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ЭКСПЕРИМЕНТАЛЬНАЯ ХИРУРГИЯ, АНЕСТЕЗИОЛОГИЯ И РЕАНИМАТОЛОГИЯ ЛАБОРАТОРНЫХ ЖИВОТНЫХ

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ОСНОВНЫЕ ТЕМЫ КОНФЕРЕНЦИИ

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Nutritional Status of Patients with Chronic Critical Illness

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Summary

Objective: to assess the nutritional status of patients with chronic critical illness.

Material and methods. We examined 23 patients with chronic critical illness who were in a minimally conscious state (MCS) with 10.9±2.5 scores on the FOUR (Full Outline of Unresponsiveness) Score Coma Scale. Indicators of carbohydrate, lipid, protein and energy exchange metabolism were evaluated using specimens sampled in the morning hours. Nutritional support was provided by isocaloric isonitrogenic mixtures.

Results. Blood biochemistry showed decreases in total protein and albumin levels in 86.9% and 91.3% of patients, respectively. The tests also revealed decreased concentrations of several amino acids, including essential amino acids: histidine (38.3±13.07 μmol/L), methionine (12.68±3.81 μmol/L), threonine (61.6 [58.5; 87.7] μmol/L), tryptophan (33.06±15.95 μmol/L), and non-essential amino acids: arginine (40.50 [22.2; 46.9] μmol/L), glutamic acid (124.5±39.29 μmol/L), tyrosine (37.97±10.12 μmol/L). Some correlations between the concentrations of individual amino acids and other indicators were revealed, such as histidine and CRP (r=–0.68, P=0.043), tryptophan and CRP (r=–0.86, P=0.002), histidine and leukocyte count (r=–0.76, P=0.015), methionine and lysine (r=0.88, P=0.008), methionine and patient's weight (r=–0.68, P=0.042). A relationship between threonine concentration and the level of consciousness on the FOUR scale (r=–0.73, P=0.037) was also found. All patients demonstrated significant alterations of carbohydrate and lipid metabolism.

Conclusion. Alteration of adequate protein metabolism seems to be the most affected constituent in the nutritional status of patients with chronic critical illness. It is manifested by a decrease in the concentration of total protein and a number of essential and non-essential amino acids, which implies the importance of high-protein nutritional support and correction of the amino acid profile.

Keywords: nutritional status; critical illness; protein metabolism; amino acid profile; amino acids; prolonged disturbance of consciousness

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

Introduction

The number of patients surviving critical illness caused by exposure to a significant damaging factor is steadily rising due to advancements in medical care, the development of new technologies and equipment, as well as manipulations and therapies. Unfortunately, the prevalence of late complications and prolonged critical illness (PCI), which is linked to a lower quality of life and a less effective rehabilitation, is also rising [1].

The most frequent side effects of prolonged ICU stays are muscular and neurological deficits, which increase the risk of chronic critical illness and poor outcomes in this patient population [2].

Many patients with intact consciousness still experience respiratory problems, muscle weakness, and decreased exercise tolerance years after being discharged from the intensive care unit. Psychological issues like depression, sexual dysfunction, and social isolation frequently coexist with the medical conditions in these patients [3, 4].

This extensive list of symptoms and conditions is known as post-intensive care (PIC) syndrome [5].

As a result, many patients leave the unit for only a brief time because of commonly required readmission [6].

Further investigation is needed into the predictors, treatment, and, most importantly, prevention of PIC syndrome and chronic critical illness.

Adequate nutritional support is one of the most important aspects of therapy. Unfortunately, the optimal nutritional support strategy in the ICU remains an unsolved issue. There are numerous guidelines on nutritional support for patients written by ESPEN (European Society of Parenteral and Enteral Nutrition), ASPEN (American Society of Parenteral and Enteral Nutrition), RSPEN (Russian National Association of Clinical Nutrition and Metab-

olism), and other national organizations, but their implementation in clinical practice remains difficult [7–9]. The choice of the proper nutritional support is further complicated by the quantitative and qualitative variations in metabolite levels that depend on the type of prolonged disorders of consciousness and circadian phases [10].

Current international clinical guidelines favor enteral nutrition (EN) for critically ill patients when feasible. The physiological benefits, side effects of parenteral nutrition (PN), and increased cost of PN have led to the dominance of the EN concept. Often, EN alone is not sufficient to provide adequate energy and substrate to the patient, especially in the critically ill, due to the severity of illness and energy cost, marked catabolism, and gastrointestinal dysfunction [11–13].

It is important to maintain adequate levels of precursors of large molecules other than macronutrients, such as proteins, fats, and carbohydrates, which play an equally important role in ensuring adequate levels of metabolism, transition from catabolism to anabolism, and improved outcomes. In particular, an adequate supply of amino acids, which are components of protein structures, helps to reduce inflammation and loss of muscle mass, and increases resistance to oxidative stress [14].

In addition to macronutrients, micronutrients are also important in correcting protein-energy deficiencies. The necessity of micronutrient administration is determined by their participation in the normal functioning of cells and molecular structures. The presence of antioxidant properties in some micronutrients is extremely important, as their deficiency can provoke oxidative stress, especially in critical illness [15]. Oxidative stress, in turn, plays a crucial role in the pathophysiology of critical illnesses such as acute respiratory distress syndrome, reperfusion syndrome, and multiorgan failure [16].

It is important to emphasize that there are still problems in formulating a fully balanced amino acid solution for parenteral nutrition. In particular, all parenteral nutrition formulations do not contain sufficient concentrations of cysteine because it is not stable in solution [17]. Providing adequate concentrations of tyrosine and glutamine is also challenging due to their poor solubility. N-acetylated tyrosine, a water-soluble derivative of tyrosine, is used in some amino acid solutions, but this is associated with side effects because it takes a long time to convert to tyrosine in humans and is poorly reabsorbed by the kidneys [18].

At present, solutions containing some amino acids are unbalanced due to the unique characterstics of their metabolism. Thus, the adequate maintenance and supply of protein to a critically ill patient remains both a scientific and clinical problem.

In this regard, the dynamic control of macro- and micronutrients in patients throughout all stages of treatment may represent a necessary approach to adequate nutritional support.

The aim of this study was to evaluate the nutritional status of chronically critically ill patients.

Materials and Methods

An observational, prospective, single-center study included chronically critically ill patients after severe brain injury treated in the intensive care units of the Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology (FRCCICMR) in 2022. The patients' condition was assessed during the first 3 days after admission for treatment and rehabilitation.

The study was approved by the Ethics Committee of the FRCCICMR, protocol 4/21/9 dated 29.09.2021.

The study included 23 chronically critically ill patients with a mean age of 46.91±15.09 years, ranging from 24 to 79 years. The age of most patients ranged from 30 to 60 years.

Among the patients, 12 were male (52%) and 11 were female (48%).

The level of consciousness according to the FOUR (Full Outline of Unresponsiveness) scale was 10.9±2.5 points.

Inclusion criteria were

- time from exposure to the initial damaging factor to admission to the FRCCICMR units more than 30 days;
- minimal consciousness;
- breathing through a tracheostomy tube.

Exclusion criteria were:

- vasopressor or intravenous support;
- drug sedation;
- hepatic or renal failure;
- diabetes mellitus.

All patients received isocaloric isonitrogenous formulas. The mean caloric intake was 1673.91±243.49 kcal/day, with protein 1.2±0.12 g/kg/day, carbohydrate 3.1±0.38 g/kg/day, and fat 1.01±0.12 g/kg/day.

Patient assessment protocol:

1. Anthropometric measurements (height, weight, body mass index calculation).

2. Complete blood count parameters (hemoglobin, red blood cells, white blood cells, WBC differential, platelets).

3. Serum biochemistry (total protein, albumin, glucose, cholesterol, triglycerides, C-reactive protein).

4. Amino acid profile: alanine (Ala), alpha-aminobutyric acid (Aba), arginine (Arg), asparagic acid (Asp), asparagine (Asn), citrulline (Cit), gamma-aminobutyric acid (GABA), glutamic acid (Glu), glutamine (Gln), glycine (Gly), histidine (His), hydroxyproline (Hyp), isoleucine (Ile), leucine (Leu), lysine (Lys), methionine

Table 1. Biochemical parameters of patients

Parameter	Values		Reference range	Number of patients with values outside the reference range, *N* (%)
	M±*m* / *Me* [*Q1*; *Q3*]	min–max		
Total protein, g/L	54.61±7.77	40.3–70.7	66.0–83.0	20 (86.9)
Albumin, g/L	29.88±5.2	22.3–38.8	35.0–52.0	21 (91.3)
Glucose, mmol/L	5.87 [5.3; 6.4]	3.56–9.0	4.1–5.9	5 (21.7)
Triglycerides, mmol/L	1.46±0.73	0.66–2.6	0.0–1.7	7 (30.4)
Total cholesterol, mmol/L	3.61±0.94	1.62–5.28	0.0–5.2	1 (4.3)

(Met), ornithine (Orn), phenylalanine (Phe), pipecolic acid (PA), proline (Pro), sarcosine (Sar), threonine (Thr), tryptophan (Trp), tyrosine (Tyr), valine (Val).

Calculation of Glu/Gln index.

5. Daily urinary nitrogen losses and nitrogen balance.

Biochemical parameters were measured by AU480 biochemical analyzer (Beckman Coulter, USA), blood was taken from patients at 6:00 am.

Blood amino acid concentration was measured by AB Sciex QTRAP 5500 (AB Sciex, Concord, ON, Canada).

Indirect calorimetry was performed using a Medgraphics Ultima CPX gas exchange analyzer (MGC Diagnostics Corporation, USA).

Daily urinalysis to determine nitrogen losses was performed on an AU480 analyzer (Beckman Coulter, USA). Due to the presence of non-urea nitrogen losses with urine, its excretion with stool and through the skin, 4 g were added to the obtained values [19].

The data obtained were analyzed using Statistica 12.5 software (TIBCO Software, USA).

Normality of the distribution was checked using the Shapiro-Wilk criterion. For data with normal distribution, values were presented as mean±standard deviation, otherwise median and 1 and 3 quartiles were reported.

Correlations with normal distribution were evaluated by Pearson's test. For non-normal distribution, Spearman's criterion was used. The results of statistical analysis were considered significant at $P \leqslant 0.05$.

Results

A decrease in the levels of total protein and albumin was found in almost 90% of the studied patients (Table 1). Abnormal triglyceride, cholesterol and glucose levels were observed in almost 30% of patients.

According to indirect calorimetry, the level of resting energy expenditure was 1400.5±370.0 kcal/day, with a positive nitrogen balance of 4.25±2.05 g/day.

The amino acid profile indicated a reduction in the levels of several essential amino acids, including histidine, methionine, threonine, and tryptophan. Moreover, there was a decrease in the levels of non-essential amino acids, with arginine, glutamic acid, and tyrosine being notably affected (Table 2).

Table 2. Amino acid profile of patients

Parameter	Values		Reference range	Number of patients with values outside the reference range, *N* (%)
	M±*m* / *Me* [*Q1*; *Q3*]	min–max	значения	
Alanine, μmol/L	210.4±82.88	80.3–344.1	160.0–530.0	5 (21.7)
Alpha–aminobutyric acid, μmol/L	17.80 [8.6;18.5]	6.6–19.9	10.2–40.1	10 (43.5)
Arginine, μmol/L	40.50 [22.2;46.9]	16.0–107.2	35.0–125.0	10 (43.5)
Asparagic acid, μmol/L	16.10 [14.3; 16.4]	10.6–28.4	<15.0	8 (34.8)
Asparagine, μmol/L	36.4±12.83	19.7–61.2	20.0–80.0	3 (13)
Citrulline, μmol/L	15.8±5.93	8.9–26.3	21.4–48.8	18 (78.3)
Gamma–aminobutyric acid, μmol/L	0.4±0.2	0.0–0.6	0.0–5.0	0 (0)
Glutamic acid, μmol/L	124.5±39.29	72.6–178.2	15.0–130.0	10 (43.5)
Glutamine, μmol/L	515.78±127.96	337.0–703.0	311.6–732.2	0 (0)
Glycine, μmol/L	260.76±45.47	199.80–348.5	140.0–420.0	0 (0)
Histidine, μmol/L	38.3±13.07	22.1–56.5	52.8–88.5	20 (86.9)
Hydroxyproline, μmol/L	9.40 [7.5; 9.6]	2.5–24.2	5.0–40.0	3 (13)
Isoleucine, μmol/L	55.36±17.23	32.0–84.4	30.0–120.0	0 ()
Leucine, μmol/L	92.46±22.06	58.9–117.7	60.0–180.0	3 (13)
Lysine, μmol/L	131.87±42.81	80.0–220.8	85.0–230.0	5 (21.7)
Methionine, μmol/L	12.68±3.81	7.5–19.3	15.0–40.0	18 (78.3)
Ornithine, μmol/L	56.48±22.02	33.9–100.6	25.0–110.0	0 (0)
Phenylalanine, μmol/L	47.96±15.21	30.1–73.0	25.0–80.0	0 (0)
Pipecolic acid, μmol/L	0.60 [0.5; 1.3]	0.5–5.3	<3.1	3 (13)
Proline, μmol/L	116.63±33.54	74.7–182.4	90.0–350.0	5 (21.7)
Sarcosine, μmol/L	8.92±1.63	5.7–11.1	2.0–19.4	0 (0)
Serine, μmol/L	98.06±27.47	50.2–130.3	60.0–170.0	5 (21.7)
Threonine, μmol/L	61.6 [58.5; 87.7]	53.5–243.6	67.2–211.1	15 (65.2)
Tryptophan, μmol/L	33.06±15.95	10.5–52.5	25.0–80.0	10 (43.5)
Tyrosine, μmol/L	37.97±10.12	22.7–53.7	35.0–110.0	13 (56.5)
Valine, μmol/L	155.91±36.71	102.2–206.2	120.0–320.0	5 (21.7)
Glutamic acid / Glutamine	0.25±0.1	0.141–0.466	0.22–0.88	10 (43.5)

We identified correlations between the lowest amino acid levels and other patient data. We observed a negative relationship between histidine levels and CRP concentration (r=–0.68, P=0.043), as well as with WBC count (r=–0.76, P=0.015). There was a strong association between methionine and lysine (r=0.88, P=0.008), and between methionine and patient weight (r=0.68, P=0.042). Furthermore, we observed a weaker negative association between threonine and the level of consciousness on the FOUR scale (r=–0.73, P=0.037). Additionally, a negative relationship was found between tryptophan and CRP levels (r=–0.86, P=0.002).

Discussion

We found significant abnormalities in the amino acid profile, indicating a predominant disturbance in protein metabolism in chronically critically ill (CCI) patients.

We would like to pay special attention to the amino acids whose levels were reduced more than others.

Citrulline is almost entirely produced by intestinal cells and its plasma level is regarded as a biomarker of the functional capacity of small intestinal enterocytes. Given the existing protein-energy deficiency in CCI patients and the inability to correct it through adequate enteral administration of both micro- and macronutrients, the decrease in citrulline concentration suggests impaired absorption of these elements. Because citrulline is converted into arginine in the kidneys, which play a crucial role in the regulation of citrulline metabolism, an increase in citrulline may also be a sign of renal failure. There was no evidence of renal failure in the patients studied [20, 21].

The kidneys metabolize 83 percent of all citrulline absorbed from the intestine, «consuming» about 1.5 g of citrulline from the blood per day, or about 35 percent of total circulating citrulline [22]. The kidneys can provide all the arginine the body needs, given adequate renal function and citrulline intake. An increase in muscle protein synthesis was observed in a study of aged mice given citrulline, suggesting that it may directly stimulate protein synthesis in myofibrils and sarcoplasm [23]. Furthermore, oral citrulline supplementation of healthy subjects increased muscle protein synthesis even when they were consuming a low protein diet compared to an isonitrogenic diet group [24]. Therefore, supplementation with this amino acid appears promising in CCI patients.

Another deficient amino acid was histidine, which plays an important role in nutritional status by participating in iron binding to hemoglobin and myoglobin and by being an active regulatory component of metalloenzymes (anhydrase, cytochromes, etc.). The histidine-rich glycoprotein present in the plasma of vertebrates is essential for the immune function [25].

Histidine deficiency does not involve a sudden development of negative nitrogen balance. Instead, the body compensates for histidine deficiency by activating the catabolism of hemoglobin and muscle tissue resulting in their decrease [26]. In earlier studies conducted at FRCCICMR, a decrease in iron levels and also a severe reduction in muscle mass in patients with severe brain injury were noted, which may also be due to low histidine levels [27].

Histidine has an important role in maintaining a positive nitrogen balance, but after a longer period of time, which has been demonstrated in both mice and humans. For example, a prolonged deficiency followed by a histidine-rich diet has been shown to increase nitrogen balance parameters even with a low-protein diet [28].

Methionine is an essential amino acid and although it is essential for survival, its limited intake in mammals results in beneficial effects such as reduced likelihood of obesity, increased insulin sensitivity, decreased inflammation and oxidative stress, and ultimately increased survival [29].

