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Уважаемые Авторы!

Благодарим вас за выбор журнала «Общая реаниматология» для публикации своих статей.

Информируем, что в 2023 г. редакция особенно приветствует статьи, содержащие результаты фундаментальных клинических и экспериментальных исследований по тематике журнала.

Для сопровождения своих статей рекомендуем дополнительно использовать графическую форму резюме и хайлайта (главных тезисов статьи), а также аудио- или видео-форматы (mp3, mp4, не более 2 минут). В них вы можете представить резюме статьи, кратко прокомментировать полученные результаты и/или представить авторскую точку зрения на основные проблемы в исследуемой области, задать дискуссионные вопросы профессиональному сообществу по теме вашего исследования.

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Применение графического, аудио- и видео-форматов в сопровождении статьи расширяет аудиторию читателей, повышает интерес к представленному материалу, способствует лучшему пониманию результатов и, как следствие, увеличивает их цитирование.

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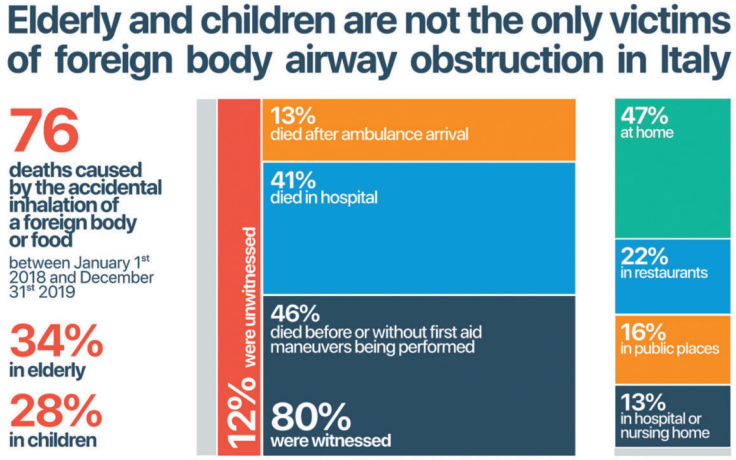
Highlights



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Желаем успехов в вашей научной и практической деятельности и дальнейшего взаимно плодотворного сотрудничества!

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Regional Anesthesia for Carotid Endarterectomy in Patients with Acute Ischemic Stroke (Pilot Study)

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Summary

Objective. The aim of this study is to assess the safety of the use of regional anesthesia for performing carotid endarterectomy (CEA) in patients in the acute phase of ischemic stroke.

Material and methods. The study included 66 patients in the acute phase of ischemic stroke (atherothrombotic subtype according to the TOAST classification) who underwent carotid endarterectomy. The inclusion criteria for the study were as follows: acute phase of atherothrombotic ischemic stroke (first 28 days), ipsilateral symptomatic ⩾ 50% stenosis of the internal carotid artery, 1–4 points neurological deficit according to the modified Rankin Scale (mRS), 1–13 points neurological deficit according to the National Institutes of Health Stroke Scale (NIHSS), size of the cerebral ischemic lesion ⩽ 4 cm. This single-center prospective cohort study compared two anesthetic approaches, regional anesthesia (RA, 46 patients) and general anesthesia (GA, 20 patients). The RA techniques included ultrasound-guided superficial and deep cervical plexus blocks on the side of the surgery.

Results. The study found no significant differences in the baseline patient characteristics, surgery techniques and clinical outcomes between the groups. There were no neurological or cardiovascular toxic reactions to the local anesthetics. Conversions from RA to GA were not performed. In the RA group, recurrent ipsilateral ischemic strokes, myocardial infarctions, wound hemorrhagic complications and lethal outcomes did not occur.

Conclusion. This pilot study has demonstrated the safety of RA for performing CEA in patients in the acute phase of ischemic stroke. RA provides adequate neuromonitoring and timely intraoperative recognition of «new» ischemic complications. To compare the efficacy of RA and GA for performing CEA in patients with acute ischemic stroke, large randomized controlled trials are needed.

Keywords: carotid endarterectomy; regional anesthesia; cervical plexus block; ischemic stroke

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

Introduction

Currently, the main options of anesthesia for performing carotid endarterectomy (CEA) include regional anesthesia (RA), general anesthesia (GA), and combined anesthesia [1–3]. RA and GA are most often compared to each other as two diametrically opposite anesthetic approaches [4, 5]. Under RA, the patient retains consciousness (from the full wakefulness to superficial sedation) and spontaneous breathing. Under GA, the patient's consciousness and spontaneous breathing are pharmacologically switched off. Various papers indicate both the advantages and disadvantages of each approach.

On the one hand, RA provides a more appropriate neuromonitoring of the operated patient (determination of the level of consciousness, development of movement disorders in the contralateral limbs or their worsening, speech changes), a lesser effect on cerebrovascular autoregulation, hemodynamic stability, better postoperative pain relief, a lower frequency of using a temporary intraluminal shunt and shorter hospital stay [2, 5–7]. On the other hand, such factors as additional psycho-emotional stress, difficulty in the reliable control of external respiration, lack of cerebral protection and muscle relaxation are considered among the disadvantages of RA [8–10].

The National Guidelines for the Management of Patients with Brachiocephalic Arteries Diseases (2013) indicate that GA and RA have the same safety in carotid surgery [4]. The type of anesthesia is determined by a joint decision of the anesthesiologist and surgeon, and is agreed with the patient [4]. These recommendations are largely based on the only large randomized controlled trial, the GALA trial (General Anesthesia versus Local Anesthesia for Carotid Surgery, 2008), comparing RA (n=1773) and GA (n=1753) in 3526 patients who underwent CEA [5, 11]. No benefit was found for either type of anesthesia [5, 11]. The patients in

the acute stage of ischemic stroke were not included in this work, and CEA was performed for both symptomatic and asymptomatic lesions of the internal carotid artery (ICA) [5].

By the acute period of ischemic stroke, we mean the first 28 days after the onset of the disease [12]. In the 2019 American Heart Association (AHA) and American Stroke Association (ASA) Guidelines for the Early Management of Acute Ischemic Stroke, emergency or urgent CEA for acute ischemic stroke is classified as Class IIb recommendation with a B-NR level of evidence [13]. To date, there are no unequivocal recommendations regarding the type of anesthesia for performing CEA in patients in the acute period of ischemic stroke [13].

The aim of this study is to assess the safety of RA for performing CEA in patients in the acute period of ischemic stroke, i. e., in the first 28 days after the onset of the disease.

Material and Methods

This pilot study included 66 patients in the acute stage of ischemic stroke with symptomatic ICA stenosis, who underwent CEA surgery in the Buyanov City Clinical Hospital (Moscow, Russia) in the period from 2015 to 2021.

Study hypothesis: RA is a safe type of anesthesia for performing CEA in patients in the acute period of ischemic stroke.

Study design: a single-center prospective cohort clinical study.

The present study was approved by the local ethics committee of the Pirogov Medical University (protocol 2, dated January 27, 2016). All patients signed an informed consent before the operation.

The inclusion criteria for the study were as follows:

— acute period of atherothrombotic ischemic stroke (first 28 days),

— ipsilateral «symptomatic» stenosis of the internal carotid artery of 50% or more,

— neurological deficit according to the modified Rankin Scale (mRS) 1–4 points,

— neurological deficit according to the National Institutes of Health Stroke Scale (NIHSS) 1–13 points, corresponding to minor to moderate stroke severity,

— size of the cerebral ischemic lesion $\leqslant$4 cm.

The exclusion criteria for the study:

— concomitant cardiac arrhythmia (atrial fibrillation),

— ipsilateral stenosis of the ICA$<$50%,

— neurological deficit $\geqslant$5 points according to the mRS,

— neurological deficit $\geqslant$14 points according to the NIHSS,

— size of the cerebral ischemic lesion $>$4 cm,

— endovascular procedures on carotid and cerebral arteries.

Patients with concomitant cardiac arrhythmias, mainly with atrial fibrillation, were not included in this study. Thus, with a certain degree of confidence, it can be argued that all of the selected patients had ischemic stroke of the atherothrombotic subtype according to the TOAST classification (Trial of Org 10172 in Acute Stroke Treatment), i. e., the main cause of the disease was atherosclerosis of large arteries [14].

The primary endpoint was ipsilateral ischemic stroke in the postoperative period. The secondary endpoints were any stroke, myocardial infarction, wound hemorrhagic complications, temporary intraluminal shunt use, duration of the postoperative period, and death.

RA was used in 46 patients (69.7%), GA was chosen in 20 patients (30.3%). Both groups were comparable in baseline patient characteristics (Table 1).

RA was performed under ultrasound guidance, using an ultrasound machine «LOGIQ e» (GE Healthcare, USA). Using the aseptic technique, we performed a combined superficial and deep cervical plexus block on the side of the operation with 0.5–0.75% ropivacaine or 0.5% levobupivacaine solution in a total dose of 150–300 mg. The effectiveness of the block was assessed by determining pain and tactile sensitivity on the corresponding anterolateral surface of the neck from the edge of the mandible to the clavicle. The average time from the block to the start of the operation was 29.9±5.7 minutes. Intraoperatively, if necessary (persistent pain sensitivity), the surgeon additionally irrigated the surgical wound with 2% lidocaine solution. After opening the carotid fascial sheath, almost all patients additionally required irrigation of the carotid arteries with a local anesthetic (5 ml of 2% lidocaine solution) due to the development of pain syndrome during their mobilization. In addition, irrigation of carotid glomus with local anesthetic (5 ml of 2% lidocaine solution) was routinely performed in all patients. In all cases, RA was supplemented with intravenous bolus injections of fentanyl in a total dose of 200–300 μg for optimal analgesia and superficial sedation. To prevent involuntary arm movements and to prevent the patient falling off the operating table during surgery, we used wrist restraints and a thigh belt. We placed a squeaky toy in the contralateral hand for non-verbal communication with the patient.

In the GA group, we used balanced endotracheal anesthesia with tracheal intubation. Induction of GA was carried out with fentanyl, propofol and an intermediate-acting neuromuscular blocking agent (atracurium, cisatracurium, or rocuronium); the maintenance of anesthesia — with fentanyl, sevoflurane and a neuromuscular blocking agent. Tracheal extubation was performed on the operating table 10–15 minutes after the end of the operation

Table 1. Comparative baseline characteristics of patients in the RA and GA groups.

Parameters	Parameters values in groups		*P*-value
	Regional anesthesia (*n*=46)	General anesthesia (*n*=20)	
Age (years)	64.9±7.0	63.6±10.6	0.65
Men (*n*, %)	34 (73.9)	13 (65)	0.46
Comorbidities (*n*, %)			
Arterial hypertension	45 (97.8)	19 (95)	0.54
Coronary artery disease	18 (39.1)	9 (45)	0.66
Previous myocardial infarction	7 (15.2)	5 (25)	0.34
Previous stroke	10 (21.7)	6 (30)	0.47
Diabetes	15 (32.6)	5 (25)	0.54
Smoking	21 (45.7)	7 (35)	0.42
Baseline neurological deficit			
mRS (scores)	3.4±0.7	3.3±0.8	0.8
NIHSS (scores)	5.8±2.8	5.6±2.8	0.95
Number and size of cerebral ischemic lesions			
Single lesion (*n*, %)	23 (50)	8 (40)	0.45*
Several lesions (*n*, %)	23 (50)	12 (60)	
Lesion dimensions (mm)	15.9±10.4	17.6±13.7	0.81
Thrombolysis			
Systemic thrombolytic therapy (*n*, %)	3 (6.5)	2 (10)	0.62

Note. * — Chi-Square test was used for multi-field tables.

to conduct an early assessment of the patient's neurological status.

