments during the treatment.

Material and methods. The study was prospective and treatment-randomized. Forty-eight male patients aged 20 to 45 years with delirium and acute 1,4-butanediol poisoning were enrolled. Of them, 24 patients were administered with succinate-containing drug 40 ml daily, 24 patients received standard treatment without antihypoxic agents. We studied the evolution of delirium, changes in anaerobic metabolism parameters, systemic hemodynamics, respiratory function, and the volume of fluid compartments. Impedance measurement method adjusted for interference was used in the study.

Results. At the «peak» of delirium (days 1–3), the hyperdynamic circulation, increased systemic arterial tone, stroke output, respiratory function parameters, and metabolic lactate acidosis were recorded. A decrease in total fluid volume and extracellular fluid volume was clearly observed during day 1 of intoxication delirium along with increased permeability of cell membranes. On day 3 of delirium, a decrease in intracellular fluid volume and increase in extracellular fluid volume were noted. After the cytoflavin administration, shorter delirium duration (7.5 [6; 8] days), more rapid correction of lactate acidosis, stabilization of respiratory parameters and stabilization of cell membrane permeability by day 5 were found. In the control group, delirium persisted for up to 14 [11; 15] days (z=-5.9; P=0.00011) with more frequent development of complications such as nosocomial pneumonia (χ^2=8.4, P<0.001).

Conclusion. The severity of delirium in acute poisoning with 1,4-butanediol was associated with metabolic lactate acidosis, changes in systemic hemodynamics and pulmonary function. A positive effect of adjunctive antihypoxic therapy with succinate-containing agent on cardio-respiratory parameters, cell membrane permeability, water balance due to elimination of tissue hypoxia and prompt switching to tissue aerobic metabolism has been found.

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Introduction

Intoxication delirium is a severe complication of regular use of psychoactive substances and one of the main factors of mortality, which makes our research especially relevant [1–6].

The studies have shown that intoxication delirium is primarily caused by neurotransmitter dysfunction, as indicated by the correlation between high blood dopamine levels and delirium severity [7–9]. In turn, researchers associate an excessive neurotransmitter release with tissue hypoxia, which determines the severity of the medical condition [10, 11]. Despite the popularity of the neurotransmitter theory among most authors, there is no complete understanding of the mechanisms of delirium development [12].

Currently, special emphasis in the study of intoxication delirium is placed on patients with chronic alcoholism, as evidenced by the literature data [13–16].

The current reality, witnessing the appearance of new substances with narcotic effects and their precursors on the «illegal market», naturally indicates an increase in acute poisonings with these substances [17–19]. At present, poisonings with precursors of gamma-hydroxybutyric acid (GHBA) (1,4-butanediol (1,4-BD), gamma-butyrolactone), available for purchase via Internet, prevail in metropolitan areas [20, 21].

1,4-BD is an industrial alcohol [22]. Systematic use of 1,4-BD leads to a wide range of psychiatric and medical disorders resistant to standard therapy and psychotropic drugs [23–25].

In our opinion, to develop the effective treatment methods for patients with 1,4-BD poisoning complicated by delirium, changes in systemic hemodynamics, respiratory function, and fluid compartments should be considered. Bioimpedance measurement test based on the assessment of electrical conductivity of various body tissues and blood flow impedance remains the most accessible and proven method of their diagnosis [26, 27]. However, there are no data on the use of this diagnostic method in patients with 1,4-BD poisoning complicated by delirium receiving standard therapy, which highlights the novelty of our study.

The aim of the study was to reveal the specific clinical patterns of delirium in patients with 1,4-butanediol poisoning as well as to assess the changes in systemic hemodynamic parameters, respiratory function, body fluid compartments during the therapy.

Material and Methods

A prospective (treatment-randomized) study was performed. The study included male intensive care unit (ICU) patients aged 20 to 45 years (main group) (n=48) with acute 1,4-BD poisoning complicated by delirium.

Patients of the main group were further divided into two groups based on a treatment strategy. Group 1 (n=24) included patients whose intensive therapy included cytoflavin (OOO NTFF POLYSAN, St. Petersburg) 20 ml twice a day in 10% glucose solution, intravenously administered with 10-hours interval between injections. Group 2 (n=24) included patients whose standard treatment regimen did not contain cytoflavin or other antihypoxic agents. The median ages of the group 1 and group 2 patients were similar (29.5 [26; 35] years and 31.5 [26; 37] years, respectively).

The patients were studied days 1, 3, 5, and 7 after delirium diagnosis, all investigations were made in the morning time. The instrumental methods included GHBA measurement in biological fluids using gas chromatography on GCMS-QP2010 SE mass spectrometric detector (Shimadzu, Japan); systemic hemodynamic parameters assessment using stroke and cardiac indices (SI and CI), reserve ratio (RR) based on stroke volume of blood, systemic arterial tone (SAT) index, respiratory effort index (REI), severity index based on cell membrane permeability (SICMP) measured by integral thoracic rheography method by Tishchenko (1973) and Sramek (1994); electrical equivalents of the total (TFV), extracellular (EFV) and intracellular (IFV) fluid volumes by integral dual frequency impedance measurement method using the computerized hardware and software complex «Diamant-v.11.06.2018» (Diamant CJSC, St. Petersburg, Russia). The severity index was calculated based on reference impedance values at the applied frequencies as a percentage ratio of impedance at 28 KHz/115 KHz (with its values of 83.3% and less considered as high, and that of 88.3% and higher taken as low). The following types of circulation were identified based on RR: normodynamic (90 to 110%), hyperdynamic (>110%) and hypodynamic (<90%).