Protein-bound methionine and its oxidized form, methionine sulfoxide, play an important role in regulating the antioxidant system as a buffer, although elevated methionine sulfoxide is considered undesirable and associated with decreased survival. Activation of sulfoxidation upregulates various transcription factors in response to a stimulus, modulating the activity of signaling protein kinases and cytoskeletal changes. Mutual conversion of methionine and methionine sulfoxide provides stability of proteins and their interactions [30, 31].

The observed decrease in methionine levels in CCI patients may reflect the characteristic severe dysfunction of many organs and systems.

Threonine is necessary to ensure optimal development and function of the animal's immune system. The function of the intestinal wall, its ability to digest and absorb nutrients, and the normal performance of the intestinal cell barrier are critically dependent on an adequate intake of threonine. Both deficiency and excess of threonine can have negative effects on the immune and digestive systems. In addition, threonine plays an important role in neuropsychiatric health, adequate response to physiological stress, and anti-inflammatory response [32]. The observed decrease in threonine, as well as citrulline, in CCI patients may indicate digestive disorders.

Tryptophan is also important for nutritional status, and both its elevation and depletion can have negative consequences due to the production of toxic metabolites from excessive tryptophan oxidation. Tryptophan is one of three aromatic amino acids, along with phenylalanine and tyrosine. These amino

acids have potent antioxidant effects [33]. According to some studies, when tryptophan metabolism is activated through the kynurenine pathway, the activity of chronic inflammation increases [34, 35].

The kynurenine/tryptophan ratio is a biomarker of age-related changes. It is known to increase with age, with tryptophan decreasing and kynurenine increasing [36]. Given the observed low tryptophan level, we can assume the activation of chronic inflammation in the studied patients, which is also evidenced by the increased CRP concentration (55.6± 39.5 mg/l) and WBC count (8.8±4.7 thousand) compared to reference values.

Arginine turnover depends on citrulline metabolism and their concentrations are closely correlated. Arginine is implicated in the regulation of vascular tone and is a metabolite involved in the production of nitric oxide by the vascular endothelium [37]. Prolonged plasma arginine deficiency leads to oxidative stress, degradation of intracellular arginine and inhibition of its production from the precursor citrulline, resulting in vasospasm due to insufficient nitric oxide formation [38]. In addition, arginine plays an important protective role in ammonia metabolite intoxication and participates in muscle development [39]. Correction of low citrulline levels in CCI patients may be required before restoring arginine levels.

Glutamate (glutamic acid) is essential for mammalian brain function. It is both an excitatory neurotransmitter and a precursor of the inhibitory neurotransmitter gamma-aminobutyric acid, an important structural component of proteins, an energy substrate, and can also be a neurotoxin [40]. It appears that the decrease in the concentration of this amino acid is due to impaired neurotransmitter metabolism and nervous system regulation.

Tyrosine is produced from phenylalanine. Due to its special structure, it is able to be both an electron and proton donor in the reactions of enzyme metabolism and therefore can be found in the active part of many enzymes, both oxidases and reductases [41]. Studies have found that additional tyrosine supplementation reduces the risk of developing type 2 diabetes and also affects the functioning of neurotransmitters such as dopamine [42]. Reduced tyrosine level with no decrease in phenylalanine in CCI patients could indicate a greater expenditure of tyrosine for the formation and functioning of enzymes, and their greater loss is due to the existing chronic inflammation and dysregulation of organs and systems resulting from brain disorders.

High plasma glutamate concentrations and elevated glutamate-to-glutamine ratios are associated with an increased risk of heart failure, cancer, immunodeficiency virus infection, and indicate a risk of loss of cell mass in healthy individuals [43, 44]. Glutamate potentiates oxidative stress and induces apoptosis, whereas glutamine is involved in myocardial metabolism and exerts potent antioxidant and anti-inflammatory effects by inducing the expression of hemoxygenase-1, heat shock proteins (HSP) and glutathione [45, 46]. Glutamate and glutamine are also involved in energy metabolism. Low values of their ratio indicate the possibility of hyperammonemia or vitamin B1 deficiency [47, 48].

Lack of predetermined sample size was the limitation of our study.

Conclusion

The study found that the most common defect in the nutritional status of chronically critically ill patients is inadequate protein metabolism. No significant disturbances in carbohydrate or lipid metabolism were observed.

Abnormal levels of both essential and non-essential amino acids were also revealed, suggesting the importance of protein-rich nutritional support and correction of the amino acid profile.

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Assessment of Risks for Gastrointestinal Bleeding in Patients with Brain Injury

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Summary

The aim of the study was to develop a risk model for upper gastrointestinal tract (GIT) bleeding in patients with brain injury of various etiologies.

Material and methods. Case histories of 33 patients were included into a retrospective descriptive study: 22 patients had severe brain injury of various etiologies, and 11 patients after elective surgery for cerebral aneurisms with uneventful postop period were taken for comparison. The patients were grouped in two arms: Group 1 included patients with obvious signs of GIT bleeding (*N*=11) and Group 2 had no obvious signs of bleeding (*N*=22). Complaints, life and medical history, comorbidities, specialists' exams data, results of laboratory and instrumental examinations, therapeutic regimens were analyzed. Presence of disproportionate pathologic sympathetic overreaction to acute brain injury, i. e., paroxysmal sympathetic hyperactivity (PSH), was assessed on admission and on Days 1, 3 and 5 after brain injury.

Results. A model for upper GIT bleeding risk assessment was designed using logistic regression. The resulting model gains high quality rating: χ^2=33,78, 3; p<0,001; OR=315. The risk of upper GIT bleeding exceeded 95% in patients having combination of 4 symptoms in their medical history (presence of PSH on Day 1 after acute brain injury; Karnofsky performance scale index <75; lack of neurovegetative stabilization in the acute period of brain injury; gastric and/or duodenal ulcer).

Conclusion. Determining the risk factors thresholds enables stratification of patients by the risk for upper GIT bleeding. Modification of the identified four risk factors (presence of PSH on Day 1after acute brain injury; Karnofsky performance scale index <75; lack of neurovegetative stabilization in the acute period of brain injury; gastric and/or duodenal ulcer) will probably reduce the occurrence of upper GIT bleeding in patients with acute brain injury of various etiology.

Keywords: gastrointestinal bleeding; brain injury; risk assessment; paroxysmal sympathetic hyperactivity; logistic regression; gastric lesion; duodenal lesion; gastrointestinal tract

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

Introduction

Acute erosive lesions of the upper gastrointestinal tract have a multifactorial etiology and can complicate many diseases and worsen outcomes [1–5].

Acute gastric and duodenal lesions often develop in critically ill patients. The pathogenesis of these conditions is determined by a shift in the balance of aggressive versus protective factors [6]. The development of new treatments, as well as the improvement of existing ones, is a pressing issue in intensive care.

In 1867, T. Billroth demonstrated the relationship between surgical trauma and damage to the gastric and duodenal mucosa. In 1823, J. Swan described gastric mucosal defects in children after fire injury, while B. Curling described the so-called Curling ulcers in the middle of the 19th century. G. Selye elaborated the stress theory, coined the term «stress ulcer» and showed a causal relationship between psychosomatic diseases and the development of peptic ulcers [6–9].

Acute lesions of the GI mucosa are a common complication of severe brain injury. They were first described by G. Cushing and later named after him [10].

According to different authors, peptic bleeding in critical patients accounts for 5–47% of all gastrointestinal bleeding cases. This wide variation in data is due to the heterogeneity of the population, different definitions of gastrointestinal bleeding (GIB), and diagnostic difficulties. There is no single registry for GIB because of its multifactorial nature [7–9].

Risk factors for bleeding from damaged gastric and duodenal mucosa include lung ventilation, coagulation disorders, acute renal and hepatic failure, traumatic and other brain injury, paroxysmal sympathetic hyperactivity (PSH), and vary with disease severity [11–16].

Clinical signs of PSH include hyperhidrosis, fever, changes in heart rate, respiratory rate, blood pressure, mydriasis, and musculoskeletal system changes. Typically, non-medication, medical and preventive methods are used to treat PSH. The management is based on general intensive care principles (maintenance of adequate parameters of hemodynamics, gas exchange, blood volume, electrolyte balance, blood glucose, body temperature, and nutritional support). The first step in drug treatment is symptomatic therapy. In lack of efficacy, continuous opioids and propofol are suggested. After dexmedetomidine was introduced into practice, alpha-2 adrenergic agonists were successfully used for the treatment of PSH [16].

Given the large number of risk factors, it is necessary to develop a mathematical model that enables the precise, sensitive, and specific identification of these factors from the general array in order to determine which of them are most crucial for patients with severe brain injury.

The study's methodology was based on the assumption that identifying important risk factors for the development of upper GI bleeding and their relationship to treatment outcomes would aid in the development of a successful plan for the prevention and treatment of this condition in patients with severe brain injury.

The aim of the study was to build a risk model for the development of overt upper gastrointestinal bleeding in patients with brain injury of various etiologies.

The study model was built on the basis of logistic regression, taking into account both quantitative and categorical variables as risk factors. The main idea of the model was to obtain the characteristics of the logistic function Ψ for the standard equation $y = \exp(\Psi) / (1 + \exp(\Psi))$.

Materials and Methods

The case histories of 33 patients treated in the Department of Anesthesiology and Intensive Care of the Russian Polenov Neurosurgical Institute between 1992 and 2022 were included in the retrospective descriptive study. Of these patients, 22 had severe brain damage of various etiologies (Table 1) and 11 (used as a comparison) had cerebrovascular aneurysms and an uneventful postoperative period after elective neurosurgical intervention.

Inclusion criteria were severe brain injury of various etiologies, age older than 18 years.

Non-inclusion criteria were brain malignancy, upper GI surgery, history of malignancy.

All patients were divided into two groups: without obvious signs of GI bleeding (*N*=22) and with overt GI bleeding (*N*=11). Criteria for overt GI bleeding were hematemesis, blood in GI aspirate, or melena. Clinically significant GI bleeding was defined as a combination of overt GI bleeding and hemodynamic changes or the need for blood transfusion or surgical intervention [17]. The fact of bleeding was confirmed according to the patient's medical record and/or upper endoscopy protocol.

Patients in the selected groups did not differ in age, Glasgow Coma Scores at hospital admission, and FOUR scores at ICU admission (Table 2).

Autonomic nervous system function was assessed using the PSH scales at admission and 1, 3, and 5 days after brain injury [16].

Seventy different clinical, assessment and laboratory parameters were analyzed (see Appendix).

The data obtained were analyzed using STATISTICA for Windows v10 software.

All quantitative variables had non-normal distributions and were analyzed using Mann–Whitney, Kolmogorov–Smirnov, and median χ^2 criteria. Frequency characteristics of qualitative parameters

Table 1. Etiology of brain injury.

Brain injury	Number of patients
Total	22
Subarachnoid hemorrhage	4
Spontaneous intracranial hemorrhage due to ruptured arteriovenous malformation	6
Closed head injury	3
Open head injury	1
Major ischemic type cerebrovascular accident	1
Hemorrhage after microsurgical removal of benign brain neoplasm	4
Hemorrhagic cerebrovascular accident with intracerebral hematoma	3

Table 2. Characteristics of the studied groups of patients, *M*±*SD*; *min*÷*max*; *Me* (*LQ*; *UQ*).

Parameters	Values in groups		*P*
	Without GIB, *N*=22	With GIB, *N*=11	
FOUR scale severity on admission to ICU	13.14±3.76; 5÷16; 16 (12; 16)	10.22±2.95; 5÷14; 10 (10;12)	0.051
Glasgow Coma Scale severity on hospital admission	14.86±0.47; 13÷15; 15 (15; 15)	12.91±2.07; 10÷15; 13 (10; 15)	0.073
Age, years	50.36±15.59; 21÷70; 54 (38; 64)	51.91±16.03; 31÷78; 48 (38; 71)	0.79

(gender, cerebral edema, performing neurovegetative stabilization regardless of PSH manifestations, etc.) were evaluated by nonparametric methods using Pearson's χ^2 and Fisher criteria. Critical thresholds and prognostic significance of risk factors in patients with hemorrhage were determined using the Classification Trees module. The odds ratio (OR) for GI bleeding was calculated using standard formulas. In the case of zero values in the four-way table, the Haldane correction was used for calculation.

The model for estimating the risk of GIB in patients with brain injury of different etiologies was created using logistic regression (Logistic Regression in the Nonlinear Estimation module). First, the models with regression coefficient analysis were used, and then the model for estimating the risk of GIB was built. It included 4 most significant variables (Table 3).

Binary categorical variables were coded as 1 (yes) or 0 (no). For 4 variables (no neurovegetative stabilization performed, PSH severity 1 day after brain injury, history of gastric mucosal injury, and Karnofsky index at hospital admission), we found a significant association with GIB and analyzed them in detail.

To verify the effectiveness of the GIB risk assessment model, a «test» group was created. For this purpose, 10 case histories of patients treated in the Department of Anesthesiology and Intensive Care in 2023 were randomly selected. Of these, 6 had no GI bleeding and 4 had GI bleeding. Inclusion and non-inclusion criteria remained unchanged. The model was verified by checking for signs of overt GI bleeding, such as severe manifestations of PSH 24 hours after brain injury, history of gastric mucosal injury, and changes in Karnofsky index at hospital admission.

Adequacy of sample size was evaluated using Lehr's formula and Altman's nomogram. The characteristic studied was gastrointestinal bleeding in patients with brain injury. The power of the study was 0.80.

Results and Discussion

Autonomic nervous system function was evaluated based on the assessment of PSH (Table 4).

The quantitative parameters assessed in the study are summarized in Table 5.

Logistic regression tools were used to build a model to assess the risk of upper GI bleeding.

This model helped to calculate the probability of overt upper GI bleeding as a function of the severity of a given set of parameters. The positive effect was predicted at $y>0.5$ and the negative effect was predicted at $y\leqslant 0.5$.

We determined the strength of the effect of a single factor or group of factors on the probability of occurrence of the expected event (overt bleeding). The logistic function was calculated as

$$\Psi=A1\times X1+A2\times X2+A3\times X3+A4\times X4+B$$ [20–22].

The parameters of the logistic function Ψ of the optimal model are shown in Table 6.

Using the coefficients from the table, we obtained Ψ to estimate the risk of GIB in patients with brain injury of various etiologies. The formula obtained was

$$\Psi=0.029\times X1+8.69\times X2+0.1\times X3+6.07\times X4-15.27$$

Each of the regression coefficients describes the magnitude of the contribution of the corresponding factor. A positive regression coefficient indicates a factor which elevation increases the overall risk. A negative coefficient indicates a factor that decreases risk as its value drops. The magnitude

Table 3. The most significant parameters for building a model of the GIB risk.

Parameter	Abbreviation
Karnofsky scale on admission to the hospital	KAROA
Performing neurovegetative stabilization regardless of PSH manifestations (0 — no; 1 — yes)	NVS
Peptic (gastric and/or duodenal) ulcer disease detected prior to admission (0 — no; 1 — yes)	PUD
Manifestations of PSH 24 hours after brain injury	PSH1

Table 4. PSH scores at 1,3 and 5 days after brain injury (*M±SD*); (*min÷max*).

Parameter	Values in the groups		*P*
	Without GIB, *N*=22	With GIB, *N*=11	
PSH1	0.27±0.70(0÷2)	3.09±2.02 (1÷7)	<0.001
PSH3	0.42±0.77 (0÷2)	2.36±1.80 (0÷5)	0.003
PSH5	0.44±0.77 (0÷2)	2.55±1.37 (0÷5)	<0.001

Примечание. PSH1, 3, 5 — manifestations of paroxysmal sympathetic hyperactivity 1, 3, 5 days after brain injury. Presented are *M±SD* and range (in brakets).

Table 5. Quantitative parameters in the studied groups.

Parameter	Характеристики	Values in the groups		*P*
		Without GIB, *N*=22	With GIB, *N*=11	
Karnofsky Index on admission to the hospital	*M±SD*	77.73±21.59	41.82±23.16	0.001
	min÷max	20÷90	20÷80	
	Me (*LQ*; *UQ*)	90 (80; 90)	40 (20; 60)	
Manifestations of PSH 24 hours after brain injury	*M±s.d*	0.27±0.70	3.09±2.02	<0.001
	min÷max	0÷2	1÷7	
	Me (*LQ*; *UQ*)	0 (0; 0)	2 (2; 5)	

Table 6. Factors for assessing the risk of overt bleeding.

Parameters of the model	Designation of variables	Value of coefficients A1-A4	Rank of predictive value
KAROA	X1	0.029	2
NVS	X2	8.69	3
PUD	X3	0.1	4
PSH1	X4	6.07	1
Intercept	B	–15.27	—

of the regression coefficients determines the impact on overall risk. Prognostic significance is a «side effect» of model building [18–20].

The constructed model includes the following values: χ^2=33.78, 3; P<0.001; odds ratio 315 (95% CI: 11.8–8,400). Increased 95% CI is explained by the small sample size. We calculated the key features of the model including sensitivity 90.9%, specificity 100%, diagnostic accuracy 97.0%, positive predictive value 100%, negative predictive value 95.7%.

Thus, a comprehensive assessment of the risk of the upper GI bleeding for an individual patient depends on all the parameters included in the equation. The importance of some parameters may be balanced by the contribution of others.