Oxygenation was monitored using pulse oximetry with target values of 99–100%. Invasive blood pressure monitoring was performed through a 20G catheter placed in the radial artery. It began before the induction of anesthesia and lasted for 24 hours. In addition, ECG monitoring with ST-segment analysis, non-invasive measurement of blood pressure, and urine output assessment were carried out. During GA, bispectral index/cerebral oximetry, respiratory mechanics indicators, analysis of gas mixture in the respiratory circuit, and body temperature monitoring were performed as well.

Intraoperatively, the cerebral tolerance to ischemia was assessed objectively and subjectively. As an objective criterion, stump pressure was measured in all patients (groups RA and GA) during clamping of the common and external carotid arteries. In cases of mean stump pressure below 30 mm Hg and the absence of a characteristic stump pressure waveform, the indications for the insertion of a temporary intraluminal shunt were presented. In the RA group, subjective criteria for assessing the cerebral tolerance to the cross-clamping were additionally used (dynamic neuromonitoring including assessment of the patient's level of consciousness, cognitive status, motor function of the contralateral upper limb by squeezing and releasing a squeaky rubber toy in the hand, and speech). Subjective indications for the insertion of a temporary intraluminal shunt were the development of depression of consciousness or confusion, the appearance or deterioration of paresis in the contralateral hand, the appearance or deterioration of aphasia. Dynamic neuromonitoring continued throughout the entire period of cross-clamping and made it possible to track the slightest changes in the patient's neurological status. In addition, since 2020, we have begun to routinely perform cerebral oximetry of both cerebral hemispheres using INVOS technology for all patients in our study. Thus, we got a second objective criterion for assessing the cerebral tolerance to the clamping — the absolute values of ipsilateral rSO_2 below 40–50%.

Statistical analysis of clinical data was performed using Statistica 12 software for Windows (StatSoft Inc., USA). The sample size was not predefined. Normality of data distribution was assessed using the Kolmogorov–Smirnov test and Shapiro–Wilk's test. To compare continuous variables with a normal distribution, Student's *t*-test was used for independent samples; to compare variables that do not have a normal distribution, the Mann–Whitney *U*-test was used. Nominal data were compared using Pearson's Chi-Square test. The differences between the groups were considered significant at $P<0.05$. The data obtained during the study were analyzed according to the basic principles of evidence-based medicine.

Results

Significant differences in surgery types and clinical outcomes between both groups were not found (Table 2). There were no neurological or cardiovascular toxic reactions to the local anesthetics. No conversion from RA to GA was performed. The frequency of using a temporary intraluminal shunt was lower in the RA group (23.9% vs 35%), but no significant differences were found due to the small size of the groups (P=0.35). At the hospital stage in the RA group, recurrent ipsilateral ischemic stroke, myocardial infarction, wound hemorrhagic complications, as well as deaths did not occur. However,

Table 2. Comparative results of the use of RA and GA for CEA in the acute period of ischemic stroke.

Parameters	Parameters values in groups		*P*-value
	Regional anesthesia (*n*=46)	General anesthesia (*n*=20)	
Time from stroke to surgery (days)	8.8±5.3	7.0±4.3	0.26
Operation in the first 72 hours after the onset of the stroke (*n*, %)	5 (10.9)	3 (15)	0.64
Duration of surgery (minutes)	97.2±26.0	91.8±18.8	0.56
Duration of cross-clamping (minutes)	26.8±11.0	26.6±15.4	0.78
Temporary intraluminal shunt (*n*, %)	11 (23.9)	7 (35)	0.35
Duration of the postoperative period (days)	5.2±1.8	5.6±2.0	0.46
Length of hospital stay (days)	11.6±5.3	11.2±4.2	1.0
Death (*n*, %)	0 (0)	0 (0)	1.0
Postoperative complications (*n*, %)			
Ipsilateral ischemic stroke	0 (0)	0 (0)	1.0
Any stroke	2 (4.4)	0 (0)	0.34
Myocardial infarction	0 (0)	0 (0)	1.0
Wound hemorrhagic complications	0 (0)	1 (5)	0.13
Neurological status at discharge			
mRS (scores)	1.1±1.1	1.0±1.1	0.5
NIHSS (scores)	1.9±2.1	2.0±1.7	0.67

two strokes (4.4%) happened in the RA group: an intracerebral hematoma in the area of previously described gliosis lesions on the side of the operation (1 patient) and an ischemic stroke on the contralateral side (1 patient). Both patients were discharged from the hospital with moderate neurological deficit. A postoperative wound hematoma developed in the early postoperative period in one patient from the GA group (5%), which required its revision and hemostasis.

Discussion

Currently, RA is becoming a more and more popular method of anesthesia in carotid surgery, although the use of a specific type of anesthesia is largely determined by the preferences of the vascular surgeon, anesthesiologist and the individual patient [2, 5, 6]. The wide use of RA was facilitated by the universal implementation of ultrasound guidance and neurostimulation, as well as the emergence of more effective and safer local anesthetics and sedatives [7, 15, 16]. In addition, the popularity of RA in carotid surgery is explained by the imperfection of surrogate methods of neuromonitoring (cerebral oximetry, transcranial Doppler, bispectral index, electroencephalography, somatosensory evoked potentials), which are commonly used during GA and do not always accurately reflect the state of the brain during cross-clamping [6, 17, 18]. It should be noted that patient cooperation is a crucial factor during operations under RA. Therefore, psychiatric disorders, irregular or unpredictable behavior, claustrophobia are contraindications to RA.

Surgical stress, cited as one of the main drawbacks of RA, is currently successfully suppressed using sedation [10]. A number of works indicate the need for additional use of opioids (fentanyl, remifentanil) and sedatives (dexmedetomidine, clonidine, benzodiazepines, propofol, etc.) when performing CEA under RA, which reduces the level of perioperative stress, provides the necessary psychological comfort to the patient, especially in the case of incomplete pain relief [10, 19]. Based on the measurement of plasma cortisol levels, Szabo P. M. et al. (2020) demonstrated that additional target controlled propofol infusion during RA has a significant positive effect on perioperative stress [10]. In our study, fentanyl was administered for complete analgesia but sedation was not routinely used. However, if it was necessary to use a temporary intraluminal shunt, the propofol infusion was adjusted to ensure neuroprotection and prevention of psychomotor agitation during cross-clamping. In patients being operated on in the acute period of stroke, delayed placement of intraluminal shunt or arteriorrhaphy may create a risk of new ischemic cerebral complications. Therefore, before the carotid artery clamping, arteriotomy and shunt placement, we made an intravenous bolus of propofol at a dose of 50–100 mg and started an intravenous infusion of propofol at a rate of 300–400 mg/hour. After reaching the required level of sedation (the Richmond Agitation Sedation Scale of –3 or –4 points, the Ramsay Sedation Scale of 5 points), the arteries were clamped and a temporary shunt was inserted. Similar steps were taken before extraction of the shunt and arteriorrhaphy. Propofol infusion was continued during the cross-clamping periods. During intravenous sedation, the patient was observed to maintain adequate spontaneous breathing. After recovery of clear consciousness, the strength of the contralateral hand and speech were assessed.

Temporary intraluminal shunt. Opinions about the use of a temporary intraluminal shunt for CEA are controversial, and the rate of its use in patients operated on under RA, according to the literature, ranges from 8.9% to 31.6% [20–22]. In our study, a temporary shunt was used in 23.9% of cases in the

RA group and in 35% of cases in the GA group (not significant difference). Reducing the frequency of temporary shunting is really important, since the intraoperative shunt use itself may be an additional risk factor for cerebral ischemic complications [18]. Rocha-Neves J. M. et al. (2020) showed that the use of the temporary shunt has not demonstrated an advantage in the incidence of perioperative complications of CEA (stroke, hyperperfusion syndrome, myocardial infarction, surgical hematoma) among patients operated on under RA, who developed neurological deficit during carotid cross-clamping [21]. Zakirzhanov N. R. et al. (2021) succeeded in avoiding the use of temporary shunt in patients in hyperacute and acute stages of ischemic stroke [23]. The authors used RA, which, in combination with intraoperative transcranial Doppler and dynamic neuromonitoring in real time, provided an accurate and qualitative assessment of the cerebral tolerance to ischemia during carotid cross-clamping [23].

Neurological complications. In the largest randomized clinical study, the GALA trial, the incidence of stroke in the RA group was 3.7% (7 of 66 strokes were contralateral to the side of the operation), and in the GA group it was 4% (15 of 70 strokes were contralateral); the difference between the groups was insignificant [5]. Orlický M. et al. (2019) compared the incidence of asymptomatic strokes (according to diffusion-weighted magnetic resonance imaging of the brain) in patients undergoing CEA under RA (n=105) and under GA (n=105). MRI was performed before surgery and 24 hours after it. The frequency of newly identified asymptomatic ischemic lesions was significantly lower in the RA group: 6.7% versus 17.1% (P=0.031). Most lesions after RA (71.4%) were associated with embolization, and more than half of the new ischemic injuries after GA (55.5%) were due to cerebral hypoperfusion [24]. The authors believe that such asymptomatic ischemic damages may further impair cognitive function [24]. There was no significant difference in the incidence of strokes, transient ischemic attacks and other perioperative complications [24]. The literature describes various reactions to cerebral hypoperfusion during carotid cross-clamping under RA including depression of consciousness or confusion, psychomotor agitation, aphasia, paresis of the contralateral limbs or seizures [7, 18].

According to the literature, the frequency of conversion from RA to GA in CEA patients ranges from 0.3% to 14.3% [5, 19, 25]. The main reasons for conversion are insufficient anesthesia, psychomotor agitation of the patient, claustrophobia, intravascular injection of local anesthetic, manifestations of severe respiratory failure, prolongation of surgery due to various reasons [5, 19, 20, 25]. In our study, conversions from RA to GA were not performed, and the appearance of pain due to the expansion of the surgical field or due to the opening of the carotid fascial sheath was stopped by irrigating the surgical field with 2% lidocaine solution and additional IV administration of opioids. The development of pain syndrome during mobilization of the carotid arteries is due to the fact that the carotid sheath is abundantly innervated by the glossopharyngeal and vagus nerves and cannot be anesthetized with cervical plexus blocks [15]. Irrigation of carotid glomus with a local anesthetic (5 ml of 2% lidocaine solution) was carried out to suppress unwanted hemodynamic reactions (bradycardia, excessive arterial hypertension, blood pressure fluctuations). We emphasize that we use the irrigation technique instead of the injection technique in order to exclude the possibility of inadvertent intravascular injection.

According to Grieff A.N. et al. (2021), RA was accompanied by a significantly lower incidence of cranial nerve injury compared to GA: 1.7% versus 2.9%, respectively (P<0.002) [26]. Analysis of the literature has shown that the most commonly injured during CEA are hypoglossal nerve and the marginal mandibular branch of the facial nerve followed by glossopharyngeal, vagus and spinal accessory nerves [7, 26]. Damage to the hypoglossal nerve is manifested by deviation of the tongue towards the injury. Damage to the marginal mandibular branch of the facial nerve usually causes permanent paralysis of the muscle of the corresponding half of the lower lip and is manifested by a drooping mouth corner and an asymmetric smile [27]. Manipulations with the vagus nerve cause hemodynamic reactions (bradycardia, hypotension), nausea and vomiting. Damage to the vagus nerve (for example, after compression with a Farabeuf retractor) is manifested by persistent sinus tachycardia after surgery. Most cranial nerve palsies spontaneously resolve within 1 year, with the exception of the spinal accessory nerve palsy, which may be irreversible [26].