Laboratory tests included arterial blood gas and acid-base evaluation using COBAS B221 analyzer (Roche, Germany), lactate concentration in

capillary blood using Accutrend Plus portable biochemical analyzer (Roche Diagnostics, Germany).

The level of consciousness was assessed by the Glasgow Coma Scale (Teasdale G. M., Jennett B. J., 1974), the severity of delirium using the DRS-R-98 psychometric scale (Trzepacz et al., 1988). The diagnosis of delirium was made in accordance with the ICD-10 (WHO, 1992).

The study was approved by the local Ethical Committee of the institute (protocol No.1 from 07.02.2020).

Statistical analysis. Statistical analysis of the data was performed using Statistica for Windows (version 10) software. The data were presented as medians (*Me*) and 25–75 percentiles [Q25; Q75]. To study the parameter changes within groups we used the nonparametric Wilcoxon criterion, to make intergroup comparisons we used nonparametric Mann–Whitney *U*-criterion. Differences between the studied parameters were considered significant at $P<0.05$. Nonparametric correlation analysis (ρ-Spearman) was used to compare quantitative parameters. Qualitative variables were compared using Pearson Chi-square test (χ^2) with adjustment for continuity. Odds ratio (OR) with upper and lower 95% confidence intervals (95%CI) were calculated to assess the association between specific outcomes and risk factors.

Results and Discussion

The severity of patients with acute 1,4-BD poisoning on admission was caused by toxic encephalopathy with depressed consciousness down to coma I level (7.7±0.48 points on Glasgow scale).

Delirium was diagnosed 8 [6,3; 9,8] hours after admission.

Tables 1, 2, and 3 show intra- and intergroup comparisons of the main studied laboratory and instrumental parameters.

On day 1, the severity of patients was due to metabolic lactate acidosis, hyperdynamic circulation, increase in CI up to 4.5 in group 1 and to 4.3 l/min×m² in group 2, SI up to 50.6 in group 1 and to 49.8 ml/m² in group 2, SAT up to 82.9 and 82.6 units in groups 1 and 2, respectively, and REI up to 44.2 and 43.5 units in groups 1 and 2, respectively (Table 1). Clinical manifestations of acute delirium included allopsychic disorientation, confusion, restlessness, and intense anxiety with «horror» expression on the face. Hallucinations during the advanced psychotic period were characterized by «frightening images» of a «scene-like, violent nature». Anthropomorphic «teasing» visual true hallucinations predominated, «beckoning» or «closely approaching» the patient. The patients made repeated attempts to «shout out» the imaginary «interlocutors», made defensive actions, trying to shield themselves with their arms, or «to drive them away».

On days 1–3 changes in the fluid compartments were recorded. Extracellular dehydration dominated in both groups on day 1 (decrease of EFV by 3.8 and by 3.7% in groups 1 and 2, respectively), along with the loss of TFV up to 4.9 and 4.6% (Table 2), respectively, plasma low osmolarity, low blood electrolyte level, and relative intracellular hyperhydration. However, clinically, dry skin, especially in axillary and inguinal areas, dry tongue, tachycardia up to 115.6 [105.3; 119.9] per minute,

Table 1. Effect of treatment on systemic hemodynamics and respiratory function in patients with acute 1,4-BD poisoning complicated by delirium, *Me* [Q25; Q75].

Parameter	Group	Value in groups on various days			
		1	3	5	7
SI, ml/m²	I	50.6 [43.1; 51.6]	53.7 [45.5; 57.5] P=0.02*	44.8 [33.7; 47.1] P=0.001*; P=0.02#	40.7 [38.1; 49.2] P=0.001*; P=0.03#
	II	49.8 [43.3; 54.1]	56.9 [46.2; 51.3] P=0.001*	50.3 [42.6; 51.1] p=0.03*	44.4 [40.8; 50.1] P=0.001*
CI, l/min×m²	I	4.5 [2.9; 6.1]	4.8 [2.5; 6.5]	3.9 [2.4; 4.3] P=0.02*; P=0.03#	3.4 [3.2; 3.9] P=0.02*
	II	4.3 [3.2; 5.6]	4.5 [3.2; 5.4]	4.2 [2.3; 5.1]	3.6 [3.7; 4.1] P=0.03*
RR, %	I	119.1 [101.1; 123.1]	124.1 [117.5; 134.1] P=0.04*	105.6 [97.9; 106.3] P=0.03*; P=0.001#	109.2 [98.2; 104.4] P=0.03*
	II	116.7 [111.1; 121.1]	129.4 [108.1; 136.7] P=0.04*	112.3 [95.4; 116.6]	110.7 [104.5; 117.7] P=0.04*
SAT, units	I	82.9 [76.2; 83.3]	80.7 [80.2; 80.8] P=0.04*; P=0.03#	75.6 [74.1; 78.4] P=0.01*; P=0.001#	77.7 [76.1; 75.3] P=0.02*; P=0.04#
	II	82.6 [74.2; 83.2]	83.4 [82.1.4; 84.6] P=0.04*	81.8 [76.1; 82.7]	79.5 [76.6; 80.4] P=0.02*
REI, units	I	44.2 [27.5; 54.8]	54.5 [29.7; 51.1] P=0.001*; P=0.04#	28.8 [21.4; 29.6] P=1.4×10⁻⁴*; P=0.04#	24.3* [24.1; 25.9] P=1.2×10⁻⁴*; P=0.03#
	II	43.5 [24.6; 53.9]	56.7 [34.6; 64.6] P=0.002*	30.8 [24.6; 31.9] P=1.4×10⁻⁴*	30.6 [24.1; 31.5] P=1.4×10⁻⁴*

Note. SI — stroke index; CI — cardiac index; RR — reserve ratio; SAT — systemic arterial tone; REI — respiratory effort index; P* — significant intragroup differences; P# — significant differences between groups 1 and 2.