The key values of Ψ were used to assess the risk of GIB: Ψ<–2.94 indicated the risk of less than 5%, Ψ<0 indicated the risk of less than 50%, Ψ>0 indicated the risk of more than 50%, while Ψ>2.94 represented the risk of more than 95% (see Fig. 1).

Using the classification tree building module, we identified critical threshold criteria. Figure 2 shows how the threshold for the Karnofsky index and PSH was determined when the patient was admitted to the hospital.

Risk factors for the development of overt GI bleeding and their thresholds were as follows: KAROA⩽75 (OR=34.0), NVS=1 (OR=10.0), PUD=1 (OR=17.5), PSH1⩾1 (OR=128.1).

Figure 3 illustrates the variations in the risk of GIB in relation to changes in several parameters. The efficiency of the identified thresholds is demonstrated in Table 7.

Performance testing of the model on the test group showed that there were no false negatives and only one false positive. The characteristics of the obtained model of GIB risk assessment in the test group were as follows: sensitivity — 100%, specificity — 83.3%, diagnostic accuracy — 90%, positive predictive value — 80%, negative predictive value — 100%.

Meanwhile, the positive Ψ values in 4 patients with GIB were in the range of 6.24–24.45, indicating a risk of GIB of more than 95%. The positive value of Ψ in one patient without GIB could be explained by the greater adaptive capacity of this 19-year-old individual or by the influence of as yet unidentified genetic factors.

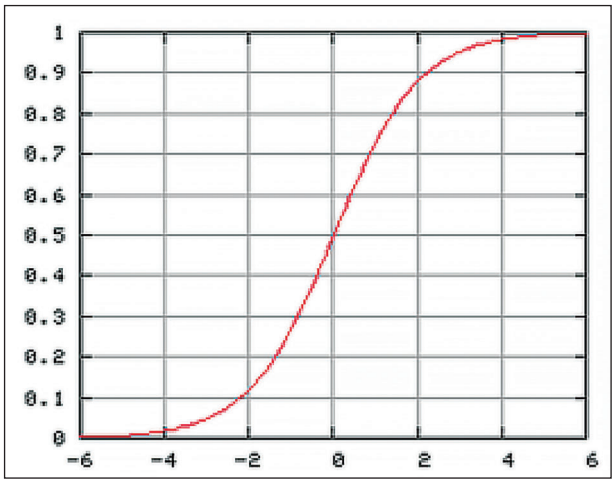

Fig. 1. Logistic curve.
Note. To assess the risk of GIB, Ψ (horizontal axis) was calculated from real data (X1–X4), and then y = exp(Ψ) / (1 + exp(Ψ)) was calculated using the logistic curve, and the probability of GIB was determined (vertical axis).

Table 7. Frequency of GIB with respect to risk factors.

Number of points	Values in groups, *N* (%)		Total, *N*	*P*
	Without GIB, 22 (66.67)	With GIB, 11 (33.33)	With and without GIB, 33	
Performing neurovegetative stabilization regardless of PSH manifestations (0 — no; 1 — yes)				
0	11 (91.67)	1 (8.33)	12	0.007
1	11 (52.38)	10 (47.62)	21	
Peptic (gastric and/or duodenal) ulcer disease detected prior to admission (0 — no; 1 — yes)				
0	21 (77.78)	6 (22.22)	27	0.046
1	1 (16.67)	5 (83.33)	6	
Karnofsky Index on admission to the hospital				
>75	17 (94.44)	1 (5.56)	18	<0.001
⩽75	5 (33.33)	10 (66.67)	15	
Manifestations of PSH 24 hours after brain injury				
<1	19 (100.00)	0 (0.00)	19	<0.001
⩾1	3 (21.43)	11 (78.57)	14	

Note. Fisher's criterion was used in the calculations.

Limitations of the presented model include a wide (95%) confidence interval due to the small sample size, sensitivity of 90.7%, power of 0.80, use of a history parameter (history of GI mucosal injury), correlated predictors (manifestations of PSH and neurovegetative stabilization), scale-based assessment of PSH.

Conclusion

The logistic regression model predicted the risk of GIB in patients with brain injury of different etiology with high sensitivity, accuracy and specificity. Significant risk factors for GIB included PSH severity on day 1 after brain injury, history of gastric mucosal injury, and Karnofsky index at hospital admission. Thus, identification of risk factor thresholds allows stratification of patients into risk groups for development of upper GI bleeding, while management of risk factors may help reduce the incidence of upper GI bleeding in patients with brain injury.

Supplement

The following 70 parameters were analyzed: sex, age of the patient; number of full days of neurovegetative stabilization without and with the administration of a sedative; length of hospital stay; Karnofsky Index scores on admission to the hospital, on admission to the intensive care unit, and on discharge; PSH scores on admission to the hospital; FOUR scores on admission to the intensive care unit; systolic blood pressure on admission to the intensive care unit; systolic blood pressure on admission to the hospital; the fact of prescription and timing of neurovegetative stabilization before the manifestations of paroxysmal sympathetic hyperactivity and after their appearance; repeated brain surgery; death; pneumonia; lung ventilation longer than 24 and 48 hours; temporary tracheostomy; cerebral edema and cerebrospinal fluid flow abnormalities on CT or MRI; ventriculoperitoneal shunt; systemic inflammatory response; meningitis; hepatitis; recurrent hemorrhagic lesions of the brain; administration of anticoagulants, antiplatelet agents, corticosteroids, administration of corticosteroids at a dose of more than 8 mg per day for 2 days, administration of non-steroidal anti-inflammatory drugs more than once per day for at least 3 days, administration of proton pump inhibitors, antacids, H2 histamine antagonists, upper endoscopy prior to hospitalization; history of gastric and/or duodenal ulcer disease; blood in stool and/or vomit during hospitalization; tube feeding during treatment; coagulopathy; sepsis; increase in urea and creatinine levels more than 1.5 times the upper limit of normal; hemoglobin and

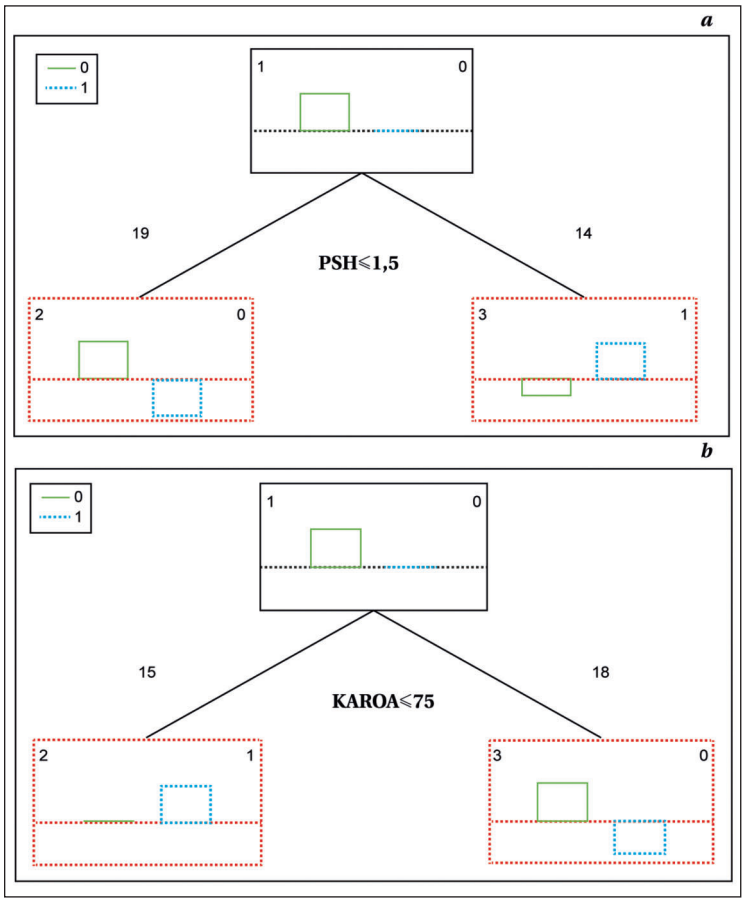

Fig. 2. Example of classification tree construction for PSH (*a*) and Karnofsky index (*b*) at patient admission to the hospital.
Note. Rectangles represent parts of classification trees; black solid lines represent splits; red dashed lines represent terminal nodes; green solid line represents a class without overt GI bleeding; blue dashed line represents a class with overt GI bleeding; numbers above rectangles indicate the number of observations that fell into nodes from the split; the number in the upper left corner of the rectangle is the ordinal number of the node; the number in the upper right corner indicates the predicted class.

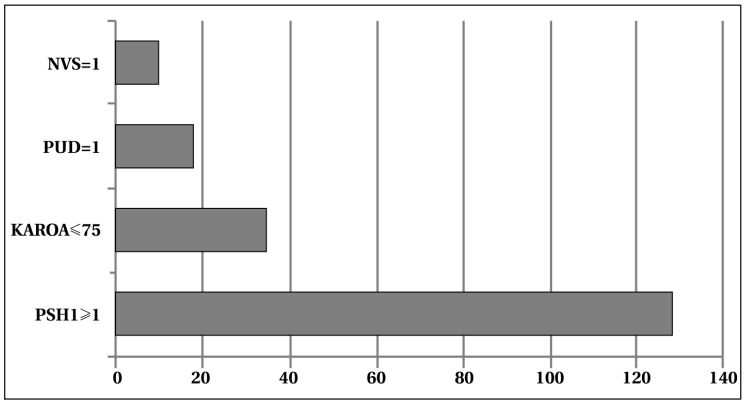

Fig. 3. Variation of the risk of GIB with changes in some parameters.

lactate levels on admission to hospital and after confirmation of brain injury; changes in vegetative (Kerdo) index and Glasgow Coma Scale scores during different periods; manifestations of PSH during different periods; inotropic support during hospitalization; body mass index; diabetes mellitus; documented mucosal lesions of the upper GI tract; documented gastrointestinal bleeding (blood in stool and/or vomiting with blood); documented clinically significant gastrointestinal bleeding.

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Features of Mechanical Lung Ventilation During Robot-Assisted Radical Prostatectomy in Patients with Different Body Mass Index

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Summary

The aim of the study. To evaluate effects of carboxyperitoneum and steep Trendenburg position on respiratory biomechanics and gas exchange indicators in patients with different body mass index (BMI) during robotic-assisted radical prostatectomy (RRP). To develop an algorithm for choosing the optimal mechanical lung ventilation (MLV) regimen.

Materials and methods. The study included 141 patients with verified prostate cancer who were candidates for RPR. Participants were divided into 2 groups based on BMI: group I included 88 patients with BMI<30 kg/m^2, group II — 53 patients with BMI≥30 kg/m^2. Indicators of respiratory biomechanics and gas exchange during ventilation in various modes (Volume Controlled Ventilation (VCV), Pressure Controlled Ventilation (PCV), Pressure Controlled– Inverse Ratio Ventilation (PC-IRV) were analyzed in each group at 5 consecutive stages of the procedure.

Results. The key parameters evidencing the effectiveness and safety of MLV during RRP procedure did not vary significantly under various ventilation regimens in the group of patients with a BMI<30 kg/m^2. Whilst in obese patients the use of VCV mode resulted in a significant increase of airway peak pressure (P_{peak}) already at the stage of placing them into a steep Trendelenburg position (35°), thus endangering with the development of ventilator-induced lung injury. Increased Ppeak was also accompanied by the drop in oxygen saturation and significantly lower SpO_2 values, starting from the stage of applying carboxyperitoneum and until the end of surgical intervention.

Conclusion. In non-obese patients, there's no particular ventilator regimen that is crucial for achieving the safety and effectiveness of RRP anesthesia management, all regimens can be used. In patients with BMI≥30 kg/m^2 PCV regimen and PC-IRV with inhalation/exhalation ratio of 1.5:1
can be considered as the optimal strategy for MLV during anesthesia for RRP surgery.

Keywords: robotic-assisted prostatectomy; Trendelenburg position; respiratory support; obesity

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

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Introduction

Today, radical prostatectomy is the «gold standard» treatment for localized prostate cancer (PC). In recent years, robotic-assisted surgery has become an important alternative in the treatment of PC patients [1].

One of the prerequisites for optimal visualization of the surgical field during robotic prostatectomy is CO_2 pneumoperitoneum. The optimal «working» pressure of carbon dioxide, from the point of view of patient safety and surgeon comfort, is 12 cm H_2O or less. At the time of port placement and suturing of the dorsal venous complex, a short-term increase to 15 cm H_2O may be acceptable. The second requirement is to place the patient in the Trendelenburg position (with the operating table tilted up to 40°) [2–4]. Each of these factors, alone or in combination, induces important changes in various organs and systems (primarily respiratory, cardiovascular, and excretory) and requires a timely response to prevent the development of life-threatening conditions [4, 5]. To date, there are only a few clinical studies on the effect of long-term pneumoperitoneum and Trendelenburg position on the patient's physiological parameters [6, 7].

The effect of the Trendelenburg position on the respiratory system may be due to the cranial displacement of the diaphragm when the head end of the table is tilted at the 30° to 45° angle used in operating rooms. This reduces lung compliance. The Trendelenburg position also has a negative effect on ventilation, reducing functional residual capacity [8].

During prolonged ventilation, regardless of the initial status of the lung, the negative effect of ventilatory support on the lung gradually becomes apparent, eventually leading to a serious disturbance

in ventilation-perfusion relationships. The greatest negative effect of ventilation on the lung is caused by high peak inspiratory pressure [9–11].

There are two ways to perform controlled ventilation during robotic-assisted radical prostatectomy (RARP), either pressure-controlled ventilation (PCV) or volume-controlled ventilation (VCV), with ventilatory support performed with an inverted inspiratory-expiratory ratio [12, 13].

Both modes compensate for the effects of pneumoperitoneum and abnormal positioning, allowing the patient's breathing and hemodynamics to be maintained in the normal range during surgery. C. C. Balick-Weber et al. studied the effects of PCV mode ventilation versus VCV mode ventilation during prostatectomy and found no hemodynamic advantage of one mode over the other. However, pressure-controlled ventilation decreased peak pressure and increased mean airway pressure during surgery. In addition, patients undergoing pressure-controlled ventilation had a significant increase in dynamic lung compliance compared to those on volume-controlled ventilation [14].

This study was replicated during RARP by E. M. Choi et al. They reported that the PCV mode had no advantage over the VCV mode in terms of respiratory mechanics or hemodynamics, except for better adherence to mode parameters and lower peak airway pressure. In this study, the development of hypoxemia during Trendelenburg with pneumoperitoneum was associated with an increase in dead airway space [15]. The use of PCV mode is recommended for obese patients and patients with pulmonary diseases, because their peak pressure in Trendelenburg position with pneumoperitoneum very often reaches a critical value (40 cm H_2O or more). Dangerous increase in peak pressure (>40 cm H_2O) can lead to pulmonary barotrauma, which is associated with alveolar destruction, release of inflammatory mediators, pneumothorax, increased permeability of pulmonary capillaries, microhemorrhages in the pulmonary interstitium [16–19].

Often the selected ventilation mode is ineffective and does not provide adequate oxygenation of the arterial blood. In this case, an attempt to further increase the controlled pressure ($P_{control}$), positive end-expiratory pressure (PEEP), inspired oxygen fraction (FiO_2) either does not lead to an improvement in blood oxygenation or requires reaching very high values ($P_{control}$>35 cm H_2O, PEEP 10–12 cm H_2O, FiO_2>60%). Some authors recommend the use of ventilation with an inverted inhalation/exhalation ratio in such situations [18]. Our experience, combined with the results of recent large randomized trials, shows that the optimal value of PEEP during ventilation in RARP is 5 cm H_2O [20, 21].

One of the most challenging patient groups (especially for teams with little experience in robotic surgery) are obese patients with a BMI over 30, which is associated with additional difficulties during anesthesia. In a study by A. L. Wiltz, obese patients had an increased intraoperative conversion rate compared to non-obese patients (2.3% vs. 0.9%, respectively), which was associated with increased airway pressure in 80% of cases. In general, these patients often have reduced pulmonary function and are prone to develop postoperative respiratory complications [22]. According to D. Meininger, arterial oxygenation is significantly impaired during laparoscopic surgery in the Trendelenburg position in overweight and obese patients (BMI greater than 25–30) [23]. An anesthesiologist can anticipate and prevent the development of a similar situation during anesthesia in obese PC patients undergoing RARP.

Aim of the study: To evaluate the effect of CO_2 pneumoperitoneum and Trendelenburg position on respiratory mechanics and gas exchange parameters in PC patients with different body mass indexes during robotic-assisted radical prostatectomy (RARP) and to develop an algorithm for selecting the optimal mode of respiratory support.

Materials and Methods

After approval by the Ethics committee of the Federal Research Center of Intensive Care Medicine and Rehabilitology, No. 5/20/6 dated December, 23, 2020 and obtaining written informed consents, 141 patients with verified diagnosis of prostate cancer who were to undergo RARP in 2022, were included in a prospective observational study.

The scheme of the study is presented in the Figure.

Study inclusion criteria:

— PC diagnosed using clinical, laboratory, instrumental and histological methods;

— elective RARP;

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

—signed informed consent to participate in the study.