Myocardial ischemia and myocardial infarction. In the largest randomized GALA trial, the incidence of myocardial infarction in the RA group was 0.5% versus 0.2% in the GA group (not significant difference) [5]. Grobben R.B. et al. (2016) found that troponin I elevation in the first 3 days after surgery was detected in 15.1% of patients who underwent CEA under GA, but myocardial infarction developed in 3.6% in the first 30 days [28]. Thus, clinically confirmed myocardial infarction was observed in only 23.5% of patients with elevated troponin I levels after surgery under GA [28]. Pereira Macedo J. et al. (2019) found that troponin I elevation in the first 2 days after surgery was detected in 15.3% of patients who underwent CEA under RA [29]. In the long-term follow-up period, patients with diagnosed myocardial injury after CEA under RA remained at a high risk of developing myocardial

infarction and other major adverse cardiovascular events [29]. In an earlier trial, Sbarigia E. et al. (1999) performed intraoperative 12-lead ECG monitoring with ST segment analysis [22]. In the general sample, the signs of myocardial ischemia were found in 18% of patients operated on under RA, and in 23% of patients operated on under GA (the difference was not significant) [22]. When selecting subgroups depending on the presence / absence of coronary artery disease (CAD) and the type of anesthesia (RA or GA), the most frequent episodes of myocardial ischemia occurred in the CAD-GA subgroup (83%). The data may indicate a preference for the use of RA for CEA in patients with high cardiac risk [22].

Complications of RA. Complications of RA develop in 0–4.4% of patients [5, 7, 15]. The most dangerous complications associated with inadvertent intravascular injection of local anesthetic, causing systemic toxic reactions (up to generalized seizures, coma, refractory asystole). Respiratory distress can develop as a result of an unintentional blocking of the phrenic or recurrent laryngeal nerves. A unilateral phrenic nerve block is a common complication of deep cervical plexus anesthesia (55–80%), but is usually asymptomatic [15]. Clinically significant respiratory disorders (complete paralysis of the diaphragm, asphyxia) can occur in the presence of a previous paresis of the contralateral phrenic or recurrent laryngeal nerves [7]. Among the cardiovascular complications of RA, hypertensive emergency, angina episode, tachy- and bradyarrhythmias are possible [5]. The development of RA complications leaves the multidisciplinary team with a difficult choice whether to convert to GA and perform the scheduled surgery or postpone surgical intervention. The decision is made individually in each case, but always by a team.

In a recent systematic review with meta-analysis, Harky A. et al. (2020) compared two large samples of patients operated on under RA (n=26094) and GA (n=126282), which included both cohort studies (prospective and retrospective) and randomized controlled trials [30]. The comparative analysis demonstrated the significant advantages of RA in almost all criteria: neurological and cardiovascular complications, length of intensive care unit stay, length of hospital stay, and most importantly, mortality. However, when separately comparing RA (n=1987) and GA (n=1969) in patients included only in randomized controlled trials, no significant difference was identified for any item [30].

In the international literature, we found no large randomized controlled trials comparing different types of anesthesia for performing CEA in patients in the acute period of ischemic stroke.

Our preference for RA when performing CEA in patients in hyperacute (up to 72 hours) and acute (up to 28 days) periods of ischemic stroke is due to the following considerations. The main advantage of RA in this cohort of patients is the ability to perform dynamic neuromonitoring during the entire operation. In case of a worsening of the initial neurological deficit or the development of a new one, this complication is diagnosed immediately and the necessary measures are taken in a timely manner to adjust the treatment strategy. According to Stoneham M.D. et al. (2015), observing an awake patient during cross-clamping is the most reliable method for assessing his neurological status [7]. In the case of GA, an intraoperative recurrent stroke can be diagnosed only after recovery of consciousness and tracheal extubation, with the loss of a very important time. The second advantage of RA is the reducing the frequency of temporary shunting. The third advantage of RA, in our opinion, is the possibility of performing an emergency revision of the surgical site in the first 6-8 hours after CEA without using additional anesthesia, which is extremely important in the case of local postoperative complications (neck hematoma, bleeding, arterial thrombosis).

Limitations. The present study has several limitations:

1. Our study did not use randomization to evenly and randomly allocate patients between the RA and GA groups. The type of anesthesia was determined in each case individually, taking into account the wishes of the vascular surgeon, anesthesiologist and the patient.

2. For objective reasons, the study could not be carried out in a blind manner: the entire multidisciplinary medical team and the patients themselves knew exactly about the type of anesthesia.

3. Based on many years of experience in carotid surgery, researchers have developed a clear preference for RA.

Conclusion

This pilot study has demonstrated the safety of RA for performing CEA in patients in the acute period of ischemic stroke. RA allows the most complete control and assessment of the impaired neurological status of the patient during the operation. To compare the efficacy of RA and GA for performing CEA in patients with acute ischemic stroke, large randomized controlled trials are needed.

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Selection of Target Mean Arterial Pressure in Severely Burned Patients with Septic Shock

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Summary

The timely diagnosis of both sepsis and septic shock can be challenging in severely burned patients. Monitoring methods providing early diagnosis of organ dysfunction development are of great importance. Assessment of the glomerular filtration rate with central hemodynamic parameters can be considered as a component of comprehensive monitoring of effectiveness of septic shock therapy.

Aim: to determine the relationship between the target mean arterial pressure and glomerular filtration rate parameters in the treatment of severely burned patients with septic shock.

Material and methods. 158 severely burned patients with septic shock were included in the study, of them 121 patients represented a retrospective historical group, and 37 patients constituted a prospective group. The main criteria of treatment efficacy were28-day and hospital mortality.

Results. In the patients of prospective group, 28-days mortality decreased down to 16.2% compared with 33.9% in the retrospective group, and hospital mortality dropped down to 29.7% vs 42.1%, respectively (P<0.05).

Conclusion. Extended hemodynamic and metabolic (renal function assessment) monitoring of intensive therapy of severely burned patients with septic shock helps targeted adjustment of fluid therapy and provides earlier beginning of extracorporeal blood therapy thus favoring better survival rate.

Keywords: sepsis; septic shock; burns; central hemodynamics; hemodynamic monitoring; fluid therapy; vasopressors

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

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Introduction

According to the current classification, septic shock is characterized by circulatory failure manifesting as hypotension and increased lactate level of more than 2 mmol/L (despite adequate fluid therapy), and requiring vasopressors to maintain mean arterial pressure greater than 65 mmHg [1]. Intensive care strategy proposed by Rivers E. et al. [2] aimed at optimizing oxygen delivery (increasing cardiac performance, oxygenation and hemoglobin concentration depending on clinical setting), with clear goals and monitoring algorithm, has contributed to a significant reduction of mortality, which was 44.3% versus 56.9% with the conventional approach. At the same time, several studies have shown that the baseline parameters of myocardial contractile function were not impaired (systolic dysfunction was observed in only 20% of patients), while the patients with diastolic dysfunction (50%) responded negatively to fluid therapy [3–7]. In such cases, any volume of IV fluid may be redundant, and infusion therapy strategy could be regarded as aggressive and provoking progression of diastolic dysfunction [8]. However, the impact of increased venous pressure on renal function by reducing renal blood flow and glomerular filtration rate has been noted, which certainly directly or indirectly worsens organ dysfunction [9, 10]. In the concept of «three hits» of septic shock (C. Cordemans, 2012) [11] only during the «first hit» stage, when hypotension, hypovolemia, and oliguria develop, the control of mean arterial pressure, central venous blood saturation, urine output and lactate level can effectively ensure patient safety, reflecting the treatment efficacy.

For severely burned patients, the issue of diagnosing both sepsis and septic shock is even more relevant than in other patient groups [12]. In the early phase of burn injury, the patient's clinical status may correspond to the «second hit» of septic shock, which is related both directly to the mechanism and severity of the injury and to the hyperhydration syndrome due to excessive fluid infusion. Moreover, early burn sepsis/septic shock is characterized by an extremely severe and often fulminant course with a high risk of death [13, 14]. Monitoring methods enabling accurate and specific diagnosis of the causes of organ perfusion disturbances will be of particular

importance. Despite all its limitations, the measurement of systemic arterial pressure remains an integral component of current comprehensive hemodynamic monitoring because all other elements characterizing abnormal parameters and their contribution to the development of central hemodynamic disturbances, are based on the systemic arterial pressure measurement. The latest concepts of shock therapy, including the four-phase model of fluid therapy in shock (ROS-D/ROSE concept which implies rescue, optimization, stabilization, de-escalation), suggesting a phase-based approach to hemodynamic control with sequential use of hemodynamic monitoring by echocardiography, blood flow ultrasound scan, continuous measurement of blood lactate and central venous blood saturation, as well as specific volumetric parameters, are still initially based on the measurement of blood pressure [15–17]. The prerequisites for personalization of acceptable levels of systemic blood pressure in different groups of patients have been introduced, for example, in patients with septic shock and baseline hypertension, the maintenance of higher blood pressure values is recommended [18]. Glomerular filtration rate (GFR) less than 60 mL/min/m^2 has been found to increase the risk of death from cardiovascular failure by several times compared to values between 75 and 60 mL/min/m^2 [17, 19, 20]. Adding GFR monitoring for evaluation of the efficacy of septic shock therapy helps develop a tailored approach to choosing optimal hemodynamic parameters [21, 22].

The aim of our study was to determine the relationship between target mean arterial pressure and glomerular filtration rate parameters during the treatment of severely burned patients with septic shock.

Material and Methods

A single-center screening study was performed in 328 patients with burn injury hospitalized in the Burn Unit of the Vishnevsky Research Medical Center of Surgery in 2011–2021, including a retrospective analysis of medical records of 277 patients during 2011–2017 and a prospective study in 51 patients during 2018–2021. The inclusion criteria were septic shock (diagnosed according to Russian Association of Surgical Infection Specialists (RASIS) (2004) and SSC (2008) guidelines in the retrospective 2012–2016 group and RASIS 2016 and «Sepsis 3» in the prospective group) [1, 23–26]; hemodynamic monitoring data; lactate levels; urine output; daily urine biochemical study parameters; biomarkers of systemic infection; specific treatment information and its efficacy assessment. Exclusion criteria were age <18 years; lack of the above data; arterial hypotension during fluid therapy and use of catecholamines at the time of screening. In accordance with the stated criteria, 158 patients (121 in the retrospective and 37 in the prospective groups) were included in the study.

During the analysis, a subgroup of patients with baseline hypertension (AH subgroup) was identified. At the time of inclusion, they significantly differed from the other normotensive patients in age (60.3 vs 57.0 years, respectively).

The patients in the prospective group were divided into three subgroups with vasoplegic (*n*=30), vasoplegic-hypovolemic (*n*=4), and cardiomyopathic type (*n*=2) hemodynamics based on hemodynamic monitoring data and the results of retrospective study.

Most patients (151 [95.6%]), suffered from flame burn injury with involvement of over 30% of body surface area. Seven (4.4%) patients had electrical injury in combination with electric arc-related skin thermal injuries. Inhalation burn injury was diagnosed in 38 (24.1%) patients. The overall severity of patients' condition when transferred to the intensive care unit was assessed using SAPS 3 severity and prognosis scale [27, 28]. The lethal outcome prognosis reached 73.55 (±11.2) in the retrospective group and 74.6 (±5.8) in the prospective group (Table).