Table 2. Effect of treatment on water and electrolyte balance in patients with acute 1,4-BD poisoning complicated by delirium, *Me* [Q25; Q75].

Parameter	Group	Value in groups on various days			
		1	3	5	7
IFV, %	I	+2.1 [+1.1; +2.7]	–3.3 [–2.3; –3.9]	+1.1 [–0.7; +1.9]	+0.8 [+0.1; +2.2]
	II	+2.7 [+1.7; +2.9]	–3.5 [–2.2; –4.1]	–3.9 [–2.3; –4.5]	+ 0.2 [–0.8; +2.6]
EFV, %	I	–3.8 [–0.8; –4.9]	+3.9 [+4.8; +3.2]	+1.5 [+1.5; +1.8]	+1.3 [+0.8; +1.7]
	II	–3.7 [–1.1; –4.5]	+4.1 [+4.5; +3.8]	+0.2 [–5.1; +3.4]	+1.1 [+1.3; +1.7]
TFV, %	I	– 4.9 [–2.2; –5.1]	–2.7 [–2.1; –3.9]	+1.2 [+1.1; +2.1]	+2.6 [+1.3; +3.1]
	II	–4.6 [–1.5; –4.8]	–3.1 [–2.7; –4.4]	–0.7 [–4.3; +1.1]	+0.5 [+0.3; +3.1]
Blood osmolarity, mOsm/l	I	278.5 [272.5; 281.2]	279.5 [273.5; 284.7]	279.4 [272.5; 282.3]	286.7 [279.5; 289.2] *P*=0.02*
	II	275.5 [272.5; 281.2]	276.3 [269.1; 283.2]	275.2 [274.5; 284.5]	281.2* [270.1; 281.3] *P*=0.002*
Cl, mmol/l	I	98.1 [95.1; 100.5]	94.3 [94.7; 97.7] *P*=0.04*	98.9 [95.1; 99.1]	98.4 [95.7; 99.1]
	II	96.6 [94.1; 99.4]	95.3 [94.9; 96.6] P=0.04*	97.2 [95.6; 97.4] *P*=0.03*	98.1 [96.4; 99.7] *P*=0.03*
K, mmol/l	I	3.5 [3.2; 3.9]	3.5 [3.1; 4.0]	4.7 [3.6; 4.9] *P*=0.001*	4.6 [4.2; 4.7] *P*=0.001*
	II	3.7 [3.1; 3.5]	3.9 [3.5; 4.4] *P*=0.04*	4.3 [3.9; 4.4] *P*=0.03*	4.4* [3.5; 4.5] *P*=0.02*
Na, mmol/l	I	139.2 [137.1; 141.6]	139.2 [139.1; 142.3]	138.1 [136.1; 140.2]	140.4* [136.8; 142.1] *P*=0.03*
	II	138.4 [135.9; 140.2]	136.8 [134.4; 141.5]	135.8 [135.2; 137.8]	141.2* [130.1; 143.9] *P*=0.03*

Note. For tables 1–3: Group 1 — studied group administered with cytoflavin; Group 2 — patients not on cytoflavin; IFV — electrical equivalent of intracellular fluid volume (% of reference); EFV — electrical equivalent of extracellular fluid volume (% of reference); TFV — electrical equivalent of total fluid volume (% of reference); Cl — chloride; K — potassium; Na — sodium; * — *P* = significant intragroup differences.

Table 3. Effect of treatment on laboratory parameters, delirium severity and cellular membrane permeability in patients with acute 1,4-BD poisoning complicated by delirium, *Me* [Q25; Q75].

Parameter	Group	Value in groups on various days			
		1	3	5	7
Lactate, mmol/l	I	3.9 [3.4; 4.1]	2.8 [3.4; 3.9] *P*=0.04*; *P*=0.002#	2.1 [1.9; 2.3] *P*=0.001*; *P*=1.1×10^{-4}#	0.74 [1.1; 0.9] *P*=1.3*×10^{-4}*; *P*=1.1×10^{-4}#
	II	3.8 [3.1; 4.2]	4.3 [3.7; 4.9] *P*=0.02*	4.23[7; 4.6] *P*=0.02*	2.7 [1.8; 2.9] *P*=0.001*
pH, units	I	7.27 [7.2; 7.3]	7.37 [7.2; 7.4] *P*=0.04*	7.41 [7.3; 7.4] *P*=0.03*	7.41 [7.4; 7.4] *P*=0.03*
	II	7.29 [7.2; 7.3]	7.29 [7.2; 7.3] *P*=0.02#	7.37 [7.2; 7.4] *P*=0.001*	7.4 [7.3; 7.4] *P*=0.001*
DRS-R-98, points	I	22.5 [22.1; 24.1]	23.3 [22.1–24.2] *P*=0.04*; *P*=0.02#	17.3 [14.1–19.4] *P*=0.001*; *P*=0.01#	12.1 [10.5–13.3] *P*=1.1×10^{-4}*; *P*=0.001#
	II	23.7 [18.6–23.9]	24.9 [19.1–24.1] *P*=0.04*	20.1 [19.1–21.1] *P*=0.02*	18.8 [16.4–19.7] *P*=0.001*
Severity index, %	I	81.7 [79.8; 82.5]	82.3 [78.1; 82.6]	88.9 [86.3; 89.9] *P*=0.001*	89.6 [86.8; 89.6] *P*=0.001*
	II	81.4 [78.9; 82.6]	79.8 [77.7; 80.1] *P*=0.001*; *P*=0.04#	82.2 [81.7; 83.9] *P*=0.001#	87.7 [86.9; 91.3] *P*=0.001*; *P*=0.04#

Note. DRS-R-98 — delirium severity score; * — *P* significant intragroup differences; # — *P* significant intergroup differences.

tachypnoea 23 [21; 24] breaths per minute, depressed peristalsis were noted. Intestinal paresis and, consequently, delayed passage of intestinal contents due to increased sympathetic tone were associated with imbalance of water compartments and body dehydration [28].