Exclusion criteria:

— refusal to participate in the study or to sign the informed consent form;

— ASA anesthesia risk score⩾3;

— chronic non-specific lung diseases and/or respiratory insufficiency 2–3 degrees;

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

Patients were divided into 2 groups according to body mass index (BMI): group 1 included 88 subjects with BMI<30, group 2 included 53 participants with BMI⩾30. Respiratory mechanics and gas exchange parameters were studied in each group. Patients in each group were divided into 3 subgroups according to the ventilation mode used (VCV, PCV, PCV-IRV).

Respiratory biomechanics and gas exchange parameters were analyzed at the following key stages of surgery:

Stage 1: induction of anesthesia, horizontal position;

Stage 2: installation of CO_2 pneumoperitoneum, trocar placement;

Stage 3: 35° Trendelenburg position, 5 min after the start of the operation;

Stage 4: 45 min from the moment of bringing to the maximum Trendelenburg position;

Stage 5: horizontal position, end of surgery, pneumoperitoneum desufflation.

At each of the key stages, the following parameters were recorded:

— end-tidal carbon dioxide ($EtCO_2$), mm Hg;
— respiratory rate (RR), min^{-1};
— tidal volume (V_t), mL;
— peak airway pressure (P_{peak}), cm H_2O;
— mean airway pressure (P_{mean}), cm H_2O;
— blood oxygen saturation (SpO_2), %.

After the patient was transported to the operating room, standard monitoring (electrocardiogram, non-invasive blood pressure, pulse oximetry) was started.

The dosage of drugs for combined endotracheal anesthesia was calculated based on ideal body weight. All patients received standard premedication on the operating table with 100% oxygen inhalation through a face mask with a flow of 6–8 L/min, consisting of 0.1% atropine sulfate (0.01–0.02 mg/kg), 0.2% clemastine (0.03–0.05 mg/kg), midazolam (0.02–0.06 mg/kg), 0.005% fentanyl (1–3 μg/kg). Anesthesia was induced by propofol at 1.5–2.5 mg/kg until target BIS values of 30-40 were achieved.

While in anesthesia, patients received a calculated dose of the non-depolarizing myorelaxant rocuronium bromide 0.5 mg/kg and underwent tracheal intubation with an 8.0–9.0 endotracheal tube. Because of the risk of displacement of the distal end of the endotracheal tube toward the carina and development of single-lung ventilation after the patient was placed in the Trendelenburg position, mandatory auscultatory monitoring was performed at all stages of patient positioning. After tracheal intubation, a nasogastric tube was placed to minimize the risk of traumatic injury to the stomach during trocar placement and to prevent the development of postoperative nausea and vomiting. Anesthesia was maintained with the inhalational anesthetic sevoflurane (Sevoran®), with BIS maintained in the range of 40–50. Myorelaxation was achieved by bolus injection of calculated doses of rocuronium bromide. Lung ventilation was performed using a Drager Primus apparatus (Dragerwerk, Germany) with an oxygen-air mixture (0.4/0.6) at a flow of 1 L/min in modes specific to each subgroup of patients. Respiratory rate settings during anesthesia were adjusted to achieve an optimal expiratory pCO_2 of 4.9–6.4 vol%. To maintain normocapnia, we took into account the constant inhalation of CO_2 through the robotic trocar port and its inevitable entry into the bloodstream, followed by the adjustment of ventilation parameters [24].

At the end of surgery, all patients were extubated and transferred to the recovery room for symptomatic management and clinical and laboratory monitoring.

RARP was performed using the da Vinci Si system (Intuitive Surgical, Mountain View, USA). After tracheal intubation, the patient was placed in the lithotomy position, and special soft fixators were placed under the patient's shoulders to limit his displacement relative to the operating table during surgery. Five ports were placed in the abdominal cavity for CO_2 pneumoperitoneum with an initial CO_2 pressure of 15 mm Hg. At the end of this phase and after the patient was placed in the Trendelenburg position, the gas pressure in the abdominal cavity was reduced to a safe level of 12 mm Hg.

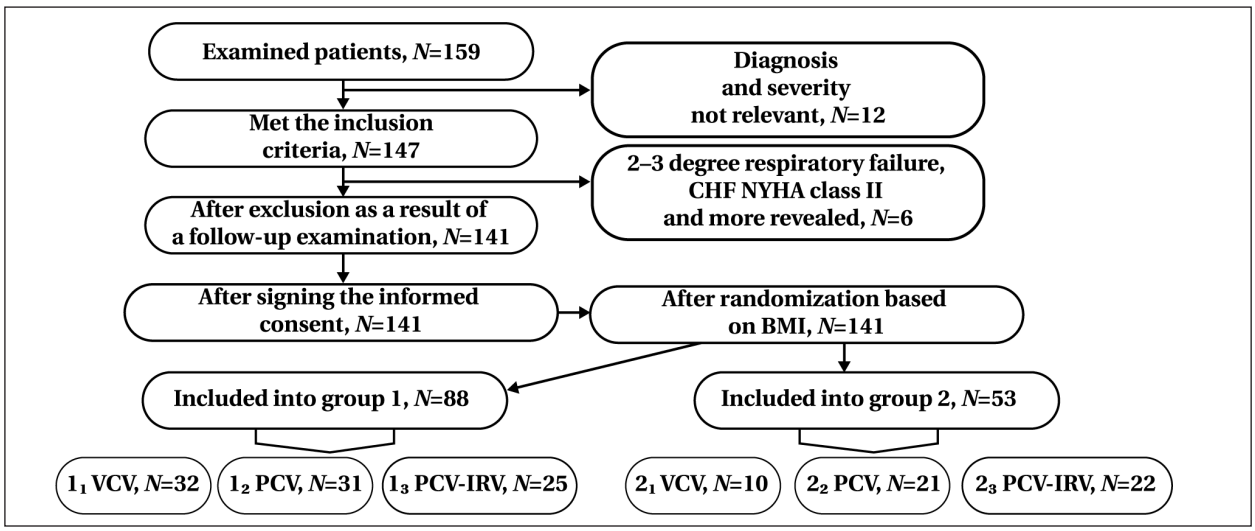

Fig. Flowchart of the study.

The sample size was determined by achieving a minimum statistical power of 80% and a first-order error of 5% according to the formula of Lopez-Jimenez F. et al. (1998). The study in group 1 (subgroup 1) was prematurely terminated after results indicating a high risk of lung volutrauma were obtained. Statistical analysis of the data was performed using Excel 2016 (Microsoft, USA) and SPSS Statistica v. 24 (IBM, USA). The Kolmogorov-Smirnov criterion with Lilliefors correction was used to test the distribution of quantitative variables for normality. Variables with normal distribution were described as mean and standard deviation (*M*±*SD*). Variables with non-normal distribution were reported as median and interquartile range (*Me* [*Q25*; *Q75*]). Qualitative parameters were expressed as absolute and relative values (*N* (%)). Significance of the difference between the studied groups for quantitative variables with normal distribution was evaluated using the Student's *t*-criterion for independent samples, in case of non-normal distribution using the Mann–Whitney criterion. The reliability of intragroup differences for repeated measurements of normally distributed parameters was assessed using Student's *t*-criterion for paired samples. One-way analysis of variance (ANOVA) was used to compare normally distributed data between three or more groups, and Kruskal-Wallis analysis of variance was used for non-normal distribution. Pearson's χ^2-squared test or Fisher's exact two-sided test for small samples was used to compare groups on qualitative variables. Differences were considered statistically significant at $P<0.05$, where P is the probability of a first-order error in testing the null hypothesis. The Bonferroni correction was used to control for the probability of a first-order error (error in rejecting the correct null hypothesis) in multiple comparisons.

Results and Discussion

The mean age of patients was 57.44±5.09 years in subgroup 1_1, 57.35±5.40 years in subgroup 1_2, and 56.60±4.35 years in subgroup 1_3 (P=0.84). The mean age of patients was 56.60±4.04 years in subgroup 2_1, 57.48±6.00 years in subgroup 2_2, and 57.86±5.09 years in subgroup 2_3 (P=0.39). The distribution of patients by age in the groups is shown in Table 1.

The BMI of the patients in the subgroups of both groups was also comparable. The median BMI was 27.0 [24.5; 29.0] in subgroup 1_1, 28.5 [24.25; 29.45] in subgroup 1_2, and 28.2 [25.15; 29.0] in subgroup 1_3 (P=0.12).

The median values in subgroups were as follows: subgroup 2_1 — 34.5 [31.25; 35.15], subgroup 2_2 — 33.25 [30.5; 35.0], subgroup 2_3 — 34.0 [31.2; 36.0] (P=0.20).

The distribution of patients by ASA is shown in Table 2. Two thirds of the included patients had ASA anesthesia risk grade 2, the differences between the groups were not significant.

When studying the respiratory biomechanics and gas exchange parameters in patients with normal BMI (Table 3) on volume-controlled ventilation (VCV), we came to the conclusion that its use in normal ventilation parameters can be considered quite safe (the maximum value of Ppeak recorded at the 4th stage of the study was 30.4±3.1 cm H_2O) and fully satisfies the physiological needs of the organism in providing adequate respiration (the minimum recorded value of SpO_2 was 96.2±3.0%). The PCV mode, used in patients with normal body mass index, also provided adequate oxygenation (the minimum SpO_2 value recorded was 96.0±1.3%) and the desired safety (the maximum P_{peak} value at stage 4 of the study was 28.5±5.6 cm H_2O). Pressure-controlled ventilation, but with inverted inspiration-expiration ratio (PCV-IRV), also created conditions to prevent pulmonary barotrauma (maximum P_{peak} value at stage 4 of the study was 29.1±2.3 cm H_2O), indicating that it could be used in patients without obesity, which is also in agreement with the study by L. Ashwort [25].

Thus, the stability of respiratory parameters in patients without obesity, regardless of the selected mode of ventilation under increased load from pneumoperitoneum and Trendelenburg position, demonstrated the adequacy and safety of anesthesia

Table 1. Distribution by age, *N* (%).

Age, years	Values in groups								*P*
	Group 1 and subgroups				Group 2 and subgroups				
	1_1, *N*=32	1_2, *N*=31	1_3, *N*=25	Total, *N*=88	2_1, *N*=10	2_2, *N*=21	2_3, *N*=22	Total, *N*=53	
45–50	—	2 (6.7)	3 (12.0)	5 (5.7)	1 (10.0)	2 (9.5)	1 (4.5)	4 (7.5)	0.73
51–55	13 (43.3)	11 (36.7)	7 (28.0)	31 (35.2)	2 (20.0)	7 (33.3)	9 (40.9)	18 (34)	0.88
56–60	14 (46.7)	12 (40.0)	11 (44.0)	37 (42.0)	6 (60.0)	8 (38.1)	8 (36.4)	22 (41.5)	0.95
61–65	3 (10.0)	3 (10.0)	4 (16.0)	10 (11.4)	1 (10.0)	—	3 (13.6)	4 (7.5)	0.57
66–70	—	2 (6.7)	—	2 (2.3)	—	4 (19.0)	1 (4.5)	5 (9.4)	0.1
71–75	2 (6.7)	1 (3.3)	—	3 (3.4)	—	—	—	—	0.29

Table 2. Distribution of patients according to anesthesia risk, *N* (%).

ASA	Values in groups								*P*
	Group 1 and subgroups				Group 2 and subgroups				
	1_1, *N*=32	1_2, *N*=31	1_3, *N*=25	Total, *N*=88	2_1, *N*=10	2_2, *N*=21	2_3, *N*=22	Total, *N*=53	
1	6 (18.8)	9 (29.0)	5 (20.0)	20 (22.7)	2 (20.0)	4 (19.0)	6 (27.3)	12 (22.6)	0.84
2	26 (81.3)	22 (71.0)	20 (80.0)	68 (77.3)	8 (80.0)	17 (81.0)	16 (72.7)	41 (77.4)	0.84

Table 3. Respiratory parameters in patients with normal BMI (*N*=88) during surgery with different ventilation modes (*M*±*SD*).

Ventilation mode	Stage				
	1	2	3	4	5
End-tidal carbon dioxide ($EtCO_2$), mm Hg					
VCV	31.1±8.4	34.3±8.1	38.2±8.4	37.7±9.2	40.1±8.9
PCV	32.3±1.2	35.1±1.1	36.7±1.3	36.8±2.5	39.2±4.3
PCV-IRV	33.1±3.2	35.3±1.6	35.2±3.4	36.4±2.1	39.5±3.2
Respiratory rate, min^{-1}					
VCV	9.1±1.7	10.3±1.2	12.5±1.3	12.1±1.1	13.0±1.2
PCV	9.1±0.5	10.2±1.4	12.1±1.6	12.2±1.1	13.6±1.9
PCV-IRV	9.4±1.3	10.3±1.6	11.7±1.2	12.5±1.6	12.6±2.4
Tidal volume (V_t), ml					
VCV	630.1±25.4	640.5±37.2	645.0±32.1	658.3±38.5	690.0±57.2
PCV	615.9±45.7	625.5±52.4	637.2±36.3	690.4±42.1	636.5±54.6
PCV-IRV	620.8±18.3	636.7±31.5	656.2±37.1	649.9±41.4	678.2±37.8
Peak airway pressure (P_{peak}), cm H_2O					
VCV	14.2±3.6	23.8±3.2	29.4±5.3	30.4±3.1	15.7±3.2
PCV	14.4±5.2	22.0±2.1	27.4±6.8	28.5±5.6	14.3±6.8
PCV-IRV	12.2±4.1	21.4±4.5	27.7±4.5	29.1±2.3	13.7±5.1
Mean airway pressure (P_{mean}), cm H_2O					
VCV	9.8±1.1	13.1±2.4	15.1±4.7	16.4±4.1	8.3±3.1
PCV	10.1±1.1	16.3±3.4	19.5±4.2	20.7±8.2	11.0±4.4
PCV-IRV	8.7±1.1	11.2±3.6	13.1±5.2	14.3±4.5	7.7±5.2
Blood oxygen saturation (SpO_2), %					
VCV	97.1±1.3	96.2±3.0	97.2±6.4	97.1±1.0	98.5±2.6
PCV	97.5±1.2	96.0±1.3	97.7±0.8	97.4±1.1	99.5±2.0
PCV-IRV	98.4±1.1	97.2±3.0	97.5±4.1	98.8±3.3	98.4±3.1

Note. The *P* values for pairwise comparisons of respiratory parameters at different stages of surgery are shown in Tables 5 and 7.

support of RARP adjusted to timely correction of ventilation parameters at different stages of surgery. In all patients with normal body mass index, regardless of the chosen mode of respiratory support, it was necessary to correct RR and V_t upward to prevent hypoventilation in the stages from pneumoperitoneum to extubation. The $EtCO_2$ values remained within the acceptable physiological range throughout the operation, but at the end of the operation their regular and significant increase was observed, requiring a slight correction of the ventilatory parameters towards hyperventilation (increase in respiratory rate and tidal volume).

The choice of ventilatory mode in this group of patients was not of fundamental importance, since any of them allowed to provide acceptable blood oxygenation without using high toxic concentrations of oxygen and preventing the risk of barotrauma. Continuous dynamic monitoring of respiratory homeostasis parameters and timely correction of ventilator parameters depending on the stage of the operation and the patient's organism response were of the utmost importance.

The choice of ventilator mode in patients with BMI⩾30 was crucial for safe anesthesia. Due to the excessive increase of the peak airway pressure (Table 4), the maximum P_{peak} at stage 4 of the study was 38.2±3.1 cm H_2O when using the controlled-volume mode, there was a real risk of lung volutrauma, which is unacceptable within the concept of safe anesthesia. The results obtained contributed to the termination of the study in this subgroup. This mode of ventilation cannot be considered safe enough to fully satisfy the physiological needs of the organism to provide adequate breathing in patients with excessive body weight.

Pressure-controlled ventilation in obese patients met the criteria of adequacy and safety (the maximum P_{peak} at the 4th stage of the study was 33.7±2.10 H_2O, the minimum recorded value of SpO_2 was 95.7±2.2%), but after the end of surgery, in order to completely eliminate the accumulated carbon dioxide, one should not rush with early extubation and weaning. In comparison with the standard PCV ventilation, PCV with inverse inhalation/exhalation ratio allowed to obtain lower values of peak pressure (the maximum P_{peak} at the 4th stage of the study was 31.7±3.1 cm H_2O) in patients with excess body weight, thus reducing the probability of barotrauma, while the blood oxygenation parameters did not decrease, with SpO_2 being even higher at the 2nd and 4th stages of the operation. The mean hospital stay of the patients in both groups did not differ and was 7±1 days.

Conclusion

In PC patients without obesity the choice of a specific ventilation mode is not crucial to achieve safety and efficiency of anesthesia support in RARP. Controlled-pressure ventilation and its variant with inversion of the inhalation/exhalation ratio (1.5:1) can be considered the optimal method of ventilatory support during anesthesia for RARP in PC patients with BMI ⩾30.

Table 4. Respiratory parameters of obese patients (*N*=53) throughout surgery with different modes of ventilation (*M*±*SD*).