Due to the different times of data collection and arrangement and the use of various sepsis treatment guidelines, the group homogeneity was not considered mandatory for comparative analyses. The results of treatment were assessed using universal criteria based on the mortality rate.

In most cases (76.9% of patients), the septic shock was associated with a wound infection. Pulmonary sepsis occurred in 23.1% of cases. Infectious nature of the complications was determined by typical clinical signs characteristic of the systemic inflammatory response. In addition, there was evidence of a significant increase in the levels of systemic infection biomarkers such as procalcitonin and C-reactive protein (Table).

All patients received intensive treatment according to the current international and national guidelines of professional medical societies on treatment of septic shock and organ dysfunction management including mechanical lung ventilation, fluid therapy, vasopressor support, and anticoagulants. Antimicrobial drugs were prescribed based on the baseline epidemiological data empirically or in a targeted manner when infection was confirmed by positive microbiological tests of tissue biopsy specimens, airway secretions, or blood.

Comprehensive invasive monitoring using PiCCO technology (Pulsion Medical Systems, Munich, Germany) was performed with the measurement of cardiac index (CI), global end-diastolic volume (GEDV), extravascular lung water index (EVLWI), and total peripheral vascular resistance (TPVR). Hemodynamic profile changes with thermodilution

General characteristics of patients and baseline criteria of infection.

Parameters	Parameters values in groups	
	Retrospective group (*n*=121)	Prospective group (*n*=37)
Sex (male/female), *n*	69/52	18/19
Age, years	58±15.7	51±11.3
Frank's index of burn severity, Units (min–max)	94 (83–188)	91 (76–179)
Soft tissue skin injury, *n*	93	36
Chest organ injury, *n*	28	1
CHF, NYHA II–III, *n* (%)	6 (4.9)	8 (21.6)
Respiratory failure grade II–III, *n* (%)	4 (3.3)	1 (2.7)
Hypertension, *n* (%)	43 (35.5)	8 (21.6)
Insulin dependent diabetes mellitus, *n* (%)	16 (13.2)	3 (8.1)
Obesity, *n* (%)	13 (10.7)	8 (21.6)
SOFA scale (points)	8.5±1.9	9.3±0.7
SAPS 3 scale, %	73.55 (±11.2)	74.6 (±5.8)
Heart rate, bpm	112.4 (94; 143) SD 17.5	116.5 (42; 139) SD 13.1
Body temperature, °C	38.4 (35.4; 38.9) SD 2.3	38.6 (35.1; 39.4) SD 1.4
PCT, ng/ml	14.2 (2.4; 97.4) SD 17.1	13.2 (1.7; 43.2) SD 12.1
CRP, mg/l	256.5 (53.6; 413) SD 62.4	356.5 (43.2; 489) SD 41.4
WBC count, $\times 10^9$/l	17.2 (2.7; 49.6) SD 8.3	24.2 (3.2; 39.7) SD 6.4
Neutrophils, %	25.3 (13; 43) SD 8.3	23.6 (9.7; 42.8) SD 7.2

Note. CHF — chronic heart failure; NYHA — New York Heart Association; SOFA — Sequential Organ Failure Assessment; SAPS — Simplified Acute Physiology Score; PCT — procalcitonin; CRP — C-reactive protein. The data of the last 6 rows are presented as *M* (min; max).

curves were recorded every 8 hours over 72 hours of treatment. Hemodynamic disturbances and methods of their correction were interpreted according to the guidelines of the Department of Anesthesiology and Resuscitation, Northern State Medical University [29].

We assessed central venous blood saturation ($ScvO_2$), lactate level, and glomerular filtration rate (GFR) every 4 hours from the start of monitoring and primary assessment of circulatory disturbance type. Continuous control of respiratory mechanics and gas exchange was performed using the capacities of the ventilator and gas analysis module of the monitoring system. Parameters of myocardial electrophysiology, heart rhythm and pulse oximetry were also recorded through the monitoring complex. Biochemical urine investigation (every 24 hours after connection to the monitoring system) was performed to determine nitrogen balance and control natriuresis due to a high risk of hypernatremia and hyperosmolar syndrome in severely burned patients, as well as to control hypermetabolism. Glomerular filtration rate (GFR) was calculated retrospectively on the basis of endogenous creatinine clearance measurement data using the results of biochemical study of daily urine by Rehberg–Tareyev method [30, 31].

The conclusion about hemodynamic stabilization was made based on the achievement of mean arterial pressure (MAP), sufficient to maintain glomerular filtration rate over 60 ml/min/m^2. If this value was not achieved at 12–24 hours of follow-up (regardless of the corresponding hemodynamic parameters), patients were started on renal replacement therapy with prolonged veno-venous hemo(dia)filtration (20–35 ml/kg/hr). The main clinical and laboratory parameters in the prospective group were recorded in correlation with the stages of data acquisition in the retrospective stage. The 28-day and hospital mortality rates were chosen as the main efficacy criteria when comparing treatment regimens in the retrospective and prospective stages.

Microsoft Access database was used to store the data obtained. Statistical analysis was performed using the STATISTICA 6.0 software package (StatSoft, USA). The data distribution was assessed using the Kolmogorov–Smirnov test. In the case of normal distribution, mean values with standard deviations (SD) were used for data analysis and presentation. If the distribution was different from normal, median values and their 25th to 75th percentiles were used. Depending on the type of data distribution, the *t*-test for independent samples was used to determine differences between independent groups, whereas Mann–Whitney *U*-Test was used as a nonparametric alternative. If necessary, intragroup pairwise comparisons were made using *t*-test for dependent samples, with a nonparametric alternative being Wilcoxon matched pairs test for dependent variables, if necessary. When assessing the significance of differences and changes, $P<0.05$ was used as a threshold value.

Results

The patients in the retrospective group were included in the study according to the criteria for septic shock diagnosis accepted at that time, and all included patients had baseline low values of mean arterial pressure (on average, less than 60 mm Hg). However, they had satisfactory cardiac performance with mean stroke volume index over 50 ml/m^2 (cardiac index up to 4.1 l/min/m^2), with arterial blood lactate level over 2 mmol/L, mean

central venous blood saturation not exceeding 61.8% and global end-diastolic volume index reaching 1000 ml/m^2. The extravascular lung water index (EVLWI) was more than 12 ml/kg. At the baseline, most patients had a dramatic decrease of total peripheral vascular resistance index (TPVRI), which was significantly lower than 1000 dyn×sec×cm^{-5}/m^2. The total volume of intravenous fluid by that time (over a period of 60–120 minutes from the discovery of hypotension) was 1105.6 (SD 210.4) ml. The mean dose of norepinephrine vasopressor support was 0.19 μg/kg/min (SD 0.39). During the retrospective phase of study, renal function was assessed based on glomerular filtration rate (GFR) using data from biochemical analysis of daily urine 24 hours after the patients' admission to the intensive care unit. Recovery of normal urinary output and satisfactory GFR values were observed in 77 patients. Linear regression analysis of the correlation between urinary flow rate and mean arterial pressure when GFR>0 ml/min/m^2 was achieved in retrospective group patients revealed a positive correlation with R=0.81. Remarkably, the values of mean arterial pressure corresponding to recovery of GFR were significantly higher (75.2 mm Hg [SD 13.4] vs. 68.8 mm Hg [SD 11.3]) in patients with hypertension (AH subgroup). The urine output rate was also higher (Fig. 1). No significant differences in norepinephrine dosages were found.

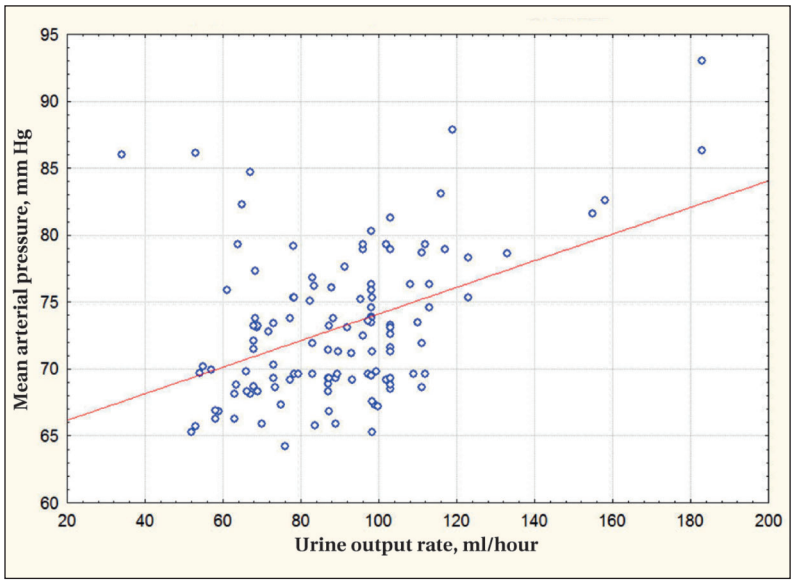

Fig. 1. Linear regression analysis of the correlation between urine output rate and MAP upon achieving a GFR>60 mL/min in the general patient cohort.

By the end of day 1 of follow-up, normalization of both volumetric and dynamic parameters of central hemodynamics was noted in patients with satisfactory GFR. The maximum value of mean arterial pressure corresponding to restoration of satisfactory renal function was 87.9 mm Hg. The values of mean arterial pressure and total vascular peripheral resistance were significantly higher compared with the baseline. There were no significant differences in central hemodynamic parameters (CI, TPVRI, CVP, SVV, ITBVI, EVLWI) between patients with and without hypertension in the retrospective group. Organ dysfunction subsided with almost complete recovery of the vital functions on days 5–7 of follow-up.

In the remaining patients (n=44, 39.6%), renal function had not recovered by day 1 of follow-up. During days 1–2 of treatment, they received renal replacement therapy (average time of initiation was 26.4 hours after the diagnosis of septic shock), in accordance with the current local protocols. All patients received prolonged veno-venous hemo(dia)filtration (20–35 ml/kg/hour) with positive clinical effect in 36 patients, which manifested as relative stabilization of hemodynamic parameters and respiratory status during days 2–3.

Eight patients in the retrospective group failed to achieve mean arterial pressure values greater than 65 mm Hg. Arterial hypoxemia in these patients was more severe with a decrease in the oxygenation index to 142.32 mmHg (SD 12.05). Global end-diastolic volume did not exceed 700 ml/m^2, and EVLWI was below 10 ml/kg, stroke volume variability reached 23% (SD 3.9%). All these patients received fluid therapy within the first hour of stay in the department with an average volume of 1000 ml of crystalloid solutions according to the then-current principles of early targeted therapy to stabilize hemodynamics. Subsequent cardiac index values remained extremely low, and the total peripheral vascular resistance exceeded 2000 dyn/sec/cm^{-5}/m^2 in all cases. Left ventricular contractility was under 1000 mmHg. These values were the reason for prescribing dobutamine in doses from 2.5 to 11 mcg/kg/min together with the vasopressor support (norepinephrine up to 3 mcg/kg/min). Despite the subsequent significant increase of cardiac index, decrease of arterial hypoxemia severity, and lactate reduction (in some cases with the extracorporeal detoxification), these patients had EVLWI increase up to 14.7 (SD 0.24) ml/kg and increase of CVP up to 15.68 (SD 1.6) mm Hg. Low global end-diastolic volume, high variability of stroke volume, and a significant increase of total peripheral vascular resistance index were observed during the follow-up. However, no significant increase of blood pressure was noted. Lactate level remained high. All patients with a similar hemodynamic pattern died

later. Mean GFR in those patients did not exceed 4.3 (SD 16.8) ml/min/m².