At the peak of severity of metabolic lactate acidosis and psychotic manifestations (day 3 of follow-up) with low plasma osmotic pressure, relatively stable levels of blood electrolytes, there was an increase in EFV by 3.9 and 4.1% in groups 1 and 2, respectively, and a decrease of TFV by 2.7 and 3.1% in groups 1 and 2, respectively. Clinically, psychomotor agitation and severe vegetative disorders such as pyrexia up to 37.2 [37.1; 37.4] °C, tachypnea up to 25 [23; 26] breaths per minute, hyperhidrosis, which caused both the general dehydration and redistribution of cellular fluid into the extracellular compartment, as confirmed by data from Goncharov VN et al. (2019) [29] were observed.

After the cytoflavin administration, normalization of cardiac and circulatory function along with reduced blood flow rate were seen, indicating a positive effect of the drug on the vascular tone,

including through sedation-mediated mechanism, as described by Deryugina A.V. and Gracheva E.A. (2020) [30]. We found a direct correlation of CI and SI with changes in delirium severity (*R* for *CI* = 0.32, *P* = 0.03; R for SI = 0.24, *P* = 0.04). Group 2 did not show similar results; a significant decrease in CI and SI was only diagnosed by day 7 of treatment.

The respiratory effort index in group 1 changed linearly with the severity of lactate acidosis (*R* = 0.41, *P* = 0.02). The blood lactate in this group dropped by 28.2%, 46.1%, and 81% on days 3, 5, and 7 of treatment, respectively. In the control group, elevated blood lactate persisted until day 7 (Table 3). Clinically, the patients in the main group showed reduced psychotic symptoms, a statistically significant decrease in the DRS-R-98 score by 23.1% on day 5 and by 46.2% on day 7 vs day 1. In group 2, the severity of delirium was significantly more intense by days 5 and 7.

Notably, as psychotic manifestations and lactate acidosis decreased with cytoflavin use, the balance restoration in fluid compartments with equal replenishment of both IFV and EFV was observed. On day 5 an increase in TFV up to 1.2%, on day 7 — up to 2.6% was recorded. In group 2 no similar changes were noted on day 5. Together with hyperlactatemia, we observed TFV depletion and extracellular dehydration down to 4.3% and 5.1% in 25% of cases, intracellular dehydration down to 4.5% in 75% of cases.

Statistical analysis failed to establish statistically significant intergroup differences among group I and II patients in plasma osmotic pressure and blood electrolyte content on the 5th and 7th days of observation.

The study of severity index, reflecting the permeability of cell membranes, based on reference and measured values of impedance, revealed intergroup differences.

Starting from day 5 of treatment, in group 1 there was an increase in median severity index values by 8.8%, and by 9.6% on day 7, indicating restoration of cellular membrane permeability. There was a high permeability in group 2 patients (χ^2=5.8, *P*=0.008), inverse relationship between severity index and hyperlactatemia (*R*=-0.39, *P*=0.02). In the control group, cellular membrane permeability recovered only on day 7 of therapy. The results obtained are consistent with the research data indicating cell membrane changes and intracellular molecular disturbances under hypoxia [31].

The mean hospital stay of patients with delirium in the main group was 7.5 [6; 8] days, in the control group 14 [11; 15] days (*z*=-5.9; *P*=0.00011).

During the study delirium was complicated by nosocomial pneumonia in group 1 in 7.4% (2), in group 2 in 28.5% (9) cases (χ^2=4.6, *P*=0.03). Thus, in patients with delirium not receiving cytoflavin the risk of complications such as nosocomial pneumonia was 83.6% higher than in those on cytoflavin (OR for group 1=0.07 [95%CI, 0.02–0.29], *P*=0.04; OR for group 2=0.47 [95%CI, 0.26–0.85], *P*=0.04).

Conclusion

The peak of delirium severity in patients with 1,4-BD poisoning occurred on days 1–3 and was characterized by predominantly complex manifestations. Prolonged delirium was associated with metabolic lactate acidosis, systemic hemodynamic and respiratory function disorders. Metabolic disorders in delirium were accompanied by hyperdynamic circulation, increased cardiac output, respiratory effort and cellular membrane permeability, changes in fluid compartments (depending on intensity of psychotic manifestations and hyperlactatemia).

Importantly, the use of an antihypoxic succinate-containing agent (cytoflavin) 40 ml daily reduced the severity of delirium and the risk of complications by preventing tissue hypoxia and stabilizing systemic hemodynamic parameters, respiratory function, and cell membrane permeability.

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Involvement of Urokinase-Type Plasminogen Activator Receptor in the Formation of a Profibrotic Microenvironment in the Epicardial Region

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Участие рецептора активатора плазминогена урокиназного типа в формировании профиброзного микроокружения в эпикардиальной области

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Summary

The study of the mechanisms of development and progression of fibrosis is one of the key directions of modern cardiology. Our work suggests that the urokinase-type plasminogen activator receptor (uPAR) is involved in the regulation of mesothelial cell activity and epicardial fibrosis development, which, when interacting with specific ligands and intermediate proteins, can activate intracellular signaling, trigger the cascade of proteolytic reactions, including local plasmin formation and activation of matrix metalloproteinases, providing matrix remodeling.