Ventilation mode	Stage				
	1	2	3	4	5
End-tidal carbon dioxide ($EtCO_2$), mm Hg					
VCV	34.4±3.2	37.3±1.8	40.2±1.8	42.3±2.6	44.3±2.4
PCV	33.6±2.5	34.4±1.4	42.1±2.3	41.5±2.9	43.3±1.6
PCV-IRV	32.7±1.6	33.8±0.8	41.6±1.7	42.1±2.1	42.6±1.4
Respiratory rate, min^{-1}					
VCV	12.6±0.5	14.0±1.2	15.0±1.1	16.4±1.3	16.2±1.6
PCV	12.1±2.3	13.5±0.8	16.3±1.3	17.0±2.2	16.2±0.8
PCV-IRV	13.7±1.8	13.1±1.3	16.2±2.2	16.3±3.3	15.2±0.8
Tidal volume (V_t), ml					
VCV	610.8±9.1	600.3±13.4	605.9±21.5	565.7±23.4	629.1±34.3
PCV	600.7±18.4	580.7±31.8	608.7±24.5	595.9±29.1	646.3±26.4
PCV-IRV	616.5±27.7	591.7±39.2	589.5±45.1	596.2±47.3	637.7±37.9
Peak airway pressure (P_{peak}), cm H_2O					
VCV	16.3±2.2	31.1±2.1	37.0±4.5	38.2±3.1	16.7±4.2
PCV	15.2±1.1	33.5±1.1	32.2±2.1	33.7±2.1	16.5±3.0
PCV-IRV	14.4±1.1	30.2±1.3	30.5±2.1	31.7±3.1	15.5±3.0
Mean airway pressure (P_{mean}), cm H_2O					
VCV	11.1±2.1	18.4±2.1	22.6±3.3	23.2±4.3	10.2±5.1
PCV	10.4±2.3	21.1±3.3	22.4±2.4	23.5±3.1	9.7±3.4
PCV-IRV	11.4±1.2	22.1±4.4	19.8±5.1	21.7±4.1	11.1±3.4
Blood oxygen saturation (SpO_2), %					
VCV	96.8±1.2	94.7±1.1	93.7±2.0	93.8±1.4	96.9±2.1
PCV	96.8±1.9	95.7±2.5	96.5±3.6	95.7±2.2	97.5±1.3
PCV-IRV	96.4±4.1	96.5±1.2	96.4±3.1	97.7±1.4	97.8±3.1

Note. The *P* values for pairwise comparisons of respiratory parameters at different stages of surgery are shown in Tables 6 and 7.

Supplement

Table 5. *P*-values for pairwise comparisons of respiratory parameters at different stages of surgery in patients with normal BMI (*N*=88) and with different modes of ventilation (*M*±*SD*).

Ventilation mode	Stage									
	1–2	1–3	1–4	1–5	2–3	2–4	2–5	3–4	3–5	4–5
End-tidal carbon dioxide ($EtCO_2$), mm Hg										
VCV	0.06	<0.001	<0.001	<0.001	0.08	0.02	0.01	0.41	0.14	0.21
PCV	0.37	0.03	0.004	<0.001	0.19	0.12	0.04	0.84	0.02	0.03
PCV-IRV	0.19	0.05	0.06	<0.001	0.74	0.17	0.09	0.34	0.03	<0.001
Respiratory rate, min^{-1}										
VCV	0.11	<0.001	<0.001	<0.001	0.01	<0.001	<0.001	0.52	0.06	0.01
PCV	0.02	<0.001	<0.001	<0.001	0.002	0.001	<0.001	0.89	0.03	0.003
PCV-IRV	0.06	<0.001	<0.001	<0.001	0.03	<0.001	<0.001	0.26	0.02	0.83
Tidal volume (V_t), ml										
VCV	<0.001	<0.001	<0.001	<0.001	0.83	0.02	<0.001	<0.001	<0.001	<0.001
PCV	0.43	0.02	<0.001	<0.001	<0.001	0.001	<0.001	<0.001	<0.001	<0.001
PCV-IRV	0.02	<0.001	<0.001	<0.001	0.001	<0.001	<0.001	0.71	<0.001	<0.001
Peak airway pressure (P_{peak}), cm H_2O										
VCV	<0.001	<0.001	<0.001	0.89	<0.001	<0.001	<0.001	0.34	<0.001	<0.001
PCV	<0.001	<0.001	<0.001	0.98	0.06	<0.001	<0.001	0.42	<0.001	<0.001
PCV-IRV	0.003	<0.001	<0.001	0.71	<0.001	<0.001	0.001	0.12	<0.001	<0.001
Mean airway pressure (P_{mean}), cm H_2O										
VCV	<0.001	<0.001	<0.001	0.13	0.01	<0.001	<0.001	0.5	<0.001	<0.001
PCV	<0.001	<0.001	<0.001	0.87	0.004	0.01	<0.001	0.83	<0.001	0.047
PCV-IRV	<0.001	<0.001	<0.001	0.58	0.01	<0.001	<0.001	0.34	0.003	<0.001
Blood oxygen saturation (SpO_2), %										
VCV	<0.001	0.91	0.98	<0.001	0.63	0.03	<0.001	0.93	<0.001	<0.001
PCV	<0.001	0.07	0.68	<0.001	<0.001	0.01	<0.001	0.24	<0.001	<0.001
PCV-IRV	0.10	0.48	0.44	0.99	0.82	0.24	0.19	0.36	0.76	0.85

Table 6. *P*-values for pairwise comparisons of respiratory parameters at different stages of surgery in obese patients (*N*=53) and with different ventilator modes (*M±SD*).

Ventilation mode	Stage									
	1–2	1–3	1–4	1–5	2–3	2–4	2–5	3–4	3–5	4–5
End-tidal carbon dioxide ($EtCO_2$), mm Hg										
VCV	0.002	<0.001	<0.001	<0.001	<0.001	<0.001	0.001	<0.001	0.01	0.21
PCV	0.40	<0.001	<0.001	<0.001	<0.001	<0.001	0.20	<0.001	<0.001	0.03
PCV-IRV	0.17	<0.001	<0.001	<0.001	<0.001	<0.001	0.62	<0.001	0.50	<0.001
Respiratory rate, min^{-1}										
VCV	0.02	<0.001	<0.001	<0.001	0.04	<0.001	<0.001	0.003	0.003	0.67
PCV	0.03	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.19	<0.001	0.41
PCV-IRV	0.67	0.13	0.09	0.01	0.01	0.01	0.001	0.90	0.40	0.13
Tidal volume (V_t), ml										
VCV	0.69	0.01	0.03	0.08	0.004	0.009	0.05	0.95	0.14	0.53
PCV	0.01	0.42	0.21	<0.001	0.04	0.28	<0.001	0.21	<0.001	<0.001
PCV-IRV	0.01	0.001	0.001	<0.001	0.93	0.79	<0.001	0.83	<0.001	<0.001
Peak airway pressure (P_{peak}), cm H_2O										
VCV	<0.001	<0.001	<0.001	0.98	<0.001	<0.001	<0.001	0.79	<0.001	<0.001
PCV	<0.001	<0.001	<0.001	0.78	<0.001	0.53	<0.001	0.20	<0.001	<0.001
PCV-IRV	<0.001	<0.001	<0.001	0.99	0.40	0.001	<0.001	0.13	<0.001	<0.001
Mean airway pressure (P_{mean}), cm H_2O										
VCV	<0.001	<0.001	<0.001	0.79	<0.001	<0.001	<0.001	0.66	<0.001	<0.001
PCV	<0.001	<0.001	<0.001	0.64	0.03	<0.001	<0.001	0.32	<0.001	<0.001
PCV-IRV	<0.001	0.001	<0.001	0.91	0.12	0.61	<0.001	0.14	<0.001	0.005
Blood oxygen saturation (SpO_2), %										
VCV	<0.001	<0.001	<0.001	0.84	<0.001	<0.001	<0.001	0.88	<0.001	<0.001
PCV	0.09	0.70	0.18	0.34	0.79	0.98	0.03	0.69	0.19	0.07
PCV-IRV	0.96	0.99	0.48	0.61	0.98	0.06	0.26	0.19	0.34	0.96

Table 7. *P*-values for pairwise comparisons of respiratory parameters in different modes of ventilatory support during surgery in patients with normal BMI and obesity.

Ventilation mode	With normal body mass index (*N*=88)					With obesity (*N*=53)				
	Stage					Stage				
	1	2	3	4	5	1	2	3	4	5
End-tidal carbon dioxide ($EtCO_2$), mm Hg										
VCV-PCV	0.74	0.71	0.53	0.72	0.83	0.53	<0.001	0.05	0.40	0.32
VCV-IRV	0.39	0.67	0.08	0.70	0.63	0.20	<0.001	0.005	0.94	0.09
PCV-IRV	0.68	0.88	0.42	0.79	0.76	0.27	0.14	0.45	0.60	0.04
Respiratory rate, min^{-1}										
VCV-PCV	0.96	0.88	0.58	0.88	0.40	0.55	0.41	0.09	0.49	0.98
VCV-IRV	0.71	0.97	0.23	0.61	0.69	0.18	0.13	0.18	0.99	0.06
PCV-IRV	0.36	0.90	0.57	0.45	0.38	0.03	0.60	0.95	0.77	0.03
Tidal volume (V_t), ml										
VCV-PCV	0.68	0.49	0.46	0.26	<0.001	0.30	0.42	0.88	0.06	0.19
VCV-IRV	0.26	0.89	0.53	0.76	0.50	0.66	0.77	0.26	0.04	0.86
PCV-IRV	0.64	0.62	0.14	0.13	0.23	0.23	0.66	0.43	0.98	0.77
Peak airway pressure (P_{peak}), cm H_2O										
VCV-PCV	0.92	0.27	0.66	0.56	0.67	0.43	0.04	0.03	0.003	0.88
VCV-IRV	0.37	0.18	0.55	0.37	0.36	0.07	0.65	0.001	<0.001	0.57
PCV-IRV	0.16	0.80	0.96	0.84	0.90	0.28	0.001	0.36	0.18	0.64
Mean airway pressure (P_{mean}), cm H_2O										
VCV-PCV	0.84	0.11	0.15	0.45	0.37	0.46	0.11	0.89	0.77	0.67
VCV-IRV	0.19	0.38	0.75	0.39	0.89	0.73	0.02	0.05	0.37	0.69
PCV-IRV	0.09	0.04	0.01	0.19	0.46	0.27	0.47	0.04	0.14	0.55
Blood oxygen saturation (SpO_2), %										
VCV-PCV	0.32	0.88	0.60	0.46	0.26	0.99	0.36	0.03	0.25	0.52
VCV-IRV	0.05	0.47	0.96	0.002	0.88	0.72	<0.001	0.02	<0.001	0.35
PCV-IRV	0.05	0.19	0.88	0.003	0.19	0.53	0.14	0.93	0.01	0.83

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Postoperative Neurocognitive Disorders: the Legacy of Almost 400 Years of History (Review)

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Summary

The history of the study of postoperative neurocognitive disorders (PND) looks as a long and thorny path of more than 400 years. Despite all accumulated data on PND risk factors and outcomes, there's still no complete understanding of the etiology and pathogenesis of this complication. Moreover, current anesthesiology-resuscitation practice still faces challenges and has pending questions in diagnosis and classification of postoperative neurocognitive disorders.

The purpose of the review. To contemplate the evolution in the perceptions of the international medical community (IMC) regarding diagnostic approaches and algorithms in PND management. The review covers the history of development of such PND concepts as postoperative delirium, postoperative cognitive dysfunction, emergence agitation and emergence delirium. Also, the pre-existing and current international classifications of postoperative neurocognitive disorders are discussed in chronological order, supplemented by the analysis of their strengths and weaknesses. The paper also delves into current viewpoints concerning the etiology of particular postoperative neurocognitive disorders, and PND potential relevance for postoperative outcomes.

Conclusion. Current algorithms and modalities used for PND diagnosis, are novel but yet not ultimate for IMC in the context of continuous progress in medical practice. Early postoperative neurocognitive disorders remain the most poorly studied phenomena with no approved definitions and diagnostic modalities to identify. It is probably the time for IMC to undertake a joint effort to find answers to current unresolved questions regarding postoperative neurocognitive disorders.

Keywords: postoperative neurocognitive disorders; delirium; postoperative delirium; emergence delirium; agitations; postoperative cognitive dysfunction; delayed neurocognitive recovery; classifications

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

Introduction

When it comes to a history of more than 400 years, it is difficult to expect recovering the exact first mention of a phenomenon. We can only assume that the first mention of acute changes in the consciousness of patients after surgery belong to the writings of Ambroise Paré (16th century). He described these complications as «a transient condition that commonly followed fever and pain due to wounds, gangrene, and operations involving severe bleeding of the patient» [1]. A similar condition, «delirium nervosum», was described by another famous surgeon, Baron de Dupuytren (XIX century): «...and finally the brain itself may be seized by pain, terror, or even joy, and reason abandons the patient at the moment when it is most necessary for his well-being that he remain calm and unperturbed» [2]. Interestingly, the first references to postoperative acute transient changes in consciousness appeared several centuries before the discovery of anesthesia. This fact invalidates the current and rather widespread notion that postoperative delirium has been and remains exclusively an anesthesiological problem.

On the other hand, it would be ridiculous to deny that postoperative neurocognitive disorders (PND) are indeed closely related to anesthesia. In 1887, G. Savage suspected a causal relationship between similar cases of «insanity» and later development of «chronic dementia» after nitrous oxide anesthesia in patients of different age groups [3]. In the same year, the American dentist S. Hayes noted the development of «dementia» as a probable

complication of nitrous oxide administration without proper addition of atmospheric air [4]. This was apparently the first time that the «disreputable» role of general anesthesia in the development of PND was suspected.

The body's response to both general anesthesia and surgical stress includes changes in all vital organs and systems, but the main victim of anesthetics is undoubtedly the central nervous system [5]. In 1916, H. D. Bruns published a paper reporting postoperative delirium and subsequent «dementia» in elderly patients undergoing cataract surgery [6]. The question of whether surgery can be a trigger that stimulates the progression of a pre-existing cognitive deficit or whether it initiates cognitive impairment has continued to attract the attention of scientists and remains a relevant problem today, as researchers around the world report a relatively high incidence of cognitive impairment in the postoperative period [7].

Despite the continuing interest in the problem of postoperative neurocognitive dysfunction, a systematic approach to the study of this phenomenon emerged only in the second half of the 20th century and was marked by the emergence of a group of conditions and terms for their designation, although the terms are not widely accepted until today.

Postoperative Delirium (POD)

Background. The rapid development of cardiac surgery, which began in the mid-50s of the last century, became a major impetus for the study of PND. Clinicians discovered that cognitive deficits were particularly common after this type of surgery, significantly complicating the medical and social rehabilitation of patients [8]. The work of P. Blachy and A. Starr (1964) is considered a pioneering study in this area [9]. In addition to identifying several risk factors for the development of PND, the authors noted an extremely high incidence of delirium (57%) and introduced the new concept of «postcardiotomy delirium». The subsequent surge of research activity on risk factors and outcomes of delirium in open heart surgery [10–15] resulted in developing the first classification of postoperative recovery in terms of cognitive status (1970) [16]. S. Heller et al. distinguished 3 variants: «pure» (without abnormalities) cognitive status, early postoperative organic brain syndrome, and postcardiotomy delirium. The term «early postoperative organic brain syndrome» implied impaired orientation in space and time in patients recovering from anesthesia. Importantly, this term had 2 «strict» characteristics, such as:

(1) specific cognitive (not motor) impairment, and

(2) the absence of a lucid interval during recovery from anesthesia.

In other words, the diagnosis of «early postoperative organic brain syndrome» could be made quite accurately, avoiding overly subjective assessments.

However, the term «early postoperative organic brain syndrome» was greeted coldly by contemporaries and soon forgotten, probably for two reasons: first, it was cumbersome and inconvenient to use, and second, after its appearance in 1970, the term competed with concepts such as emergence excitement, emergence agitation (EA), and emergence delirium (ED), which had already been actively used by the medical community for more than 10 years to describe inadequate awakening after surgery [17].

Another author's concept, postcardiotomy delirium, first led researchers to focus on the relationship between cognitive impairment and the timing of surgery, defining postoperative delirium as only that which occurs after a lucid interval of 2 to 5 postoperative days (see Figure). Without adopting the term itself, the medical community adopted the definition and relegated it to the more convenient name of «postoperative delirium» (POD). For the next 10 years, this relationship between the time of onset of delirium and the time after surgery remained the only accurate definition of the condition under discussion.

Notably, the term POD remained «off the radar» of the medical community for a long time. The DSM-1 (1952) [18] and DSM-2 (1968) [19] manuals used the terms «acute cerebral syndrome» and «psychoses,» respectively, which were not widely utilized outside of psychiatry [20]. In addition, no clear diagnostic criteria were proposed to guide researchers.

The most important works of those years that considered the principles of diagnosis of postoperative delirium were the studies of G. Engel and J. Romano [21], and then the work of Z. Lipowski [20].

G. Engel and J. Romano proposed relatively simple test batteries consisting of a small number of questions/answers for the diagnosis of delirium. Some of these questions are still used in modern tests [22–25].