A total of 41 patients (33.9%) died in the retrospective group by day 28 of treatment, the overall hospital mortality was 42.1%. Mean arterial pressure values were significantly higher in surviving patients than in those who later died (75.2 mm Hg [SD 4.8] versus 68.01 mm Hg [SD 7.3] at $P<0.001$).

Vasoplegic hemodynamic disturbance was most frequently observed in the patients during the prospective phase of treatment (n=30). The therapeutic strategy in such patients was based on norepinephrine at the average dose of 0.12 (SD 0.36) mcg/kg/min, which was not significantly lower than the average norepinephrine dose in the retrospective group of patients with vasoplegic circulation. No fluid therapy was administered for the early targeted treatment of septic shock due to satisfactory volumetric preload values.

Vasoplegic-hypovolemic disorders were observed in four patients. All these patients had more than 15% increase in stroke volume during passive leg raising test and responded well to fluid therapy. However, the total volume of fluid therapy during the first 24 hours of follow-up was significantly lower in the prospective patients than in the retrospective group (1605.8 ml and 2046.9 ml, respectively, P=0.027) (Fig. 2).

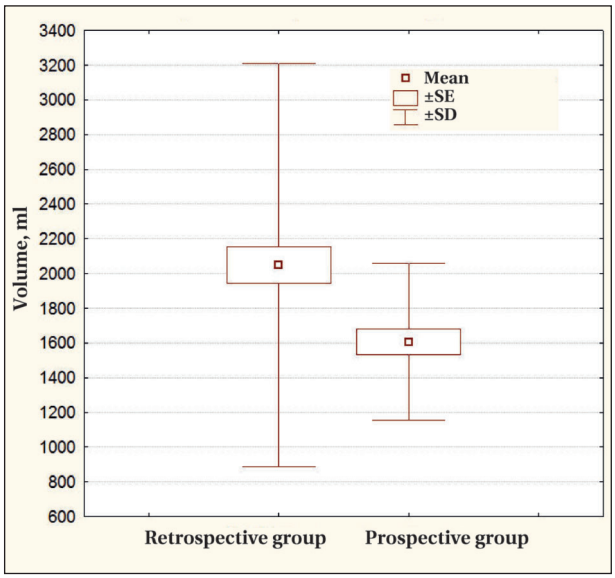

Fig. 2. Comparison of fluid therapy volumes during the first 24 hours of treatment in the retrospective and prospective groups.

Two patients included in the study at the prospective stage had a cardiomyopathic hemodynamic profile. Initially, they were hypertensive (AH subgroup) and had atherosclerotic vascular renal, coronary, and cerebral lesions.

One patient was found to develop superior mesenteric artery thrombosis during the study follow-up, which resolved during endovascular intervention. Septic shock in these patients was resistant, they demonstrated no cardiac performance improvement during the passive leg raising test. In addition to standard doses of norepinephrine and dobutamine, these patients received hydrocortisone infusion up to 200 mg per day for additional hemodynamic correction. In all patients, glomerular filtration rate was determined every 4 hours of follow-up during the prospective phase of the study. By 12 hours of follow-up, 22 patients (59.5%) had satisfactory GFR. Different therapeutic strategies were used depending on hemodynamic type until satisfactory mean arterial pressure was achieved. The MAP was increased based on the retrospective data. Average MAP in patients without hypertension was 80.7 (SD 10.4) mm Hg, in patients with baseline hypertension (AH subgroup), 82.4 (SD 9.7) mm Hg (differences were insignificant at $P\geqslant0.05$). In one patient from the AH subgroup normalization of GFR was achieved at MAP of 101 mmHg. However, patients in the AH subgroup had significantly higher values of total peripheral vascular resistance index, while their extravascular lung water index was lower. Taking into account the retrospective data, further increase in mean arterial pressure had no clinical perspective with regard to restoration of adequate renal function. Meanwhile, as in patients in the retrospective group, there was a weak positive correlation between the urine output rate and glomerular filtration rate (Fig. 3).

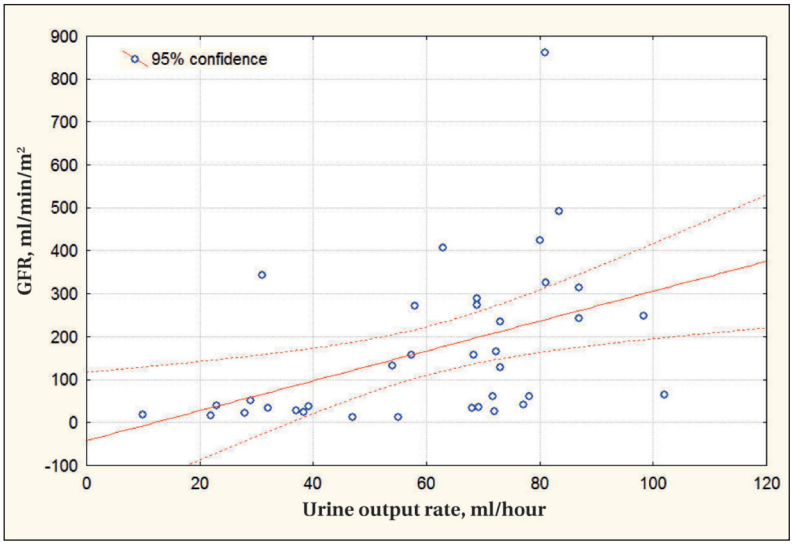

Fig. 3. Paired correlation coefficient between GFR and urine output rate in patients during the prospective phase of treatment, r=0,44261.

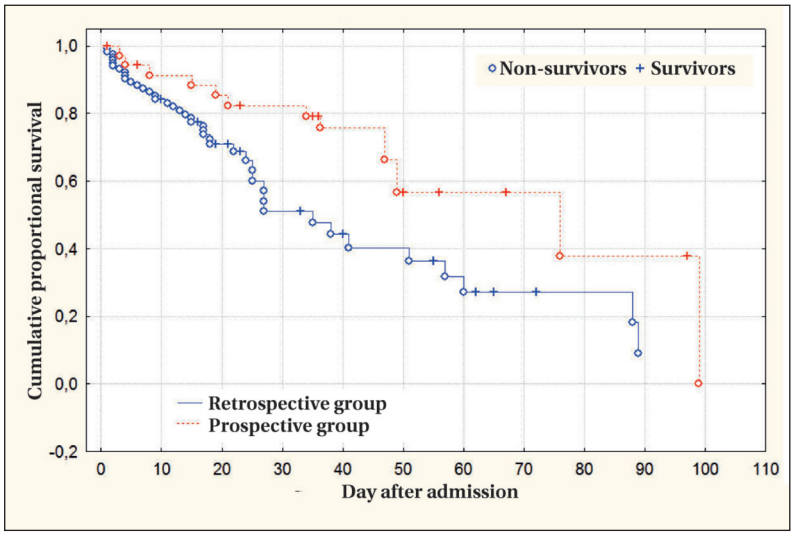

Fig. 4. Cumulative proportional survival of patients in the retrospective and prospective groups (Kaplan–Meier).

Consistent with the study design, patients with satisfactory hemodynamic and urine output rates with reduced GFR were started on renal replacement therapy (*n*=15 [40.5%]) after an average of 12.4 hours (SD 0.4), which was significantly earlier than in patients in the retrospective group. By 72 hours of follow-up, positive clinical effects were observed in 9 patients, in 6 patients (including 2 with a cardiomyopathic hemodynamic profile) shock was resistant. These patients died, setting the 28-day mortality in patients at the prospective stage at 16.2%, which was almost half that of the retrospective stage (33.9%). Hospital mortality in patients at the prospective stage was also significantly lower, with 11 of them dead (29.7% vs. 42.1%) (Fig. 4).

Discussion

Over the past decades, the clinical variant with relative hypovolemia and decreased cardiac performance due to reduced preload caused by fluid redistribution into extravascular space has been considered typical for patients with septic shock [32–34]. However, most patients in our study had hyperdynamic cardiovascular response along with a dramatic drop in total peripheral vascular resistance but with an adequate preload. According to national experts V. Kuzkov and M. Kirov, this hemodynamic profile corresponds to the most common septic shock course [35]. Most likely, it is associated with aggressive fluid therapy at any stage of burn treatment and corresponds to commonly shared ideas of pathogenetic treatment of burn injury, preferably at early stages. Positive fluid balance is one of the key pillars of early intensive care of burn patients [13]. Apparently, the fluid therapy being a part of the early targeted treatment of septic shock underlies a more severe illness course in patients from the retrospective group. These patients had no baseline assessment of volume status and increased preload tests, although almost all of them showed signs of increased global vascular permeability. An increase in EVLWI and worsened arterial hypoxemia were consistently noted during the following stages of hemodynamic monitoring. These changes were especially evident in those patients in the retrospective group who had cardiomyopathic and hypodynamic circulation due to the evidence of myocardial dysfunction with a total decrease in cardiac performance and increase in total peripheral resistance due to vasopressor use. In the prospective phase such patients were classified as nonresponders to the preload test. Meanwhile, those patients had a significant decrease of left ventricular contractility index (less than 1,000 mm Hg), which was regarded as a manifestation of myocardial depression associated with sepsis, and their condition was somewhat stabilized when dobutamine was administered [36]. Norepinephrine was used as the main vasopressor agent in all cases. Doses in most patients did not exceed 0.5 μg/kg/min. The duration of norepinephrine administration in patients at both study stages averaged 2.8 days (SD 0.04).

After hemodynamic stabilization in patients with septic shock, the glomerular filtration rate was restored at MAP values ranging from 65 to 101 mm Hg. The prospective phase of the study confirmed that MAP over 75 mm Hg may have nephroprotective effects in patients without baseline hypertension. Elevated MAP was not associated with adverse effects of norepinephrine. A retrospective analysis of the data showed that the lack of restoration of adequate renal function in the first 24 hours along with satisfactory values of hemodynamic parameters did not lead to the resolution of renal failure in the next two days of observation, regardless of the increase in blood pressure to threshold values. The recovery of adequate renal function occurred with significantly higher BP values. The surviving patients had significantly higher MAP values than the non-survivors.

Severely burnt patients with baseline arterial hypertension in both groups recovered adequate values of glomerular filtration rate at levels of mean arterial pressure significantly higher than in normotensive subjects. The discovery of a group of patients with abnormal hemodynamic parameters indicating myocardial dysfunction was important. Despite the evidence of hypovolemia, these patients responded negatively to the increased preload test.

Moreover, they responded with a sharp increase in the total peripheral vascular resistance index with an even greater reduction of cardiac performance when vasopressors were administered. Restoration of adequate renal function in this situation could not be achieved. Fluid therapy as a part of early targeted treatment of septic shock without prior analysis of hemodynamic abnormalities in the retrospective group led to a significant deterioration of patients. Unfortunately, all patients with this type of circulatory disorder died despite comprehensive treatment. Apparently, this hemodynamic response in septic shock was provoked by underlying severe atherosclerotic vascular lesions.

The patterns of hemodynamic abnormalities identified in patients during retrospective data analysis and individualized management at the prospective stage helped earlier determination of renal replacement therapy requirement, which together with the maintenance of optimal mean arterial pressure improved treatment outcomes.