Objective: to perform a comparative study of fibrogenic activity of the epicardium in the hearts of uPAR-/- and wild-type animals and evaluate the effect of cardiac microenvironment factors on the migration activity of epicardial mesothelial cells.

Material and methods. We used histological and immunofluorescent staining, microarray analysis of proinflammatory cytokine levels, and a method for assessing the migratory properties of epicardial cells.

Results. Results. We found that compared to wild-type animals, uPAR-/- animals show significant thickening of the epicardial area (2.46+0.77 (uPAR-/- mice) and 1.02+0.17 (Wt mice) relative units, *P*=0.033) accom-

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panied by accumulation of extracellular matrix proteins. Deficiency of uPAR gene leads to formation of proinflammatory microenvironment in the heart (increased levels of proinflammatory factors such as IL-1, IL-13, IL-17, RANTES and MIP1), increased migratory activity of epicardial mesothelial cells, accumulation of TCF21+ fibroblast/myofibroblast precursors (29.8+13.7 (uPAR-/- mouse) and 3.03+0.8 (Wt mouse) cells per visual field, *P*=0.02), as well as development of subepicardial fibrosis.

Conclusion. These findings suggest that uPAR is a promising candidate for the developing targeted agents to prevent the development and progression of cardiac fibrosis.

Highlight

Deficiency of urokinase-type plasminogen activator receptor contributes to the formation of proinflammatory microenvironment and fibrogenic remodeling of epicardial area.

Keywords: fibrosis; epicardial mesothelium; urokinase receptor

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

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Introduction

Extracellular matrix (ECM) proteins are an important regulators of the structural organization of human heart, coordinating the efficient electromechanical coupling of myocardial cells, as well as forming a unique microenvironment to maintain the fundamental characteristics of cells and perform their reparative functions [1]. In a healthy heart, the balance of ECM components is maintained through their enzymatic degradation and de novo synthesis, which ensures the normal microenvironment homeostasis. However, when pathological conditions develop, this balance is disturbed, leading to excessive matrix deposition, known as cardiac fibrosis, which has a significant impact on cardiac function by increasing myocardial stiffness and impairing electrical conduction. Fibrosis of various organs is estimated to be directly or indirectly responsible for almost 45% of deaths in developed countries, which is highly important from a social point of view and carries an enormous economic burden on society [2, 3]. To date, there are no effective ways to reverse the pathological reorganization of the cellular microenvironment and influence the activity of fibroplastic processes in the heart, which inevitably leads to the development of severe heart failure and death. Therefore, the search for new biological targets and the study of the mechanisms of cardiac fibrosis development remains relevant. In this respect, attention has turned to the epicardium, the outer membrane-like layer of the heart, formed by a heterogeneous population of epicardial mesothelial cells and extracellular matrix proteins. Studies of transgenic mouse lines using Cre-lox homologous recombination targeting Wilms tumor genes 1 (Wt1) and Tcf21 revealed a population of progenitor cells in the epicardium that undergo epithelial-mesenchymal transition (EMT) during embryonic development and differentiate into a resident fibroblast line [4–8]. In the adult heart, when ischemia or pressure overload develop, the epicardial microenvironment remodeling occurs, leading to re-expression of fetal epicardial genes and fibroblast-like cell transformation [9–11].

This study suggested that urokinase-type plasminogen activator receptor (uPAR) may act as a regulator of epicardial microenvironment remodeling [12, 13]. It is an integral part of the urokinase system, which also includes urokinase (uPA) and two inhibitors (PAI-1 and PAI-2). uPAR is anchored in the cell membrane via the GPI anchor, which ensures its mobility in the membrane bilayer and allows it to focus the proteolytic activity of urokinase locally in the direction of cell movement. The cascade of proteolytic reactions triggered by urokinase, including local formation of plasmin and activation of matrix metalloproteinases, provides matrix remodeling. However, in addition to the activation of extracellular proteolysis, most cellular responses modulated by the urokinase system are enabled by transmembrane signaling, which is mediated by the interaction of components of this system with intermediary proteins, such as integrins.

Aim of the study: a comparative study of epicardial fibrogenic activity in the heart of uPAR-/- and wild-type animals and investigation of the influence of cardiac microenvironmental factors on the migratory activity of epicardial mesothelial cells.

Material and Methods

Animals. Male C57BL/129 mice (wild-type; n=20) and C57BL/129 uPAR gene knockout mice (uPAR-/- mice; *n*=20) donated by the Faculty of Fundamental Medicine, Lomonosov Moscow State University, were used in the study. The experiments were approved by the ethical committee of National Medical Research Center for Cardiology.

Detection of collagen fibers in the epicardial area. Visualization of collagen in the epicardial zone was done by staining the cryosections with pi-

crosirius red, according to the technique described in the literature [14].

Detection of TCF21+ fibroblast progenitor cells in the epicardial area. TCF21 cells were analyzed by immunohistochemical staining using a commercial ABC Elite Kit (Vector Lab, USA). Cryosections were thawed at room temperature (30 min), washed in phosphate-salt buffer (5 min), and fixed in 3.7% parapharmaldehyde solution (10 min). After fixation, the sections were washed with phosphate-buffered saline (PBS) (3 times for 5 minutes), permeabilized with 0.1% Triton X100 solution (5 minutes), endogenous peroxidase was blocked using the 3% H_2O_2 solution followed by washing with PBS. Next, the sections were blocked with a solution containing 1% bovine serum albumin (BSA) and 10% of the second antibody donor serum in PBS (30 min). After that, cryosections were stained with antibodies to TCF 21 marker (Biolegend, USA) for 1 hour. Afterwards, the slides were washed with PBS (3 times for 5 min each) and secondary biotinylated antibodies were applied to the sections for 30 min. Next, the slides were washed with PBS and treated with ABC kit for 30 minutes. The slides were then washed with PBS and stained with the substrate included in the DAB substrate kit. After staining, the slides were washed with distilled water, dehydrated, and mounted using xylene-based medium.