Z. Lipowski, in turn, created criteria for the diagnosis of delirium, which were subsequently adopted by the first clinical guidelines on the problem under discussion [20].

The year 1980 became a milestone in the history of PND research. First, the DSM-3 [26] was published, in which the term «delirium» appeared for the first time to define cognitive impairment. Clear diagnostic criteria for the condition, such as disorientation, fluctuations in cognitive status, sleep-wake cycle disturbances, and others, also appeared [26]. Secondly, Z. Lipowski in his work distinguishes two types of delirium occurring after surgery:

1. Late postoperative delirium, which occurs after a lucid interval of 24 hours after surgery (see Figure), and

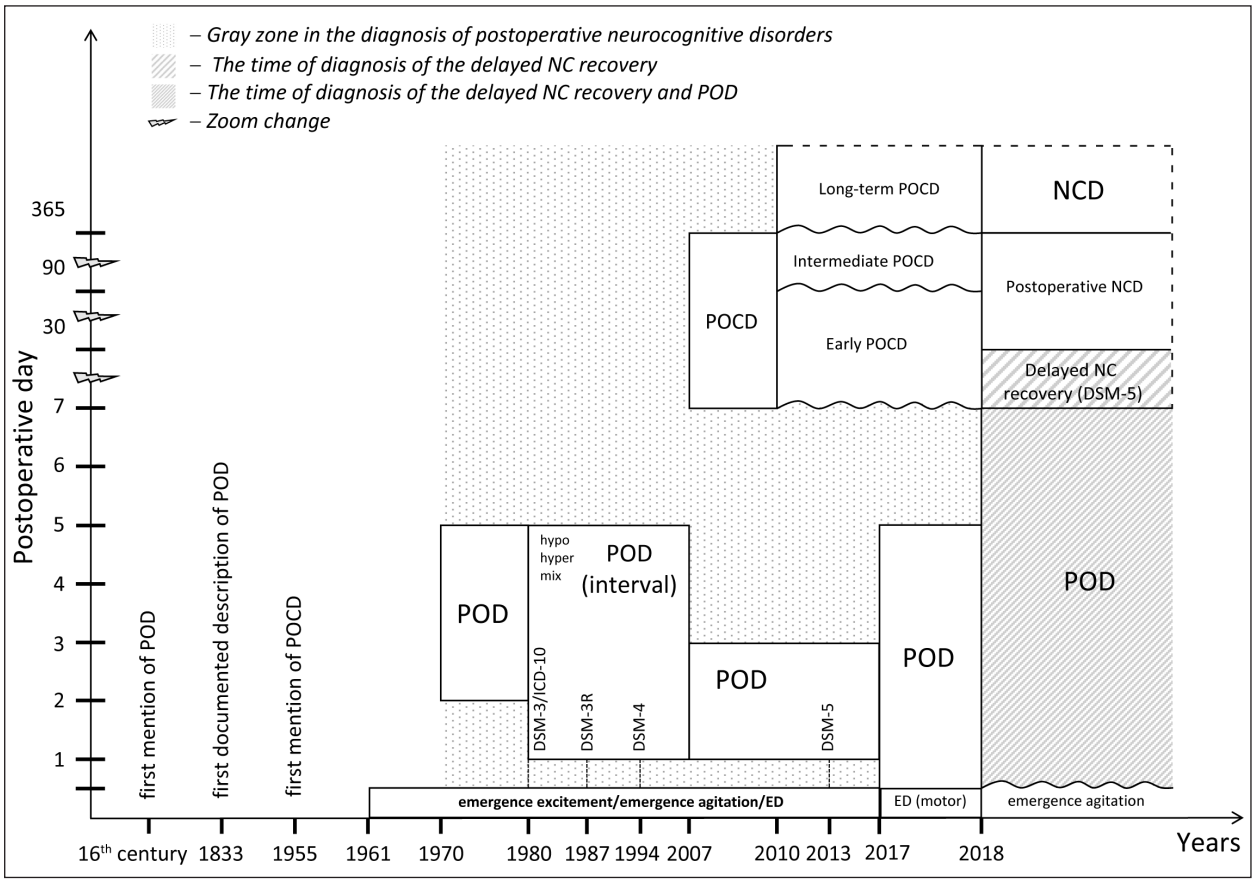

Fig. The timeline of ideas about postoperative neurocognitive disorders.
Note. POD — postoperative delirium; Hypo POD — hypoactive postoperative delirium; Hyper POD — hyperactive postoperative delirium; Mix POD — mixed postoperative delirium; POCD — postoperative cognitive dysfunction; NCD — neurocognitive disorders; NC — neurocognitive; ED — emergence delirium; ED (motor) — emergence delirium after anesthesia, diagnosed using scales to assess patients' motor signs; DSM — Diagnostic and Statistical Manual of Mental Disorders; R — Revised; ICD — International Classification of Diseases.

2. Emergence delirium, which occurs within the first 24 hours after surgery [27].

The term «emergence delirium» in Z. Lipowski's classification has not been widely used in the medical community because it has already been used for a different time interval after surgery. At the same time, Z. Lipowski's definition of late postoperative delirium will become the main definition of POD for the next 30 years. During the same period, the classification of postoperative delirium into hypoactive, hyperactive, and mixed delirium based on clinical manifestations appeared (see Figure) [27]. The emergence of relatively clear and unambiguous definitions of PND triggered the development of the first diagnostic tests, including those for POD. Thus, in 1987, the updated version of DSM-3-R [28] was published, and in 1994, in coordination with ICD-10 [29], DSM-4 [30], which clarified the concept of delirium, defining the extent of cognitive impairment, the rate of its development and evolution as the main characteristics of this condition. By the way, 1994 can be considered as the official year of appearance of the term «postoperative delirium» in the framework of international documents (ICD-10) [29]. On the basis of DSM-3, several scales for the diagnosis of postoperative delirium were created, such as the «Delirium Symptom Interview» [31] and the «Saskatoon Delirium Checklist» [32], which are currently of mostly historical interest.

At the same time, based on the DSM-3-R, the Confusion Assessment Method (CAM), one of the most popular scales for the diagnosis of delirium, was developed in 1990 [33]. This scale is currently so widespread that it has been translated into 10 languages [34]. The scale has a variant for the diagnosis of delirium in ventilated patients, the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) [22, 23]. The current questionnaire for rapid assessment of cognitive status in patients, 3D-CAM (3-minute diagnostic assessment for CAM-defined delirium) [24], is an improved version of the CAM scale. Other well-known delirium assessment tools include the Intensive Care Delirium Screening Checklist (ICDSC), developed in 2001 based on the DSM-4 [35], and the Nursing Delirium Screening Scale (Nu-

DESC), developed in 2005 specifically for nurses [25]. There are several other less popular scales for diagnosing and grading the severity of delirium [36].

The last decade of the 20th century was marked by the study of risk factors and methods of prevention of postoperative delirium. This focus was due to the creation in 1990 of a new method for diagnosing delirium, the Confusion Assessment Method, which was popular among perioperative physicians [33], as well as the appearance of the first significant papers demonstrating the relationship between postoperative delirium and mortality [37].

Anesthesiologists, on the other hand, were primarily concerned with studying the relationship between postoperative delirium and the type of anesthesia and surgical procedure. The key work in this direction was the review by C. Dayer et al. based on the analysis of all publications on the subject between 1966 and 1992 [38]. The authors first determined the approximate frequency of postoperative delirium development (36.8%), emphasized the absence of a unified method of diagnosing this condition, and showed that this situation leads to a high frequency of missed cases of delirium (up to 28%). In addition, the authors pointed out the lack of studies on risk factors for postoperative delirium and the need for further efforts to study this issue [39].

Meanwhile, in the first decades of the 21st century, anesthesiologists have been studying and categorizing the results of studies on different types of postoperative PND. For example, in 2007, the journal Anesthesiology published an article identifying the association of delirium with surgery only in the period up to 72 hours after surgery (see Figure) [40]. However, J. Silverstein's classification still included the presence of a «lucid interval» in the first 24 hours after surgery.

In 2017, the European Society of Anesthesiologists published guidelines that extended the time interval for the association of delirium with surgical intervention (see Figure) [41]. The authors returned the upper time limit for the occurrence of postoperative delirium to 5 days postoperatively, as it was in the classifications of S. Heller [16] and Z. Lipowski [27]. At the same time, the authors of the 2017 PND classification tried to solve the shortcoming of all POD classifications that has persisted for almost 50 years, i.e., the «gray» (unclear and unexplored) zone between the patient's awakening and the end of the minimum duration of the lucid interval. In the 1980 classification, Z. Lipowski proposed to describe the changes in cognitive status at this point as «emergence delirium», but the term had already been used to characterize the awakening of patients after anesthesia [17].

Based on the available evidence that cognitive impairment observed in the recovery room is predictive of postoperative delirium [42, 43], C. Aldecoa et al. suggested that the lower limit of the time interval for postoperative delirium may be later than the time of «arrival at the recovery room» [41]. The authors proposed that neurocognitive disturbances occurring before this (rather conventional) time point should be considered as «emergence delirium». This reasonable proposal, however, has led to even more confusion. The reasons are obvious: the lower limit of the time of onset of postoperative delirium was arbitrarily chosen and not related to the patient's condition. Moreover, it turned out that the interval could vary depending on the requirements of the patient's status, which determined whether he or she could be transferred to the recovery room, intensive care ward, or surgical ward. In a number of less «advanced» hospitals there are no recovery rooms at all, which makes the use of this classification practically impossible. This is the reason for its low popularity.

Taking into account the above-mentioned circumstances, in 2018 L. Evered proposed a new PND classification (see Figure) [44], which has 3 fundamentally important aspects:

1. The proposal to shift the lower time limit of postoperative delirium to the time of the end of the surgical procedure. Thus, any delirium after surgery should be classified as postoperative. Meanwhile, the presence or absence of a «lucid interval» is only considered an individual variation of POD.

2. The second aspect is to raise the upper time limit for the development of postoperative delirium. L. Evered et al. proposed to increase the time limit for the diagnosis of delirium to 7 postoperative days or until discharge (whichever comes first). One can only speculate about the reasons for such a proposal, as the authors did not explain their position. And finally,

3. The third aspect is the use of diagnostic criteria for delirium according to the DSM-5 [7]. The seemingly unremarkable proposal to use DSM-5 [7] criteria instead of DSM-4 [30] is in fact a significant step forward in standardizing approaches to the diagnosis of POD. The publication of DSM-5 [7] in 2013 was not a high-profile event in the anesthesiology/critical care community because of the absence of the term «postoperative delirium». However, according to L. Evered et al., postoperative delirium is a type of delirium associated with surgical intervention. Consequently, POD, as a variant of delirium, should be diagnosed according to the latest delirium criteria. Although this position is simple and straightforward, it is important to note that the DSM-5 [7] and DSM-4 [30] have a concordance rate of only 91% [45]. The presence of some inconsistency between these diagnostic criteria has made it necessary to revalidate the existing diagnostic tools for postoperative delirium, including the afore-

mentioned ICDSC, Nu-DESC, and various versions of the Confusion Assessment Method (CAM).

After validation, 3D-CAM [46], CAM-ICU [47] and ICDSC [47] confirmed high agreement with DSM-5 [7] as the new gold standard for the diagnosis of delirium. However, Nu-DESC showed a very low sensitivity (42%) during validation [48]. Based on such results, it is probably not worth considering the Nu-DESC scale as a tool for diagnosing postoperative delirium at this time.

Postoperative delirium has since been defined as «neurocognitive impairment meeting DSM-5 criteria and occurring within 7 days of surgery or before discharge (whichever occurs first)». The simplicity and precision of the definition of «postoperative delirium» make this classification successful, although not exhaustive. The time frame «within 7 days of surgery» is not substantiated in any way, which implies the possibility of subsequent changes.

Current status of POD research. According to the DSM-5 [7], delirium is currently defined as a combination of the following diagnostic criteria

A. Disturbance of attention (i. e., reduced ability to direct, focus, maintain, and shift attention) and consciousness (reduced orientation to the environment).

B. This disturbance develops over a short period of time (usually hours to a few days), represents an acute change from baseline attention and awareness, and tends to fluctuate in severity throughout the day.

C. An additional disturbance in cognition (e. g., memory deficit, disorientation, language, visuospatial ability, or perception such as delusions).

D. The disturbances in Criteria A and C are not better explained by a pre-existing, established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal such as coma.

E. There is clear evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication, or withdrawal (i. e., from a drug of abuse or medication).

Delirium itself is divided into 3 subtypes [7]:

1. Hyperactive, with increased arousal, psychomotor abnormalities, and hypervigilance (hallucinations, delusions, agitation, and disorientation);

2. Hypoactive, with lethargy and lack of interest. This type of delirium is particularly easy to overlook in clinical practice, so it often goes unrecognized or masquerades as dementia;

3. Mixed when the patient either has a normal level of psychomotor activity or can «switch» between the two types of delirium described above.

Despite the existence of the DSM-5, the only official document that currently includes postoperative delirium in the list of neurocognitive disorders is the ICD-10 [29]. According to ICD-10, postoperative delirium is defined as a nonspecific organic cerebral syndrome characterized by disturbances of consciousness, attention, perception, thinking, memory, psychomotor behavior, emotions, and sleep-wake cycle [49]. We would like to draw attention to two points:

1. This definition points to organic damage as the direct cause of POD. This observation is supported by extensive evidence of the association of delirium with underlying dementia, Parkinson's disease, and perioperative cerebral infarction [50–54].

2. The hallmark of postoperative delirium is impaired consciousness, which is not characteristic of any other PND.

Currently, the predominant concept of POD development suggests the presence of predisposing (advanced age [55–58], administration of some medications in the perioperative period [59, 60], comorbidities [61–63], etc.) and provoking (intraoperative blood loss [64, 65], depth of hypnosis [66], hypovolemia [67], etc.) factors. A combination of several predisposing and provoking factors may initiate PND. The trigger appears to be the onset of neuroinflammation as a form of systemic inflammatory response that damages brain neurons and manifests as PND. Clinical manifestations of this response are usually observed by an anesthesiologist [68].

The incidence of postoperative delirium can vary within a fairly wide range, from 15% to 53% [7]. Meanwhile, postoperative delirium is a risk factor for an unfavorable postoperative recovery period. Thus, postoperative delirium has been shown to be associated with

1. Increased mortality in adult patients [69–73].

2. Longer ICU and hospital stays in adult patients [71, 74, 75].

3. Cognitive impairment in adult patients [73, 76].

There are no specific pharmacological methods for the prevention and treatment of POD [77, 78]. Numerous recommendations to eliminate predisposing and provoking factors, to create a friendly atmosphere, to provide a protective regimen in intensive care units, etc. have limited efficacy [79]. Analysis of RCTs shows that the use of a drug with putative neuroprotective activity (dexmedetomidine) has controversial results [77]. Nevertheless, the prophylactic use of this drug is approved by some clinical guidelines [80].

Postoperative Cognitive Dysfunction

Background. As mentioned earlier, the first description of postoperative cognitive dysfunction can be found in the work of G. Savage (1887), where the author first associated the fact of anesthetic use with the development of «chronic dementia» in elderly patients [81]. However, the era of studying

postoperative cognitive dysfunction did not begin until more than half a century later. It is difficult to overestimate the importance of the pioneering work of P. Bedford [82]. The author conducted a retrospective analysis of 4,250 case histories of patients over 65 years of age, 1,193 of whom had undergone various surgeries under general anesthesia during the previous fifteen years (i. e., at the age of 50 years or older), and found that in at least one third (410) of the cases, close relatives or friends noted personality changes after surgery, with the phrase «The patient will never be the same».

The next stage of research into the problem of POCD began in the 1970s, when a number of studies in the field of anesthesiology were initiated to investigate changes in psychoemotional and intellectual functioning in patients after exposure to general anesthesia [83–85]. At this point in the research, a number of unresolved problems have surfaced. The first is the lack of agreement regarding how to diagnose POCD. Guidelines that outlined a pool of questions that should be addressed in the evaluation of patients' cognitive function were published in 1995 to address this problem [86]. Additionally, these guidelines proposed a method for evaluating cognitive dysfunction based on several tests administered concurrently, allowing for a better diagnosis of cognitive impairment in postoperative patients. Unfortunately, despite the passage of nearly 30 years, there is still no single test or battery of tests specifically designed to diagnose POCD. Thus, different tests were shown to result in different rates of POCD diagnosis in 2006 [87]. Later, in 2016, R. Benson et al. attempted to conduct a meta-analysis of the development of POCD associated with aortic surgery, but differences in study methods, cognitive test batteries, and thresholds also prevented results from being pooled [88]. This issue greatly complicates the evaluation of POCD and, without a doubt, leads to interdisciplinary disagreement among neurologists, anesthesiologists, and other physicians.

Another current challenge is the very principle of diagnosing POCD. In fact, different methods of diagnosing POCD are currently used when assessing changes in scores on a scale chosen by researchers. For example, in studies without a control group, a popular criterion for the presence of POCD is a deterioration in retest scores of one standard deviation or more from baseline [89]. In studies with a control group, a popular approach is to compare the change in a given patient's score with the expected change calculated on the basis of the control group, the so-called Z-score (RCI, reliable change index) [90, 91]. Even with this approach, there are different formulas for estimating the expected change for a battery of tests [92]. Some large studies have used a third approach, which includes the assessment of the absolute change in score as a diagnostic criterion for POCD [93]. The lack of a uniform approach to the diagnosis of POCD is a major obstacle to the study of this disorder.