Conclusion

Severely burnt patients with septic shock require a differentiated approach to the maintenance of mean arterial pressure for ensuring adequate perfusion of organs and tissues. The glomerular filtration rate measured using the direct Rehberg-Tareyev test could serve as a metabolic marker of renal blood flow adequacy. To determine the type of intervention for optimal hemodynamic compensation in patients with burns and septic shock, minimally invasive hemodynamic monitoring based on transpulmonary thermodilution analysis may be successfully used. Early initiation of renal replacement therapy in patients who have not restored adequate (based on the values of glomerular filtration rate) renal function within 24 hours improves the survival of patients in this group. Urine output rate alone cannot be considered as an adequate indicator of renal perfusion in severely burned patients with septic shock.

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The Early Use of Selective Hemoadsorption Based on a Hyper-Crosslinked Styrene-Divinylbenzene Copolymer in Patients with Toxic Rhabdomyolysis Complicated by Acute Kidney Injury (Multicenter Randomized Clinical Trial)

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Summary

Rhabdomyolysis (RM) is a clinical and laboratory syndrome with the underlying destruction of myocytes and the release of intracellular debris into the systemic circulation. In more than 55% of cases, RM is complicated by acute kidney injury (AKI), which necessitates various methods of extracorporeal detoxification and currently is a controversial issue.

Aim: to improve the results of treatment of patients with RM of toxic origin complicated by AKI by using early selective hemoadsorption (SH).

Material and methods. The study included 36 patients divided into 2 groups. Group 1 included 24 patients who received standard therapy and hemodiafiltration (HDF) as a life-saving intervention. Group 2 comprised 12 patients who underwent early SH to prevent the progression of AKI. We performed a comparative analysis of clinical and laboratory parameters and treatment outcomes in the groups.

Results. The use of SH was associated with reduced level of myoglobin on day5 of therapy from 384.1 to 112.4 μg/l (70.7%) vs 335.15 to 219.1 μg/l (34.6%) reduction in the conservative therapy group. By day 7, this parameter was 18.8 (95.1%) and 142.4 (57.5%), respectively (P=0.012). The level of cystatin-C decreased on day 5 from 17.3 to 3.2 mg/l (81.5%) in group 2 and from 14.9 to 11.7 mg/l (21.5%) in group 1. By day 7, this parameter decreased to 2.5 (85.6%) and 14.1 (5.3%) mg/l, respectively (P=0.001). The length of ICU stay in group 2 was 7 (6; 9) days, while in the conservative therapy group it was 12 (7; 13) days (P=0.04). The hospital stay was 12 (10; 16) and 22 (14,5; 24,5) days, respectively (P=0.028).

Conclusion. The early use of SH in the intensive therapy helped decrease the levels of markers of endogenous intoxication, AKI severity, improve the filtration capacity of the kidneys, and reduced the length of stay in the ICU and hospital.

Keywords: rhabdomyolysis; hemoperfusion; myoglobin; cystatin-C; hemodiafiltration; acute kidney injury

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

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Introduction

Rhabdomyolysis (RM) is a clinical and laboratory syndrome with the underlying damage of the transverse striated muscles (myocytes) of different etiology, involving release of intracellular contents into the bloodstream [1, 2].

As a result of myocyte damage and destruction, such numerous intracellular substances as myoglobin, CPK (creatine phosphokinase), lysosomal and mitochondrial enzymes, histamine, serotonin, cellular wall components, oligo-, polypeptides, etc. enter the bloodstream. The resulting systemic toxemia associates with multiple organ failure syndrome [3]. The most frequent and widespread complication in RM is acute kidney injury (AKI) syndrome, which is associated with severe disease and adverse clinical outcome [4, 5]. Myoglobin plays a fundamental role in the development and progression of AKI [6, 7].

Currently, the main concept of extracorporeal detoxification (ECD) involves removal of myoglobin and other factors of endogenous intoxication from the bloodstream [8, 9]. Various techniques and regi-

mens of renal replacement therapy (RRT) have different efficacy in reducing the myoglobin content in blood [4, 10–13]. However, the early use of various ECD techniques to prevent the development and progression of AKI currently has no enough evidence and cannot be recommended for general use [5, 6, 14].

Novel devices for selective hemoadsorption could be potentially effective in the treatment of AKI, as they can eliminate a certain range of endogenous toxic substances from the systemic bloodstream including myoglobin and other molecules. However, these sorption systems have been only occasionally employed and have been described in a limited number of studies [15–18].

Development and application of new sorption systems capable to selectively eliminate specific range of substances from the systemic circulation prompts further study of their possible effective single or combined use in treatment of RM complicated with AKI [19–21].

The aim of the study: to improve the results of treatment of patients with toxic RM complicated by AKI by using early selective hemoadsorption (SHA).

Material and Methods

A prospective multicenter randomized study included 36 patients aged 20 to 41 years who were treated in the intensive care unit of N. I. Pirogov City Clinical Hospital No. 1 and S. S. Yudin City Clinical Hospital from 2017 to 2020 with a diagnosis of toxic rhabdomyolysis complicated by AKI. Patients were randomized using the envelope method. The study was conducted in accordance with the Declaration of Helsinki after obtaining permission from the local ethical committee of the Pirogov City Clinical Hospital dated January 13, 2017. Criteria for inclusion of patients in the study were history or clinical and/or laboratory data indicating acute poisoning; rhabdomyolysis (CPK level 1000 Units/L); clinical and laboratory signs of AKI. Exclusion criteria were age less than 18 years, pregnancy, chronic muscle diseases (muscular dystrophy, inflammatory myopathy, etc.), injuries of any localization; surgical treatment; absolute contraindications for ECD methods such as ongoing bleeding, terminal state.

All RM patients included in the study had clinical and laboratory signs of persistent AKI despite the standard intensive therapy during 12–24 hours from the moment of admission to ICU. Standard intensive therapy administered to all patients upon admission included fluid therapy for acid-base and water-electrolyte balance correction; diuretic therapy; prevention of thromboembolic complications and gastrointestinal stress ulcers; nutritional support as well as, if indicated, respiratory and inotropic/vasopressor support.

At the time of inclusion in the study, the clinical groups were completely comparable and were not significantly different from each other ($P>0.05$ for all parameters, Table 1).

All patients underwent standard monitoring of hemodynamic parameters (blood pressure, heart rate, respiratory rate) and clinical and laboratory parameters (clinical blood count with leukocyte morphology, biochemical analysis, coagulation test, urinalysis, acid-base balance) during intensive therapy. Statistical analysis included the worst values of parameters registered during the day. The levels of CPK and myoglobin were assessed to evaluate endogenous intoxication and RM severity. The severity of organ dysfunction was assessed daily using SOFA scale, and the risk of adverse outcome was assessed using APACHE II scale. Diagnosis of AKI in all patients was made based on KDIGO (Kidney Disease: Improving Global Outcomes) guidelines, on admission and daily thereafter. To assess AKI markers, plasma cystatin-C level was determined, and to assess the changes in renal function, urine output rate was assessed and GFR was calculated using endogenous creatinine clearance in the blood and urine (Rehberg-Tareyev's test). Statistical analysis was performed based on the worst values of parameters during a day.

During the study, patients were randomized into two clinical groups.

Group 1 included 24 patients, whose standard intensive care during the first 24 hours in ICU did not reduce the AKI severity. During the treatment of the group 1 patients, the standard indications for the initiation of RRT were followed, i. e., life-threatening severe renal dysfunction despite the basic full-fledged intensive care therapy. These indications included severe uremia with increased blood urea level over 40 mmol/l; anuria or oliguria resistant to diuretics; increased blood potassium level over 6.5 mmol/l; severe metabolic acidosis with pH less than 7.15 resistant to fluid therapy. The above indications for urgent initiation of RRT were identified during treatment in 21 patients (87.5%) from group 1. Renal replacement therapy was performed in the HDF (hemodiafiltration) mode.

Group 2 included 12 patients with toxic RM complicated by AKI, whose basic intensive care during the first day after admission to ICU did not result in reduced severity of AKI. When no effect of basic intensive therapy was seen within 12–24 hours after admission to ICU in patients of this group, selective hemoadsorption was used for active detoxication and nephroprotection in early stages of AKI (KDIGO 1 or 2). If severe life-threatening renal failure developed, the RRT in HDF mode was initiated. In this group, indications for urgent RRT initiation were found in 9 patients (75%) during the treatment.

The post-dilution HDF using a 5008S machine (Fresenius Medical Care, Germany) was performed. High-permeability FX800HDF or FX1000HDF he-

Table 1. Baseline values of clinical and main laboratory parameters in the study groups, *Me* (*Q1*; *Q3*).

Parameter	Parameters values in groups		*P*-value
	Group 1, *n*=24	Group 2, *n*=12	
Clinical parameters			
Males, *n*	17	9	1.0
Females, *n*	7	3	
Age, years	34 (27; 36)	35 (20; 41)	0.74
Weight, kg	86 (73; 98)	92 (84; 103)	0.83
SOFA, points	5 (5; 7)	6 (5; 8)	0.92
APACHE II, points	17 (17; 20)	18 (15; 21)	0.58
KDIGO, stage	0–I	0–I	1.0
MAP, mmHg	68 (52; 74)	62 (50.1; 70.2)	0.38
Heart rate, beats per minute	107 (102; 114)	111 (99; 121)	0.81
GFR, ml/min/1.73 m^2	84 (50.5; 87)	75 (55; 80)	0.28
PaO_2/FiO_2, mm Hg	291 (282; 308)	287 (270; 312)	0.41
CVP, cm H_2O	0 (0; 1)	1 (0; 1)	0.56
Urine output, ml per hour	43 (37; 61)	40 (32; 54)	0.29
Laboratory parameters			
Red blood cells, $\times10^{12}$/l	4.64 (4.46; 5.28)	5.13 (4.7; 5.88)	0.17
Hemoglobin, g/l	162 (159; 165)	163 (153; 177)	0.78
Hematocrit, %	42.9 (40.3; 46.7)	51.3 (48.9; 55.9)	0.26
Platelets, $\times10^9$/l	221 (196; 243)	210 (196; 232)	0.83
White blood cells, $\times10^9$/l	9.2 (6.8; 11.7)	11.1 (7.2; 13.7)	0.38
pH	7.1 (7.08; 7.3)	7.12 (6.9; 7.2)	0.31
BE, mmol/l	–4.2 (–5.5; –3.15)	–5.3 (–6.3; –3.6)	0.26
Potassium, mmol/l	3.8 (3.4; 4.2)	3.7 (3.2; 4.6)	0.42
Sodium, mmol/l	138 (132; 144)	133 (129; 142)	0.67
Calcium, mmol/l	0.58 (0.44; 0.82)	0.6 (0.51; 0.77)	0.29
Chloride, mmol/l	106 (95.1; 109)	104 (92.3; 107.7)	0.81
Lactate, mmol/l	6.2 (4.6; 8.1)	5.9 (5.1; 7.3)	0.32
Total protein, g/l	69 (61.1; 73.8)	67.7 (61.2; 78.3)	0.41
Albumin, g/l	33.2 (30.3; 35.5)	34.1 (31.2; 41.4)	0.54
Urea, mmol/l	11.1 (7.45; 14.25)	12.5 (10.6; 13.7)	0.83
Creatinine, µmol/l	148.2 (124.5; 181.8)	182.6 (135.6; 197.5)	0.21
ALT, U/l	64 (47.5; 107.5)	106 (68.4; 487.6)	0.31
AST, U/l	160.1 (133.1; 213.1)	202.1 (180.2; 281.2)	0.44
Total bilirubin, µmol/l	11.9 (8.2; 15.4)	15.1 (8.3; 20.6)	0.72
Alkaline phosphatase, mmol/l	98 (72; 123)	128 (98.1; 145)	0.51
LDH, IU/l	245.1 (130.3; 348.15)	315.5 (101.5; 693.85)	0.92
CPK, U/l	10745 (6726.3; 14192)	9288 (8124; 17282)	0.76
CRP, mg/l	89 (45.7; 99.5)	74 (50.8; 88.3)	0.69
PCT, ng/ml	4.1 (2.61; 6.2)	3.86 (3.47; 5.3)	0.61
Myoglobin, µg/l	335.15 (266; 413.7)	384.1 (296.5; 428.8)	0.74
Cystatin C, mg/l	14.9 (12.5; 18.5)	17.3 (14; 18.95)	0.86
APTT, s	26.6 (23; 27.5)	25.5 (23.9; 25.6)	0.14
INR	1.08 (1.02; 1.13)	1.06 (0.9; 1.1)	0.49
Fibrinogen, g/l	4.4 (3.4; 4.9)	4.3 (3.7; 5.3)	0.95