Obtaining epicardial mesothelial cell culture. The cells were isolated according to the protocol described earlier [15].

Assembly of spheroids based on epicardial mesothelial cells. To assemble epicardial spheroids, V-shaped cups with low-adhesion GravityTRAPTM ULA Plate were used. To obtain spheroids, a cell suspension (5000 cells in 70 µl of culture medium) was plated into wells, precipitated by centrifugation (200g, 2 min), and cultured for 72 hours (in IMDM medium supplemented with 1% fetal calf serum) under standard incubator conditions (37°C, 5% CO_2).

Evaluation of migratory properties of epicardial spheroid cells exposed to conditioned medium Wt uPAR-/- cardiac explants. Formed spheroids were placed in 48-well culture dishes with conditioned medium from Wt and uPAR-\- cardiac explants (½ of conditioned medium and ½ of IMDM medium without serum or other additives). Spheroids were cultured for 3 days with image recording every 24 hours. The migration area and migration pathway length were estimated using Image J software (NIH, USA)

Microarray analysis of proinflammatory factors secretion by Wt and uPAR-\- cardiac explants cells. Hearts were extracted from the thoracic cavity, large vessels were dissected out, and thoroughly washed in PBS. Next, the hearts were placed in sterile Petri dishes and crushed with scissors to obtain 1–2 mm slices. The obtained crushed heart samples were weighed and equalized by weight. Next, the crushed samples (explants) were planted in culture cups (uncoated) in IMDM medium (Gibco, USA) without additives and incubated at 37°C in a 5% CO_2 atmosphere. After 48 h, the explants were removed and the conditioned medium was centrifuged in 2 steps (1000g, 20 min). The resulting supernatant was aliquoted and stored at –70°C until proinflammatory cytokine studies and in vitro experiments were performed. The levels of inflammatory cytokines in conditioned media of cardiac explants of uPAR-/- mice and wild-type animals were studied using Mouse Inflammation Antibody Array (Abcam, USA) strictly according to the kit manufacturer's recommendations.

Statistical analysis. The normality of distribution of variables was assessed using the Kolmogorov–Smirnov test. Differences between the groups were assessed using Mann–Whitney *U*-test considering significance at $P<0.05$. Statistical analysis of the data was performed using Statistica 8.0 software (StatSoft, Inc.). The data were presented as mean±standard deviation (*M*±*SD*).

Results

In the hearts of 1-year-old animals knockout for the uPAR gene (uPAR-/- mice), collagen fiber accumulation was observed, which was combined with 2.4x thickening of the epicardial region (2.46±0.77 (uPAR-/- mice) and 1.02±0.17 (Wt mice) relative units, $P=0.033$), which was not found in wild-type animals (Fig. 1, *a, b, c*). Considering the identified changes, we assessed the number of fibroblast precursor cells in this area of the cardiac wall. The transcription factor Tcf21 was used to identify fibroblast precursors. This marker occurs in epicardial mesothelial and proepicardial cell populations and is involved in the regulation of differentiation toward fibroblast-like derivatives [7, 8]. We found that the number of TCF21+ cells was 9-fold higher (Fig. 1, *c, d, e*) in the epicardium/subepicardium of uPAR-/- mice compared with wild-type mice (29.8±13.7 and 3.03±0.8 cells per visual field, respectively; $P=0.02$).

To identify the factors that can initiate epicardial remodeling, we studied the levels of proinflammatory cytokines in conditioned cardiac explant media samples (Fig. 2, *a*), whose elevated levels are associated with the development of fibrosis. Increased levels of proinflammatory factors (IL-1, IL-13, IL-17, RANTES, and MIP1) were observed in uPAR-/- mice compared with control explant media (from wild-type mouse hearts).

Since thickening of the epicardial layer of the heart is associated with the loss of intercellular contacts and redistribution of mesothelial cells, we analyzed the influence of proinflammatory microenvironment factors on cell migration prop-