Uncertainty regarding the timing of the described complication's diagnosis is the third challenge. For instance, it can take anywhere between «less than 24 hours» [94] and «1 year or more» after surgery [91, 95, 96] to confirm the presence of POCD in various studies. The previously discussed classification by J. Silverstein (see Figure) [40] was developed to address this discrepancy between studies. According to the classification, postoperative cognitive dysfunction can be identified over the course of weeks and months but never over the course of days. At the same time, the scientific community established an informal classification of POCD into three stages (see Figure), including early (1 week after surgery), intermediate (during the first three months after surgery), and long-term (1 year or more after surgery) [97, 98].

Only 60 years after P. Bedford's work [82] was published, L. Evered's (2018) classification [44] was able to simultaneously solve multiple issues. It did this by first defining precisely what constitutes postoperative cognitive impairment. It was recommended that POCD should be evaluated no earlier than one month and no later than one year following surgery. Even though cognitive dysfunction can persist for much longer than a year, the terms «mild/severe neurocognitive impairment» are appropriate in this situation [44]. It is advised to refer to cognitive impairment occurring up to one month after surgery as delayed neurocognitive recovery. Second, a correlation between POCD and the most recent classifications has been made. Unfortunately, POCD is not included in any of the current official classifications, neither ICD-10 [29] nor DSM-5 [7]. However, bringing the definition of POCD closer to the DSM-5 definition of neurocognitive disorders and making the association with surgical intervention more explicit may standardize the method of studying POCD and possibly aid in its inclusion in official international documents. Third, unified diagnostic criteria for POCD have been established in accordance with the DSM-5, which include a deterioration in retest score of at least one standard deviation compared to the control group [7].

But there are still some uncertainties. On the one hand, there is currently no standard method for calculating the RCI, which is required to determine the deviation of each study patient's result from that of the control group. Contrarily, there is no approved test battery to evaluate cognitive dysfunction in patients in the documents under consideration despite the DSM-5 existing definition of neurocognitive dysfunction and the availability of approved cognitive blocks.

The exclusion of the MMSE and MoCA from the diagnostic battery for postoperative cognitive dysfunction (POCD), as recommended by the DSM-5 [44], can be interpreted as a favorable advancement due to their failure to adequately assess the required cognitive domains.

Current state of the art. The incidence of postoperative cognitive dysfunction (POCD) following major abdominal and orthopedic surgeries was investigated in the ISPOCD1 study, which involved a total of 1218 patients aged 60 years and above [90]. Postoperative cognitive dysfunction was diagnosed in 25.8% of patients one week following surgical intervention, and in 9.9% of patients three months after the surgery. Only age was a risk factor for POCD; other variables for delayed neurocognitive recovery were age, anesthetic duration, poor education level, reoperation, postoperative infections and respiratory problems, and reoperation. Nevertheless, there was no observed association between hypoxemia or hypotension and the occurrence of POCD. The authors did not provide a clear explanation of the underlying mechanisms of POCD or identify any particular risk factors that could be targeted for therapeutic or preventive interventions [90]. The association between this disorder and irreversible damage to the nervous system, characterized by structural changes in the brain and neuronal loss, remains uncertain. However, research efforts in this particular area persist [101, 102]. For instance, X. Liu et al. conducted a meta-analysis that encompassed 54 observational studies. Their findings demonstrated a positive association between elevated levels of inflammatory markers, specifically CRP and IL-6, and the occurrence of both POD and POCD [103].

POCD has been reported to occur more frequently in patients whose postoperative period was complicated by POD [104–107]. Although POCD can develop in patients without a history of POD, POD does not always progress to POCD, therefore there is no obvious causal link [108].

A small body of evidence suggests that patients with POCD have a greater risk of death [109, 110], but it is already obvious that these patients need significant and prolonged medical and social adaptation, which is becoming a major challenge for patients, healthcare providers, and social services.

Numerous investigations into the effectiveness of potential medications for the prevention and treatment of POCD have been unsuccessful. There are currently no pharmacologic treatments that have been shown to be effective in POCD patients [111].

Early Postoperative Neurocognitive Disorders

Background. The history of studying the problem of early postoperative neurocognitive disorders, which at different times included «emergence excitement», «emergence agitation», «emergence delirium», etc., probably begins with the article by J. Eckenhoff et al. (1961) (see Figure) [17]. There, for the first time, the prevalence of «emergence excitement» was studied. This complication was studied on a population of more than 14,000 patients of all ages. Unfortunately, J. Eckenhoff et al. employ three names simultaneously in their study to represent early PND, including «emergence excitement», «emergence delirium», and «emergence agitation», without describing any potential overlaps or contrasts between the conditions.

Subsequent decades of research on early postoperative neurocognitive disorders have been characterized primarily by the accumulation of data on risk factors [112–120] and their impact on clinical outcomes [42, 112, 114, 115, 118, 119, 121–125]. However, terminological issues have been ignored and authors have arbitrarily and interchangeably used the terms emergence agitation, emergence delirium, emergence excitement, PACU delirium, and recovery room delirium, which may have affected the validity of the results obtained. This seems odd because the 1980 DSM-3 provided precise definitions of delirium and agitation, stating that delirium always includes a cognitive component of impaired consciousness, whereas agitation is characterized by motor agitation alone [26].

The most recent advances in early PND classification. J. Silverstein et al. [40] made the first attempt to solve the problem of terminological chaos in early PND in 2007. The authors proposed a single term «emergence delirium» to describe early postoperative neurocognitive disorders that occur immediately after anesthesia recovery. In doing so, they suggested, paradoxically, using motor characteristics of awakening to diagnose ED. This could be why colleagues overlooked this proposal.

C. Aldecoa et al. suggested in 2017 that the term ED be used to describe all neurocognitive disorders of the early postoperative period (see Figure) [41]. To say the least, this appears illogical. Calling the emergence state «delirium» and recommending motor scales to diagnose it, despite the fact that delirium implies the presence of impaired consciousness? Combining patients «with» and «without» impaired consciousness into a single term does not appear to be the best solution.

The medical community's subsequent criticism of the inaccuracy of such diagnostic considerations prompted the development of a new classification (126, 127). Furthermore, claims have been made about the time interval used to define ED from the early postanesthetic period through «arrival in the recovery room» [41]. As previously discussed, the selection of such a time point, which is not related to the patient's condition but rather to the

organization of perioperative management, became another flaw in the proposed recommendation.

The recommendations published a year later by L. Evered (2018) provided a different perspective on the issue of early PND terminology (see Figure) [44]. L. Evered et al. proposed to exclude the term «emergence delirium» from the current classification, and any condition that meets the definition of delirium according to DSM-5 during 7 postoperative days should be considered as postoperative delirium. In fact, this approach simplifies the methodology of diagnosing postoperative delirium and eliminates the problem of the «lucid interval». But the question remains, what is emergence agitation (EA)?

The problem with EA is that during the period of agitation, it is impossible to make contact with the patient to assess their cognitive status. Since there is currently no mechanism for determining cognitive status other than direct communication with the patient, it is extremely difficult to answer the question of whether agitation is purely psychomotor, as the DSM has classified it for over 40 years, or a brief episode of hyperactive delirium that resolves when the agitation subsides.

Perhaps the method proposed by E. Card et al. can help to solve this problem [128]. The authors studied the development of emergence agitation, which was diagnosed in the operating room using the RASS scale, and delirium, which was assessed by the CAM-ICU immediately after arrival in the recovery room. E. Card et al. found that of the 75 patients (19% of all participants) who had an episode of emergence agitation on recovery from anesthesia, only 60% (45 patients) had delirium on arrival in the recovery room. We would like to believe that conducting similar studies may shed light on the issue of cognitive status of patients during the period of emergence agitation after anesthesia.

Conclusion

The lack of a consistent approach makes comparing the results obtained in the study of early PND in the works of different authors extremely difficult. Thus, some anesthesiologists accept a brief disorientation with motor hyperactivity on recovery as a normal variant, attributing it to the discomfort of the intubation tube, the pain syndrome, or the erratic inhibition or recovery of various brain areas associated with the action of general anesthetics. Others define agitation as motor agitation without cognitive dysfunction, and some continue to use the terms «agitation» and «ED» interchangeably.

It is clear that anesthesiologists, psychiatrists, and neurologists must collaborate to develop an optimal classification of early PND. A classification like this will allow for a more focused search for the true prevalence of early PND and its impact on clinical outcomes. If researchers discover that early PND is more than a non-serious transient functional brain disorder and is associated with increased mortality (which is not impossible given the availability of such data for POD) or other adverse events, they will need to work hard to find ways to prevent and treat early PND.

We would like to conclude this review with a visual representation of the long history of research into postoperative neurocognitive disorders (see Figure). It also serves as a visual representation of PND's current classification. Hopefully, the scheme will be updated soon to remove inaccuracies and inconsistencies.

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Summary

Aim. To analyze the contribution of V. K. Kulagin, Doctor of Medical Sciences, Professor of the Department of Pathological Physiology of the Military Medical Academy into development of scientific perspectives concerning the etiology, pathogenesis and therapy of traumatic shock, following thorough analysis of 1950–1980s series of featured publications. We analyzed the general theoretical views of the scientist, his methodological preferences in organizing laboratory experiments, the methodology for developing standard models for conducting experiments, choosing indicators and evaluation criteria. We brought to recollection the proposed by V. K. Kulagin approach to traumatic shock staging and phases relative to the leading pathogenetic factor; highlighted some of the key topics and results of his experimental research related to individual resistance to shock, prerequisites of shock irreversibility and factors complicating the course of traumatic shock.

Conclusion. Theoretical and experimental inventions of V. K. Kulagin are relevant to the present day and are of great importance for further progress of medical science.

Keywords: Viktor Konstantinovich Kulagin; Department of Pathological Physiology; Military Medical Academy; pathogenetic factors of traumatic shock; laboratory experiment in pathological physiology; hemic hypoxia; mutual burden syndrome

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

Введение

В 2023 г. отмечается столетие со дня рождения выдающегося патофизиолога, основной сферой научных интересов которого было исследование экстремальных и пограничных для жизни состояний — Виктора Константиновича Кулагина.

Все большое видится на расстоянии — видимо, в этой народной мудрости заключается причина того, что серьезное научное наследие В. К. Кулагина в области этиологии и патогенеза травматического шока пока не получило должного осмысления и оценки. Юбилейный год — подходящий момент для подытоживания заслуг. Можно с уверенностью сказать, что современные представления о природе травматического шока, эффективных способах его профилактики и лечения сформировались во многом благодаря этому одаренному и продуктивному ученому, смелому и искусному теоретику-экспериментатору, способному к детальному анализу и широкому синтезу эмпирических данных.

Становление ученого. Виктор Кулагин появился на свет в крохотном провинциальном рабочем поселке, рос любознательным, учился на отлично. Как все выпускники 1941 г., прямо со школьной скамьи ушел на фронт, добровольно служил в разведке. В начале 1942 г. Виктор был серьезно ранен, после чего в сражениях уже не участвовал; прошел подготовку в пулеметном училище, получил звание лейтенанта, обрел командирские навыки. Как это ни парадоксально, война стала для Кулагина своеобразным социальным трамплином, позволившим осознать свое призвание и выбрать верный жизненный путь. Свою судьбу В. К. Кулагин связал с Военно-медицинской академией (ВМА), куда был зачислен курсантом в 1946 г. Здесь его интеллектуальные способности и исследовательский потенциал получили простор для воплощения. Сразу после окончания ВМА в 1951 г. отличник В. К. Кулагин был зачислен в адъюнктуру при кафедре патологической физиологии [1].

На кафедре патофизиологии с ее славными научными традициями [2] таланты новобранца науки прошли шлифовку и огранку в творческой «боттеге»[1] Иоакима Романовича Петрова, руководившего этим структурным подразделением с 1939 г. по 1964 г. Научная школа Петрова сформировалась еще до Великой Отечественной войны и заложила принципы и подходы совет-

[1] Боттега (bottega) — мастерская художников эпохи Ренессанса, где умудренные опытом мастера своего дела занимались обучением юных подмастерьев, где воспитывались молодые дарования и создавались новые техники выполнения работ. В самом процессе созидания, который шел в этих мастерских, рождалось новое знание.

ской медицинской службы к лечению травматического шока в период боевых действий. Школа была многочисленной (около 50 человек), она объединяла ученых разных возрастов и рангов вокруг общей парадигмы — нейрогенной теории травматического шока.

Под влиянием единомышленников и прежде всего самого И. Р. Петрова Виктор Константинович выбрал диссертационную тему, полностью находящуюся в русле основного научного направления кафедры — разработки принципов комплексной терапии и профилактики шока. В 1955 г. успешно прошла защита кандидатской диссертации «О ранней профилактике и механизмах развития травматического шока в эксперименте», в 1961 г. — докторской: «Материалы к патогенезу и терапии травматического шока».

Во главе кафедры патофизиологии. Примечательно, что возглавив в 1967 г. кафедру патофизиологии ВМА, Виктор Константинович Кулагин не стал ломать существующие традиции, резко менять исследовательскую тематику, что зачастую происходит при смене руководства. Он сохранил преемственность и позволил сполна реализоваться потенциалу петровской школы в лице выдающихся военных медиков старшего фронтового поколения и своих ровесников, также учеников Иокима Романовича. Он по праву стал новым интеллектуальным лидером данного научного направления, и на этом основании было бы справедливо школу изучения травматического шока в эксперименте, сложившуюся на кафедре, именовать школой Петрова–Кулагина [3].

Важно отметить, что Виктор Константинович превнес в работу кафедры множество новаторских идей. Он придал научным разработкам новый импульс благодаря усовершенствованию экспериментальной материально-технической базы и исследовательских методик. При нем было модернизировано учебное и научное оборудование, возросла роль практических и лабораторных занятий в учебном процессе: основой обучения стало моделирование и осуществление эксперимента. В 1969 г. кафедра впервые приобрела электростимуляторы, электрокардиографы и электроэнцефалографы. Были организованы биохимическая и электрофизиологическая лаборатории, что позволило интенсивно, с применением новейших методов и с активным привлечением специалистов из других кафедр академии и научных учреждений проводить исследования по актуальным вопросам военной патологии [4]. Наверно, не будет преувеличением сказать, что это был период расцвета лабораторного эксперимента в патологической физиологии.

Fig. Viktor Konstantinovich Kulagin.

В коллектив вливались свежие силы, по травматическому шоку под руководством Кулагина продолжали защищаться диссертации. В. К. Кулагин подготовил 10 докторов и 21 кандидата медицинских наук [3]. С 1975 г. по 1979 г. он исполнял обязанности Ученого секретаря академии, участвовал в работе диссертационного совета К.106.03.02, являлся членом президиума ВАК.

Кафедру отличала высокая публикационная активность. Авторству самого Кулагина принадлежит порядка 200 научных работ. Диапазон научных интересов В. К. Кулагина одновременно и узконаправлен, и чрезвычайно широк. Всю жизнь он работал в рамках единственного научного сегмента — патофизиология травматического шока, но при этом не упустил из виду ни одного значимого аспекта данной проблематики [5].

Итогом многолетних научных изысканий стала изданная в 1978 г. монография «Патологическая физиология травмы и шока», а которой Виктор Константинович дал подробный аналитический обзор современных ему представлений об этиологии и патогенезе травматического шока; обосновал типологию и классификацию шока по этиологическому признаку, предложил свою периодизацию шока, в зави-

симости от доминирующего патогенетического фактора; обозначил проблемные точки становления единой теории травматического шока; задал перспективу дальнейших исследований в этой области медицинской науки [6].

Теоретические и методологические предпочтения. Как известно, *perpetuum mobile* развития научной мысли — научная дискуссия. Чем актуальнее проблема, тем больше вокруг нее кипит споров. В 1970-е гг. постижение сущности травматического шока и поиск подходов к его терапии находились на острие научного внимания. Дебаты между представителями различных специальностей, теоретических и методологических течений разворачивались на страницах журналов, на симпозиумах, конференциях и других площадках научной коммуникации, и В. К. Кулагин был их активным участником [7]. В обсуждение и разработку проблемы шока, наряду с патофизиологами и хирургами, включились фармакологи (Виноградов В. М., Денисенко П. П. и др.), биохимики (Иванов И. И., Коровкин Б. Ф. и др.), анестезиологи (Уваров Б. С. и др.).

Что же было предметом разногласий? Выделим несколько дискуссионных моментов.

В этот период активно создавались специализированные противошоковые центры, оснащенные современной аппаратурой, позволяющей осуществлять регистрацию основных жизненных функций у пострадавших. У больных в состоянии шока стали забирать кровь для биохимических анализов еще по дороге в клинику. Все это привело к экспоненциальному росту эмпирических данных, и хирурги «впервые получили большой и разносторонний фактический материал о развитии шока непосредственно на человеке» [8].