Note. Differences between groups (*P*-values) were assessed using the Mann–Whitney *U*-test, for quantitative (binary) variables, Fisher's exact test was used. MAP — mean arterial pressure; GFR — glomerular filtration rate; CVP — central venous pressure; PaO_2/FiO_2 — ratio of the partial pressure of oxygen in the arterial blood to the fraction of oxygen in the inhaled gas; ALT — alanine aminotransferase; AST — aspartate aminotransferase; LDH — lactate dehydrogenase; CPK — creatine phosphokinase; CRP — C-reactive protein; PCT — procalcitonin; APTT — activated partial thromboplastin time; INR — international normalized ratio.

mofilters (B.Braun Avitum AG, Germany) were used as a mass-exchange device. During hemodiafiltration the following parameters were used: blood flow rate, 250–300 ml/min, dialysate flow rate, 500–600 ml/min; ultrafiltration rate per hour depended on the severity of overhydration and ranged from 100 to 1000 ml/h. The RRT was performed for 4–6 hours daily or every other day until renal function was restored.

The SHA was performed using the MultiFiltrate apparatus (Fresenius Medical Care, Germany) in hemoperfusion mode with the Efferon CT adsorption system (Russia), using a standard «multiFiltrate Cassette» cartridge (Fresenius Medical Care, Germany). The SHA was carried out at the blood flow rate of 100–150 ml/min. The duration of the session was 6 to 8 hours. Anticoagulation was achieved using continuous infusion of unfractionated heparin

Table 2. Changes in the studied parameters from days 1 to 7 of treatment, *Me* (*Q1*; *Q3*).

Group	Values			
	Day 1	Day 3	Day 5	Day 7
Myoglobin, μg/l				
1, *n*=24	335.15 (266; 413.7)	318.25 (215.2; 355.8)	219.1 (168.4; 268.7)	142.4 (129.3; 158.4)
2, *n*=12	384.1 (296.5; 428.8)	236.1 (187.3; 253.3)	112.4 (94.9; 122.45)	18.8 (15.4; 19.4)
P-value		0.28	0.003	0.012
CPK, IU/l				
1, *n*=24	10745 (6726; 14192)	2549 (2036; 5606)	1356 (1104; 3355)	789 (619; 1119)
2, *n*=12	9288 (8002; 17282)	1424 (1241; 2941)	520 (256; 702)	101 (99; 146)
P-value		0.24	0.02	0.002
Cystatin-C, mg/l				
1, *n*=24	14.9 (12.5; 18.5)	16.2 (13.2; 18.6)	11.7 (11.2; 15.4)	14.1 (9.5; 16.4)
2, *n*=12	17.3 (14; 18.9)	12.9 (11.1; 16.3)	3.2 (2.2; 5.3)	2.5 (2.2; 5.6)
P-value		0.32	0.003	0.001

Note. Differences between groups were assessed using the Mann–Whitney *U*-test.

500–1000 units/hour with coagulation parameters monitoring. To perform ECD, a double-lumen perfusion catheter was placed in a central vein.

Statistical methods. The results obtained during the study were presented as a median, 25th and 75th percentiles. The Kolmogorov–Smirnov method was used to assess the data distribution. Nonparametric Mann–Whitney and Kruskal–Wallis criteria were used to test statistical hypotheses. Groups were compared by qualitative characteristics using Fisher's exact criterion. Wilcoxon criterion was used to test the significance of differences between the changes in the values of parameters. The differences were considered significant at $P<0.05$. No adjustment for multiplicity was made. The statistical analysis of results was performed using Microsoft Excel with Real Statistics 2021 (by Charles Zaiontz).

Results

Changes in the markers of endogenous intoxication and severity of acute kidney injury.

To determine the detoxification capability of various methods of extracorporeal detoxification, we assessed the levels of myoglobin being the major pathogenetic marker of AKI (Table 2).

Significant positive intra-group changes were observed. Myoglobin level by day 3 of life-saving HDF decreased by 5.04% from the baseline (*P*=0.012), whereas in group 2 (selective hemoadsorption) a decrease of 38.5% from baseline values was observed (*P*=0.021). By day 5 of intensive therapy the decrease was 34.6% (*P*=0.002) in group 1 and 70.7% in group 2 (*P*=0.016). By day 7, it became for groups 1 and 2 57.5% (*P*=0.002) and 95.1% (*P*=0.036), respectively. Significant intergroup differences were observed on day 5 (*P*=0.003) and day 7 (*P*=0.012) of therapy. Thus, a variable decrease in myoglobin levels was observed with different methods of extracorporeal detoxification, however, it was significantly greater with the use of SHA.

Table 2 shows the changes in CPK levels from day 1 to day 7 of intensive care therapy. Significant decrease in CPK levels was observed in both clinical groups from day 1 to day 7 of intensive care therapy (*P*=0.001). In group 1, this parameter decreased by 76.3% on day 3, by 87.4% on day 5, and by 92.6% on day 7. In Group 2, the changes were 84.7%; 94.4% and 98.9%, respectively. Notably, the changes in CPK levels in group 2 CPK were more prominent than in group 1, with the appearance of intergroup differences on days 3 and 7 of intensive therapy (*P*=0.02 and *P*=0.002, respectively, Table 2).

The changes in cystatin-C levels are considered among the most important markers of renal function which increase in the setting of acute kidney injury (Table 2).

In group 1 (life-saving HDF), insignificant changes were observed: on day 3 of therapy, we observed a 8.7% increase of cystatin-C concentration in comparison with the initial value, on day 5, 21.5% decrease, and on day 7, 5.4% reduction (*P*=0.27; 0.4; 0.16, respectively). In group 2, where SHA with further HDF was performed, the reduction in cystatin-C concentration on day 3 was 25.4%, on day 5, 81.5% and on day 7, 85.6% (*P*=0.67; 0.02; 0.003, respectively). A significant reduction in cystatin-C level in this group was observed starting from day 5 of intensive therapy. Intergroup differences were registered on the 5th and 7th days of treatment (*P*=0.003; 0.001).

Glomerular filtration rate is an important indicator of the renal functional recovery in acute kidney injury. Figure 1 shows the changes of GFR in the studied groups.

In group 2, starting from day 6 of treatment, there was a significantly higher rate of recovery of renal function than in group 1 on days 6, 7, 8, (*P*=0.04, *P*=0.01, *P*=0.03, respectively).

Assessment of the frequency and duration of RRT.

In patients with toxic rhabdomyolysis, the changes in AKI progression and the rate of life-saving RRT play a crucial role. Figure 2 shows the frequency of life-saving RRT in the groups.

In the conservative therapy group, the frequency of life-saving RRT was 85.7%, in contrast to group 2, where after prior hemoadsorption, the frequency of RRT was 66.7%. This trend in RRT between the groups, however, was not significant (P=0.38).

The results of comparative analysis showed that the duration of RRT in group 1 was 16.4 days, and in group 2, 13.7 days (P=0.047) (Fig.3).

Comparative analysis of hospitalization time and disease outcomes.

One of the most significant criteria for the effectiveness of the therapy, both therapeutic and socio-economic, is the length of stay of patients in the ICU and the hospital. Table 3 demonstrates the group differences in duration of treatment.

Table 3 shows that in group 2 patients who received hemoadsorption both parameters of treatment duration (ICU and hospital stay) were significantly less than in patients of group 1 (P=0.041 and P=0.028, respectively).

No differences in mortality between the groups were found, which can probably be explained by a small sample size.

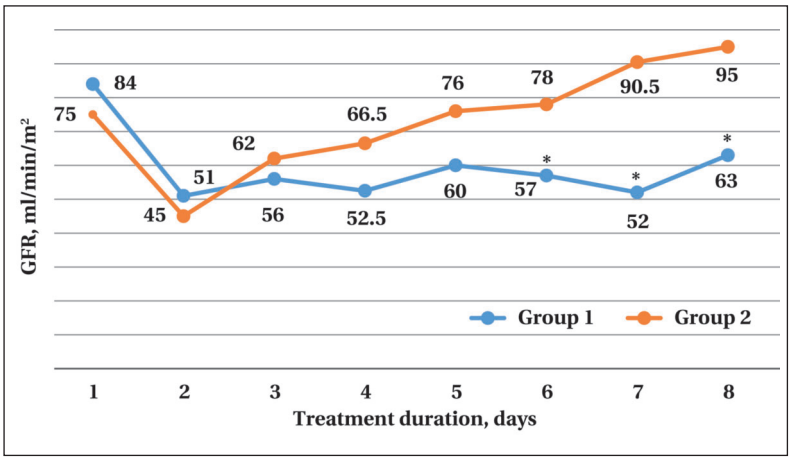

Fig. 1. Changes of GFR (Rehberg–Tareyev method) in the study groups from days 1 to 8 of intensive care.
Note. * — significant differences between groups (Mann–Whitney U-test, P<0.05).

Table 3. Duration of treatment of ICU and inpatient patients, *Me* (*Q1*; *Q3*).

Groups	Duration of treatment, days	
	ICU	Hospital
1, n=24	12 (7; 13)	22 (14.5; 24.5)
2, n=12	7 (6; 9)	12 (10; 16)
P-value	0.041	0.028

Note. Differences between the groups were assessed using the Mann–Whitney U-test, P<0.05.

Discussion

This multicenter randomized clinical trial in patients with toxic rhabdomyolysis complicated by AKI demonstrated high efficacy of early use of SHA followed by life-saving HDF compared with life-saving RRT alone. When considering the pathogenesis of rhabdomyolysis and AKI, we suggest that myoglobin level is crucial for its development being the main source and marker of systemic toxemia [8, 9, 22].

Myoglobin concentration in the SHA group decreased by 95.1% by day 7 of the therapy, in contrast to the group with life-saving RRT (57.5%) (P=0.012). Similar changes in CPK levels were obtained after using selective hemoadsorption starting from day 5 of the treatment. The high efficiency of myoglobin elimination with SHA is due to the fact that with a molecular weight of 17 kDa [23] it is removed from the bloodstream by both convection and sorption detoxification methods, while CPK molecules sized 40 to 80 kDa [24], pathognomonic for rhabdomyolysis, are removed with less efficiency [15, 16]. The elimination of endogenous intoxication factors from the systemic bloodstream manifests both in improvement of clinical and laboratory parameters and in the regression of AKI, as observed by many authors [6, 22, 25].