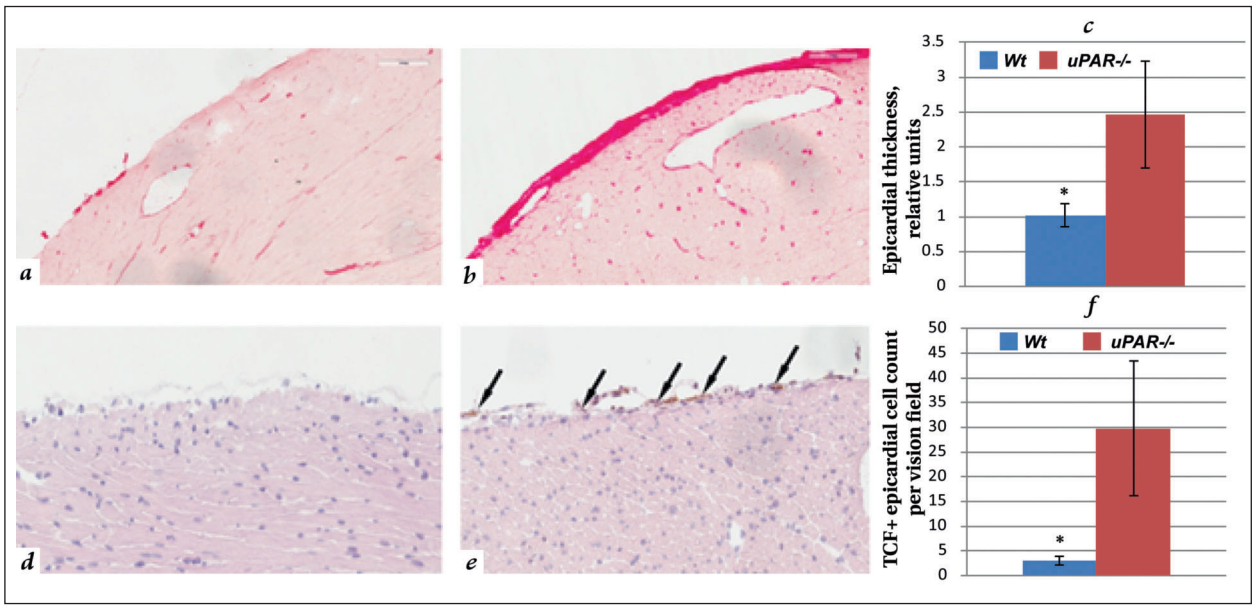

Fig. 1. Urokinase receptor deficiency is associated with epicardial thickening and increased number of TCF+ fibroblast progenitor cells.
Note. Representative staining of heart sections of wild-type (*a*) and uPAR-/- (*b*) mice with picrosirius red. *c* — quantification of epicardial zone thickness in wild-type and uPAR-/- mice. Representative staining of heart sections from wild-type (*d*) and uPAR-/- (*e*) mice with antibodies to the fibroblast progenitor cell marker, TCF21. f — quantification of TCF21+ fibroblast progenitor cells in the heart of wild-type and uPAR-/- mice. Data are presented as mean±standard deviation (*M*±*SD*). * — *P*<0.05.

erties. To study cell motility we used a 3D model of the epicardial microenvironment built according to the spheroid type that provided spatial interaction of cells and formation of cadherin intercellular contacts. Cell distribution area (day 3: 1069900±226137 (Wt explant medium) and 3329643±312000 (uPAR-/- explant medium; *P*=0.04) relative units) and maximum migration path length (day 3: 526±86 (Wt explants medium) and 987±57 (uPAR-/- explants medium) relative units; *P*=0.01) of the epicardial cells were significantly higher with conditioned media from uPAR-/- cardiac explants, compared with control media (Fig. 2, *b–d*).

Discussion

The studies showed that the absence of uPAR gene is associated with the formation of proinflammatory microenvironment in the heart, the accumulation of TCF21+ myofibroblast precursors, and the development of subepicardial fibrosis. Therefore, we hypothesize that uPAR is required to maintain the integrity of the cardiac epicardial layer and regulate the profibrogenic activity of mesothelial cells. uPAR is widely present in epithelium-like cells of different types; it is involved in tissue remodeling processes and participates in the regulation of the most important biological processes, including epithelial-mesenchymal transition, angiogenesis, fibrinolysis, inflammation, tumor invasion and metastasis [12, 13, 16]. In the absence of uPAR, urokinase system function is impaired, which is probably one of the reasons for the rearrangement of the epicardial/subepicardial microenvironment. Indeed, increased levels of proinflammatory factors were observed in the hearts of uPAR-/- mice, which may act as independent regulators of cellular function and underlie the development of fibrosis. A study by Genua [17] showed that uPAR deficiency causes polarization of macrophages in the M1 direction and promotes increased secretion of proinflammatory cytokines, which may act as the basis for the formation of a proinflammatory microenvironment. In the intact heart, the mesothelium has a polygonal epithelial-like morphology, but under the influence of inflammatory factors it may undergo transdifferentiation in the mesenchymal direction and acquires promigratory, proinvasive, and fibroblast-like characteristics. The transition from mesothelial to mesenchymal (fibroblast-like) phenotype in uPAR-/- animals may be based on the complex effect of inflammatory factors and altered activity of Ras-ERK1,2 MAPK, Rac1 and PI3K-AKT intracellular signaling pathways (due to impaired mutual influence of uPAR integrins or other intermediaries) [18, 19], which lead to disruption of intercellular contacts, cell polarity loss and cytoskeleton reorganization. Probably, the triggering of this irreversible reaction underlies the formation of fibroblasts/myofibroflasts hyperproducing extracellular matrix proteins, which are formed under the control of uPAR. The absence of the receptor leads to the inhibition of uPAR-dependent regulation of integrin functions and increased cell adhesion stimulating the transition of fibroblasts to myofibroblasts due to the formation of adhesion contacts and enhanced assembly/stabilization of smooth muscle alpha-actin fibers [20–22]. An additional unfavorable factor inducing the epicardial