Как следствие — изучение шока переместилось из лабораторий в клиники. Особенно активно в нашей стране велась работа в этом направлении на кафедре военно-полевой хирургии ВМА под руководством А. Н. Беркутова, а также в Институте скорой помощи им. И. И. Джанелидзе под руководством Г. Д. Шушкова. Практикующие врачи стали высказывать сомнения в необходимости лабораторного эксперимента как такового. Что, разумеется, вызвало категорическое отторжение со стороны теоретиков-экспериментаторов. В частности, В. К. Кулагин полагал, что роль лабораторного эксперимента на животных в изучении шока по-прежнему должна играть ведущую роль. И приводил веские доводы.

Кулагин считал, что в клинике невозможно изучать шок в полном объеме, наблюдать в динамике, отслеживая его стадийность со всеми фазовыми переходами. У врачей-клиницистов другая основная задача — не наблюдать, а действовать, спасать человеческую жизнь. Кроме того, терапевтические меры в отношении пациентов в состоянии шока являются экстренными и безотлагательными и принимаются еще до попадания больного в стационар, врач в клинике имеет дело с уже «леченным» шоком, а, следовательно, с медикаментозно измененным его протеканием [6, с. 6].

Шок у человека характеризуется большими индивидуальными особенностями, зависящими от локализации и характера травмы, степени повреждения жизненно важных органов. При сходстве травмирующего воздействия, больные, тем не менее, могут находиться на разных стадиях развития шокового процесса. Кроме того, каждый больной поступает в шоковое отделение с собственным сопутствующим «букетом» состояний и заболеваний (включая хронические). Взаимное наложение всех этих обстоятельств не позволяет обнаружить в общей картине хоть какие-то закономерности. И приводит клинических исследователей к радикальным выводам. Как отмечает В. К. Кулагин, «некоторые клиницисты (Беркутов А. Н. и др.) пришли к крайним заключениям о том, что шока как такового не существует, а есть сборная группа тяжелых состояний, которые в каждом случае имеют свою специфику» [6, с. 21]. Иначе говоря, общих механизмов шокового процесса нет, и шок у всех протекает по-разному.

Вызывала критику экспериментаторов также методика сбора эмпирических клинических данных — гигантские статистические совокупности показателей не облегчали, а затрудняли возможность научного анализа, т. к. оперировали в основном средними величинами, не более информативными нежели пресловутая «средняя температура по больнице».

Кроме того, не все необходимые методы исследования шока допустимы на человеке.

С точки зрения Виктора Константиновича Кулагина, непреодолимые для клиницистов сложности легко разрешались в грамотно поставленном лабораторном эксперименте, ведь этот инструмент позитивной науки как раз и предназначен для поиска закономерностей с помощью специально разработанных методик. Только в «чистом» эксперименте, позволяющем исключить осложняющие факторы, общие механизмы шока отчетливо проступают и позволяют себя исследовать. А на основе понимания общих закономерностей легче потом понять разнообразные комбинации, встречающиеся в клинике.

Кулагин подчеркивал важность координации экспериментальных и клинических исследований шока. Лабораторный эксперимент

ценен не сам по себе, а исключительно с точки зрения пользы для клиники. Любой эксперимент моделируется, исходя из целей и задач, которые ему предстоит решить, а задачи формулирует клиника.

Методика лабораторного эксперимента. Виктор Константинович Кулагин придавал важное значение рассмотрению методологических и методических аспектов экспериментальных исследований в военной медицине в целом [9], и при изучении патогенеза, разработке экспериментальной терапии экстремальных состояний, в частности [10]. Он, пожалуй, останется в истории медицинской науки, прежде всего, как непревзойденный мастер патофизиологического эксперимента.

Искусство эксперимента состоит в моделировании процесса, в стандартизации его условий, в отборе критериев и регистрации показателей. За основной критерий сравнения может быть взята тяжесть травмы, объем кровопотери или же состояние организма и его основных систем после травматизации. В ряде случаев полезно стандартизировать тяжесть воздействия (травмы, кровопотери) [10].

В эксперименте, где исследователь может не только наблюдать, но и управлять процессом, часто используется принцип варьирования дозы травмирующего воздействия: т. е. травма наносится не одномоментно. Особенно это важно при изучении развития шока, различных его стадий и скачкообразных переходов от одной к другой.

Важное значение имеет обоснованный выбор вида подопытных животных, каждый из которых может иметь те или иные особенности в сравнении с организмом человека [11]. Изучение шока в лаборатории кафедры патофизиологии проводилось на собаках, кроликах, кошках и крысах. В том случае, когда это имело значение для корректности результатов эксперимента, использовали ненаркотизированных животных. Отвечая на утверждения о неправомерности экстраполяции экспериментальных данных, полученных на животных, на человека, Кулагин ссылался на соответствующие исследования, «свидетельствующие о том, что генеральные закономерности развития шока у человека и экспериментальных животных, лежащие в основе нарушения функций различных систем, идентичны, что не исключает наличия ряда частных особенностей, связанных со спецификой организма человека» [6, с. 22], «поскольку в патогенезе шока большую роль играют выработанные в процессе филогенеза древние вегетативные реакции, механизмы, которые в общих чертах одинаковы у всех млекопитающих» [6, с. 22].

Очень важно было добиться стандартизации эксперимента, разработать его типовую модель, без чего была недостижима сравнимость результатов проводимых опытов [12]. Основной стандартной моделью травматического шока, применяемой на кафедре, была так называемая Модель Кеннона (реализуемая путем травматизации мягких тканей бедра, что исключает массивную жировую эмболию и повреждение крупных артерий). Но применялись и другие повреждения конечностей. Модель болевого шока создавалась путем механического или электрического раздражения смешанных нервов, чаще всего седалищных. На специальных моделях изучался плевропульмональный шок, висцеральный шок при длительном раздавливании мягких тканей, турникетный метод и т. д. Применялись типовые модели и комбинированные [12].

Во второй половине 1970-х гг. на первый план вышла проблема сопоставимости результатов экспериментов, проведенных в различных лабораториях [13]. Это осознавалось как серьезная методологическая и методическая проблема, без решения которой накопленные различными коллективами исследователей данные невозможно было сопоставлять и сравнивать, что, в свою очередь, сказывалось на эффективности разработки темы в масштабах страны [14]. По словам Кулагина, «исследования проводятся на разных экспериментальных моделях, в различные сроки развития шока, что существенно затрудняет их обобщение» [6, с. 3]. Были предприняты шаги по унификации экспериментальных моделей шока, а также периодов исследования показателей. Содружеством нескольких вузов были осуществлены по общей программе комплексные исследования, нацеленные на решение наиболее актуальных теоретических проблем шока [14].

Лабораторный эксперимент Кулагина позволял не только изучать общие механизмы и закономерности шокового процесса, наблюдая и фиксируя качественные скачки между отдельными его стадиями, но и продвигаться от общего к частному, к пониманию специфичности отдельного случая.

Кулагин провел множество исследований с целью изучения тех индивидуальных особенностей, которые влияют на резистентность или предрасположенность организма к шоку. При воспроизведении шока у животных путем маневрирования тяжестью травмы решался вопрос о разнообразии пределов и пороговых значений резистентности. Так была выявлена индивидуальная вариативность устойчивости к шокогенным факторам, обусловленная наследственными и конституциональными фак-

торами: «Неодинаковая устойчивость различных животных к шоку и различный эффект терапии зависят от ряда генотипических и фенотипических особенностей» [15]. Играли роль и дополнительные обстоятельства, такие как усталость, изможденность голодом, стресс и т. п. Понимание отличительных свойств устойчивых к шоку особей могло дать ключ к поиску средств профилактики шока в целом. Успехи терапии шока В. К. Кулагин связывал, в частности, со «знанием индивидуальных особенностей нейроэндокринной реакции организма в ответ на шокогенную травму» [15].

Вопрос о ведущем факторе травматического шока. Другим предметом неутихающих споров оставался вековой вопрос о решающем факторе патогенеза [16]. Не было единства в понимании, что первично для развития шока. Среди основных факторов, имеющих наибольшее значение в развитии шока при травме, выделяли болевую импульсацию, кровопотерю, эндотоксикоз и т. д.

В. К. Кулагина принято считать апологетом нейро-гуморальной теории, приверженцем первичности ЦНС как регулятора деятельности всех других систем организма [17]. Действительно Кулагин многократно подчеркивал, что шок — это страдание всего организма, а «нарушения функции нервной системы на всех ее уровнях интеграции организма играют выдающуюся роль в патогенезе шока. Шок как типовой патологический процесс, с присущими для него причинно-следственными отношениями и порочными кругами, невозможно вызвать в условиях глубокой нейровегетативной блокады и искусственной гипотермии» [6, с. 278].

Однако, при внимательном прочтении его трудов открывается несколько иная картина. Важно подчеркнуть, что научные взгляды и представления Виктора Константиновича эволюционировали и пересматривались на протяжении всей жизни. В конце 1970-х гг. механизм развития шока представлялся ему, скорее, «многокомпонентным» [6, с. 5]. Виктор Константинович полагал, что «в теориях патогенеза шока часто выделялась одна какая-то, решающая роль одного фактора этиологии, а остальные ради упрощения принимались за константы или выносились за скобки, что приводило к существенным искажениям и ошибкам в рассмотрении патогенеза» [16]. Он находил, что «за последнее время стала очевидной бесперспективность сведения патогенеза шока к влиянию отдельных факторов…» [17]. «В патогенезе травматического шока они могут выступать в качестве синергистов, определяя качественно иную форму патологии» [6, с. 20].

Исходя из приведенных цитат, Кулагина справедливо отнести к основоположникам полиэтиологической теории патогенеза травматического шока, наиболее распространенной в наши дни [18, 19]. По крайней мере именно данной концепции он придерживался в последние годы жизни.

Периодизация травматического шока. Концептуальные представления В. К. Кулагина о природе шока нашли выражение в данной им общей характеристике, типологии и классификации шока на основе этиологического фактора. Им была также предложена периодизация травматического шока в зависимости от ведущего патогенетического фактора, основанная на экспериментальных материалах. На первой стадии («нервной»), соответствующей эректильной фазе, доминирует реакции, опосредованные нервной системой. Итогом ее становится дискоординация работы всех органов и систем. На второй («сосудистой») — уже при развившемся торпидном шоке — ведущими становятся уменьшение объема циркулирующей крови, нарушения микроциркуляции, приводящие к гипоксии тканей. На третьей («метаболической») стадии наряду с расстройством гемодинамики возникают выраженные нарушения обмена веществ, которые резко утяжеляют течение процесса [6, с. 70]. На каждой стадии требуется применение соответствующей ведущему фактору терапии с использованием определенных групп препаратов.

В. К. Кулагин всецело принял теорию травматической болезни, в рамках которой травматический шок может рассматриваться как один из патологических процессов более широкой нозологической единицы. Концепция травматической болезни охватывает весь комплекс изменений в его жизнедеятельности от момента травмы и до окончательного исхода. В контекст ее динамики органично вписываются такие стадии, как прешок и постшок.

Кулагина отличало постоянное внимание к начальной, даже потенциальной стадии шокового процесса — к прешоку [20]. Причем, в тесной связке с проблемой профилактики шока. Именно этим вопросам посвящена его кандидатская диссертация и множество публикаций. В. К. Кулагин искал превентивные средства, препятствующие стремительному развитию шока, способные его смягчить и замедлить.

Постшоковый период характеризуется опасностью рецидивов, различными осложнениями, но при исследовании шока он остается за рамками рассмотрения. «И это является одним из серьезных аргументов в пользу выделения травматической болезни как нозологической единицы, так как при этом изменяется методология подхода врачей к диагностике, прогнозу, последовательности терапии тяжелых травм, а также статистическому учету ре-

зультатов лечения» [6, с. 81]. Кулагин подчеркивает, что шок — это процесс, для которого характерна смена качественно различных стадий, и сожалеет, что нет серьезных исследований, посвященных стадийности выхода из шока, а критерии выведения из шока остаются неразработанными.

Ключевые темы исследований. Многочисленные эксперименты В. К. Кулагина можно условно разделить на две большие группы:

1) исследование различных аспектов этиологии и патогенеза травматического шока;

2) испытание противошоковых средств, главным образом медикаментозных препаратов.

В фокусе научного внимания Кулагина постоянно оставались особенности патологии нейрогуморальных механизмов, эндокринной системы при шоке. На протяжении всей научной биографии он с неослабным вниманием исследовал эндокринные следствия травматического шока и искал действенные способы их медикаментозной гормональной коррекции. Этот интерес в целом соответствовал исходной установки ученого о доминировании роли ЦНС, как регулятора прочих систем организма, в развитии травматического шока [21]. Всего проблематике нейроэндокринных нарушений при шоке, гормоно- и ферментотерапии Кулагин посвятил в общей сложности более 50 публикаций [22–25].

Особо хотелось бы остановиться на теме гипоксии в работах Кулагина: он признавал ключевую роль кислородного голодания в генезе шока. Эксперименты Кулагина показали, что потребление кислорода в торпидной фазе травматического шока резко уменьшается при отсутствии повреждений грудной клетки. Из чего следует, что в понижении потребления кислорода не играют существенной роли функции внешнего дыхания. И даже искусственное насыщение артериальной крови кислородом ситуацию не меняет [26]. Это позволило Кулагину предположить, что причиной кислородного голодания являются нарушения гемодинамики и ограничение доставки кислорода к тканям [6, с. 137–138]. Исходя из фиксируемого в опытах возрастания артеровенозной разницы, был сделан вывод о достаточной способности тканей потреблять кислород. Оставалось одно объяснение — проблема заключается в изменении транспортных свойств самой крови, в утрате ею способности переносить кислород к тканям! Таким образом, Виктор Константинович фактически описал феномен гемической гипоксии.

Травматический шок сопровождается выраженной гиповолемией, при которой в результате избыточной потери жидкости уменьшается объем циркулирующей крови (ОЦК) в организме. При снижении ОЦК как раз и возникает гемическая гипоксия, которая выражается в уменьшении кислородной емкости крови в результате снижения количества эритроцитов в единице объема крови и в нарушении транспортных свойств гемоглобина. Гемический тип гипоксии характеризуется снижением способности гемоглобина эритроцитов связывать кислород (в капиллярах легких), транспортировать и отдавать оптимальное количество его в тканях. При токсической разновидности шока в результате интоксикации организма, наблюдается также появление патологических форм гемоглобина (карбоксигемоглобин, метгемоглобин и др.). Поэтому восполнение объема циркулирующей крови — важнейшее мероприятие комплексной терапии шока.

Именно с выраженной и продолжительной гипоксией тканей, которая поддерживается нарушениями нейроэндокринной регуляции гомеостаза в результате образования порочных кругов патогенеза, Кулагин связывал развитие необратимых состояний [27]. Он считал, что «вопрос об изменении интенсивности обменных процессов и потребности клеток и тканей в кислороде при шоке имеет первостепенное значение, так как его решение позволило бы наметить новые пути профилактики и терапии шока» [6, с. 138].

В заслугу В. К. Кулагину может быть поставлено также экспериментальное изучение сочетанных и комбинированных форм травматической патологии, в частности комбинированных радиационных поражений [28].

Результаты этих исследований позволили ему выйти на важные обобщения: «При политравмах переплетение общих и частных проявлений травм оказывается очень трудной для анализа. В таких случаях происходит суммация действия разных факторов шока. Однако, это не арифметическая сумма, а новое качественное состояние» [6, с 53]. Это состояние принято называть «синдромом взаимного отягощения», характеризующегося увеличением частоты и углублением тяжести шока, угнетением защитных сил организма, опасностью вторичного кровотечения вследствие повышенной проницаемости и ломкости капилляров, понижением свертываемости крови [29, 30]. При комбинированном воздействии механической травмы и проникающей радиации синдром взаимного отягощения характеризуется более тяжелым, чем это наблюдается при чистых формах поражений, течением и травмы, и лучевой болезни.

В. К. Кулагин постоянно подчеркивал, что необходима дальнейшая коллективная работа теоретиков и клиницистов для создания единой теории патогенеза шока [6, с. 37]. В 1980 г. он получил новое должностное назначение — На-

чальник Научно-исследовательского института военной медицины МО СССР (35 НИИ МО РФ), осуществляющего фундаментальные и прикладные исследования. В конце своей короткой жизни — в зените творческих и интеллектуальных способностей — он стоял на рубежах новых научных тем, сулящих множество свершений и открытий. Но судьба распорядилась иначе — на 59 году жизни творческий полет замечательного ученого был внезапно трагически прерван [31].

Заключение

Научная дискуссия, в которой В. К. Кулагин сыграл важную роль, в конечном итоге послужила совершенствованию методологии и методики клинических исследований шока. В продуктивном диалоге с такими сильными оппонентами как В. К. Кулагин утвердилось лидерство нового научного направления — клинической патофизиологии. Однако, торжество какой-либо точки зрения в научном мире никогда не следует считать окончательным. Наука, как известно, развивается по спирали, и в этом смысле повторное прочтение трудов В. К. Кулагина на новом методологическом и технологическом витке может оказаться кладезем тонких наблюдений, глубоких умозаключений, перспективных идей и научного предвидения, заслуживающих самого пристального внимания современных исследователей и клиницистов.

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