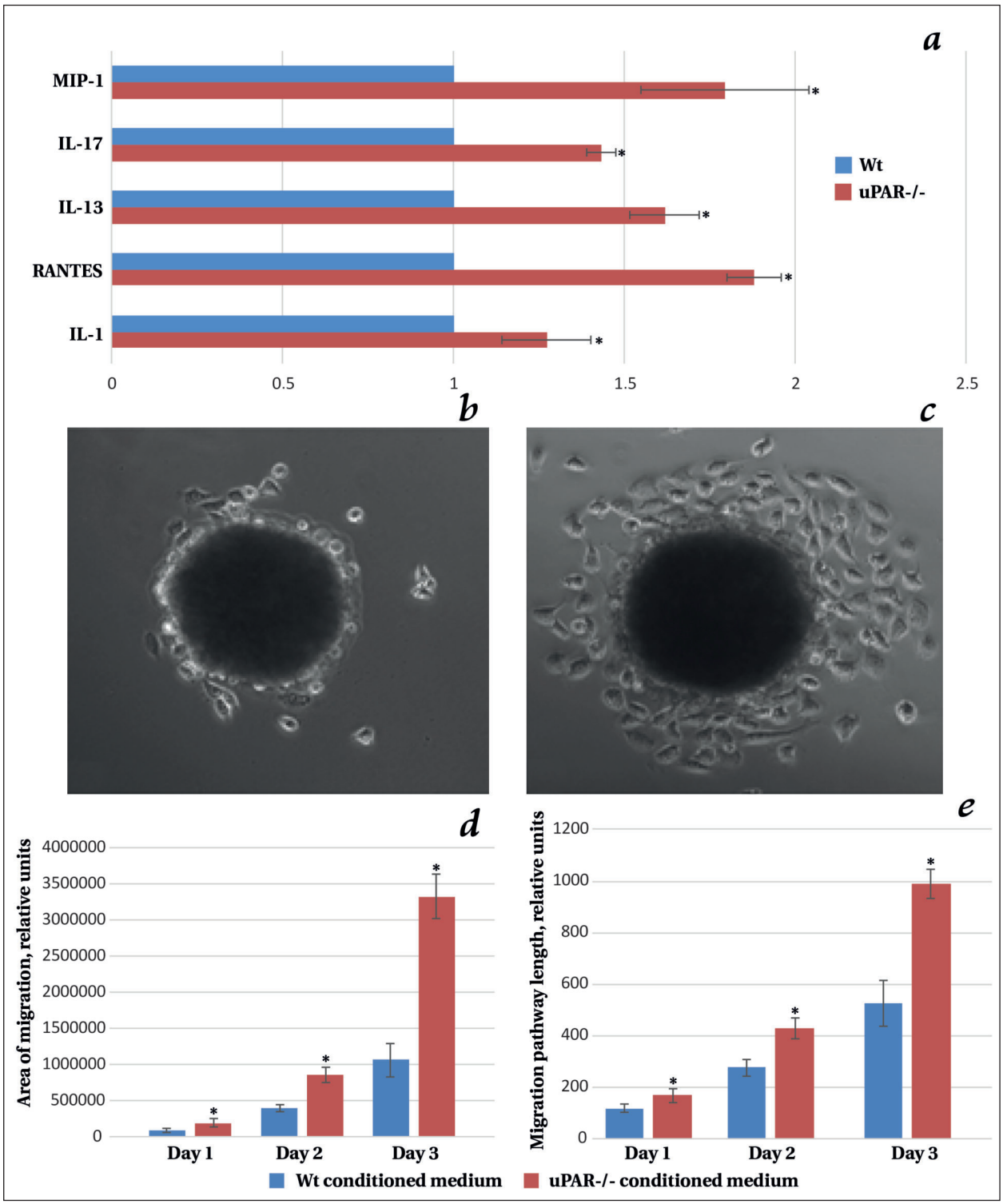

Fig. 2. Conditioned medium of uPAR-/- of cardiac explants is characterized by a high level of proinflammatory factors and has a stimulating effect on the migration properties of epicardial cells.
Note. *a* — quantification of proinflammatory factors in the medium of cardiac explants of wild-type and uPAR-/- mice; *b, c* — representative images of epicardial cell migration from spheroids under the influence of conditioned medium of cardiac explants of wild-type (*b*) and uPAR-/- mice (*c*); *d, e* — morphometric evaluation of cell distribution area and maximum migration pathway length when epicardial spheroids were cultured in conditioned medium of cardiac explants of wild-type and uPAR-/- mice. The data are presented as mean±standard deviation (*M*±*SD*). * — *P*<0.05.

microenvironment rearrangement can be accumulation of free (not related to uPAR) urokinase in the heart, which, through interaction with nucleolin, can be transported to nucleus to activate expression of EMT-associated and profibrotic genes [23, 24]. Another mechanism is possible that relates to the interaction of urokinase with alternative receptors, such as N-cholinoreceptors regulating fibrob-

last function [25] and fibrosis development/progression. The results obtained when studying uPAR-/- animals with signs of inflammatory microenvironment formation combined with cardiac fibrosis have common features with the clinical manifestations observed in patients with systemic scleroderma, a condition characterized by a loss of uPAR function due to its proteolytic cleavage by MMP12 [26]. Such patients have elevated levels of IL-1, IL-17, MCP-1/CCL2, MIP-1α/CCL3, MIP-1β/CCL4 and IL-8/CXCL8, accompanied by increased EMT activity, excessive fibroblast formation and fibrotic transformation of various tissues, including the heart [27, 28].

Conclusion

Thus, uPAR can be considered as a multilevel regulator of epicardial microenvironment. Deficiency of this gene leads to the formation of proinflammatory microenvironment in the heart, increased migratory activity of epicardial mesothelial cells, accumulation of TCF21+ fibroblast/myofibroblast precursors and development of subepicardial fibrosis. These data allow us to consider uPAR a promising candidate for the developing targeted agents to prevent the emergence and progression of cardiac fibrosis.

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ERRATUM

Obshchaya Reanimatologiya = General Reanimatology. 2021; 17 (5): 3 and 4–8

Erratum report was submitted by a reader. The reader pointed out a misprint in the title [In Engl.] on p. 3 and 4.

Correction to the article: «The 85th Anniversary of the V. A. Negovsky Research Institute of General Rehabilitology, Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology (Editorial)»

Victor V. Moroz, Artem N. Kuzovlev, Elena V. Luginina, Andrey V. Grechko

DOI: 10.15360/1813-9779-2021-5-4-8.

«... General Rehabilitology ...» should be replaced with «... General Reanimatology ...»

The correct option [In Engl.] is: «The 85th Anniversary of the V. A. Negovsky Research Institute of General Reanimatology, Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology (Editorial)»

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