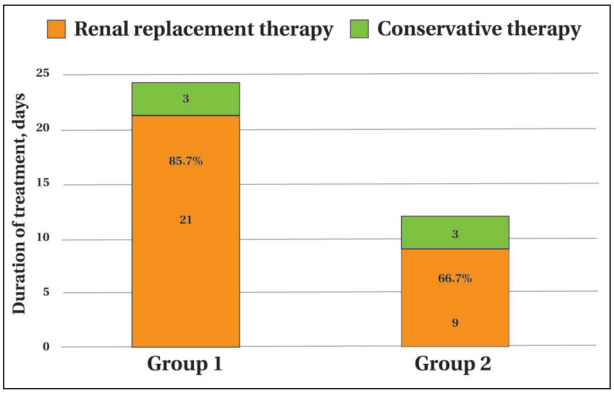

Fig. 2. Frequency of RRT in the groups.

Accelerated decrease in the levels of cystatin-C (AKI marker) after SHA is, in our opinion, directly related to the reduction of systemic toxemia factors and their nephrotoxicity, which was confirmed by other researchers [12, 22, 25, 26].

Thus, our results indicate that the earliest use of SHA results in the reduction of systemic endotoxemia and probably in an earlier recovery of renal function judging by the changes in GFR. Early use of SHA in patients with rhabdomyolysis had a positive effect on the level of endotoxemia markers, the severity of AKI, and was probably nephroprotective, which has not been yet reported in the available literature [27, 28].

Among important results of our work is a decrease in systemic toxemia expressed as reduction of myoglobin, CPK, and AKI markers, as well as an improvement in renal function and a significant decrease in the duration of RRT in SHA group, which, in our opinion, was a direct consequence of the processes described above.

Thus, the study results provide a rationale for the timely use of SHA in intensive therapy of toxic rhabdomyolysis to reduce the treatment duration in ICU and hospital [5, 10, 22, 29–33].

Conclusion

The use of selective hemoadsorption in patients with toxic rhabdomyolysis has significantly reduced the levels of endogenous intoxication markers such as myoglobin (by 70.7%) and CPK (by 94.4%) as well as the concentration of AKI markers such as cystatin-C (by 81.5%) by day 5 of treatment. This method was also associated with improved renal filtration starting from day 6 of treatment.

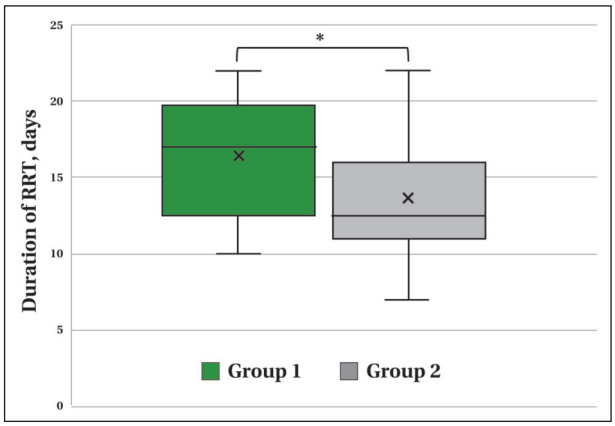

Fig. 3. Duration of RRT in the study groups.
Note. Data are presented as *Me* (*Q1*; *Q3*). * — significant differences between groups (Mann–Whitney *U*-test, $P<0.05$).

Early use of SHA reduced the length of stay in the ICU from 12 (7; 13) days to 7 (6; 9) days and in the hospital from 22 (14.5; 24.5) days to 12 (10; 16) days.

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Treating Complications of Extracorporeal Life Support in a Patient with COVID-19 (Case Report)

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Summary

We present a case of mechanical hemolysis as a complication of extracorporeal membrane oxygenation (ECMO) occurring in a COVID-19 patient as a result of pump head thrombosis. After emergency extracorporeal circuit replacement, hemoadsorption was initiated to address the negative hemolysis effects and plasma free hemoglobin rise in the setting of rapid clinical deterioration and impaired renal function. During therapy hemolysis severity reduced, the lactate dehydrogenase (LDH) levels decreased, while the P/F ratio increased two-fold. The patient was discharged from hospital on day 54 without the need for either oxygen therapy or dialysis. In the discussion section we addressed frequent issues of choosing therapy for ECMO complications.

Conclusion. The timely, properly chosen, and clinically relevant use of hemoadsorption combined with advanced high-technology therapeutic procedures can have a positive impact on the patient's outcome.

Keywords: ECMO; COVID-19; mechanical hemolysis; free hemoglobin; hemoadsorption; plasma exchange

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

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Introduction

Extracorporeal membrane oxygenation (ECMO) is one of the most high-tech accepted methods of life support in patients with refractory hypoxia who do not respond to standard ventilation techniques [1]. According to a systematic review and meta-analysis, which reviewed ECMO in COVID-19 patients and included 134 papers, ECMO procedure may be appropriate and effective in the treatment of patients with ARDS due to coronavirus infection [2]. According to the World Health Organization guidelines, the use of ECMO should be considered as a possible therapeutic option in patients with ARDS and severe COVID-19 [3].

The concept of ECMO is quite simple: it is based on a temporary maintenance of gas exchange in patients with ARDS, however, the technical implementation of this procedure presents a number of multidimensional tasks and can be associated with complications due to the mechanical effects of the system on blood components [4, 5], as well as overactivation of the complement system [6, 7]. One such complication is ECMO-associated mechanical hemolysis that develops due to damaging pressure gradients in the ECMO cannulas and circuit or thrombosis of various parts of the extracorporeal circuit. According to ELSO, hemolysis worsens the prognosis of the disease [8]. Due to impaired venous drainage into the extracorporeal circuit, excessive pressure is exerted on blood components. Damage of blood elements and increase of free hemoglobin concentration can result from this impact. Hemoglobinemia, in turn, produces a damaging effect on the kidneys and predicts the development of acute kidney injury (AKI). These processes lead to the activation of the immune response and contribute to multiple organ failure (MOF) [9]. The literature indicates that high plasma level of free hemoglobin is an independent predictor of mortality among patients undergoing ECMO [10].

Hemoadsorption has been shown to be effective in disregulated immune responses (including ones during ECMO in patients with COVID-19 [11, 12]), as well as in free hemoglobin removal [13, 14].

This paper presents a clinical observation of the efficacy of hemoadsorption in the treatment of ECMO-associated massive hemolysis in a patient with COVID-19.

Clinical Observation

Patient T., female, 49 years old, height 165 cm, weight 83 kg, body mass index (BMI) 30.4 kg/m^2,

and history of hypertension. She was on regular therapy with Telpras (telmisartan, «Laboratorios Lyconsa S.A.») and Concor (bisoprolol, «Merck KGaA»). The patient was admitted to Moscow Clinical Center for Infectious Diseases «Voronovskoe» on the 8th day from the onset of symptoms complaining of increased body temperature up to 38.5°C, malaise and dry cough. On examination the patient was found to have positive polymerase chain reaction test (PCR test) for COVID-19, severity of lung involvement according to chest computed tomography (CT) was 50% on the right side and 45% on the left side. Based on the history, physical examination and laboratory data, the clinical diagnosis of novel coronavirus infection caused by COVID-19 virus was made. The complications included bilateral multisegmental viral and bacterial pneumonia. First stage hypertension was a comorbidity. The treatment according to the standard protocol was given at the infectious diseases department according to the temporary guidelines for the treatment of novel coronavirus infection [15] which included Ilsira (levilimab, «Biocad») 324 mg, Methylprednisolone («Orion Pharma») 100 mg intravenously during an hour, then 100 mg/day, Daltep (deltaparin, «Pharmasintez») 5,000 IU 2 times/day. On day 11 of hospitalization, due to progression of respiratory failure, the patient was transferred to the ICU. On admission to the ICU, the patient complained of dyspnea and shortness of breath. Clinically, dyspnea up to 24 breaths per minute, blood oxygen saturation of 84%, moderate tachycardia up to 95 bpm at rest, NEWS score of 9 points, SOFA score of 4 points were observed. Blood pressure remained stable (123/76 mm Hg). To control hypoxemia, high-flow oxygen therapy (HFOT) was performed using the SV300 apparatus (Mindray, China) with the following parameters: flow rate 50 L/min, oxygen fraction in the breathing mixture 70%. ROX index on admission was 6.23. Prone position was used for 16 hours/day. During the next 3 days, the patient required increased respiratory support: the oxygen fraction in the inhaled mixture (FiO_2) during HFOT was increased to 90%. ROX index when transferred to noninvasive ventilation was 3.85. Noninvasive ventilation was performed with the following parameters: FiO_2 70–80%, positive end-expiratory pressure (PEEP) 8–10 cm H_2O. No effect of noninvasive ventilation was observed after 18 hours, and the patient was switched to mechanical lung ventilation (MLV) with the following initial parameters: inspiration pressure (Pinsp) 30 cm H_2O, PEEP 10 cm H_2O, FiO_2 95%. The respiratory failure deterioration was caused by increasing severity of lung damage, according to chest CT scan performed after switching to MLV, up to 75%/75% bilaterally. The P/F ratio during ventilation was 53.5 mm Hg, dynamic compliance reached 21 ml/cm H_2O, within 6 hours after transfer to MLV we used «stepwise» selection of PEEP from 10 to 15 cm H_2O, as well as prone position (without effect). Murray scale score was 3. A decision was made to transfer the patient to ECMO. Standard femoral and jugular cannulation was performed using 25 and 21 Fr cannulas (Medtronic Nextgen, Ireland). Deltastream DP3 device and Hilite 7000LT oxygenator (Medos Medizintechnik, Germany) were used for ECMO with the following baseline settings of ECMO device: flow rate 4 L/min at pump speed 6000 rpm, gas flow 4 L/min, FiO_2 100%. During the first day the patient's condition stabilized, saturation was 94%. Tracheostomy was performed 12 hours after ECMO initiation. The MLV was performed using protective parameters: Pinsp 25 cm H_2O, PEEP 10 cm H_2O, tidal volume (Vt) 272 ml (3.2 ml/kg), FiO_2 60%. Myorelaxation was used for 72 hours. After sedation was canceled, the patient was transferred to independent breathing using high-flow oxygen therapy through tracheostomy. After awakening, no pathological neurological symptoms were observed, and the Glasgow Coma Scale (GCS) score was 15.

On day 8 of ECMO impaired consciousness (9 points GCS), dark-colored urine and blood oxygen saturation reduction down to 74% were observed. CT scans of the brain and chest, as well as laboratory tests (blood chemistry) and coagulation tests were performed to diagnose possible complications of ECMO. Brain CT scan revealed no abnormalities, while a series of chest CT scans showed 90% and 95% involvement of the right and left lung, respectively, along with extensive «bacterial infiltrates» of the posterior basal areas. Laboratory tests revealed marked hemolysis with elevated LDH (7099 U/L) and indirect bilirubin (55.2 μmol/L), anemia (hemoglobin 78 g/L), increased creatinine (223 μmol/L) and urea (31.2 mmol/L). Mechanical hemolysis associated with ECMO circuit thrombosis (thrombosis of the centrifugal pump head, Fig. 1) was recognized as the cause of deterioration. The extracorporeal circuit was promptly replaced.

Hemoadsorption using CytoSorb adsorber (Cytosorbents, USA) was started immediately after ECMO circuit replacement to remove free hemoglobin and reduce the negative effects of hemolysis. The adsorber was installed in the circuit of RRT Multifiltrate apparatus (Fresenius Medical Care, Germany), operating in continuous veno-venous hemodialysis mode with a blood flow rate of 200–250 ml/min before the filter, then the entire system was connected to the lateral flow of ECMO circuit (Fig. 2).

Three consecutive hemoadsorption sessions of 24 hours each were performed. Laboratory confirmation of reduced hemolysis severity was obtained: lactate dehydrogenase (LDH) level decreased 4.3-fold (from 7099 to 1640 units/l), bilirubin down

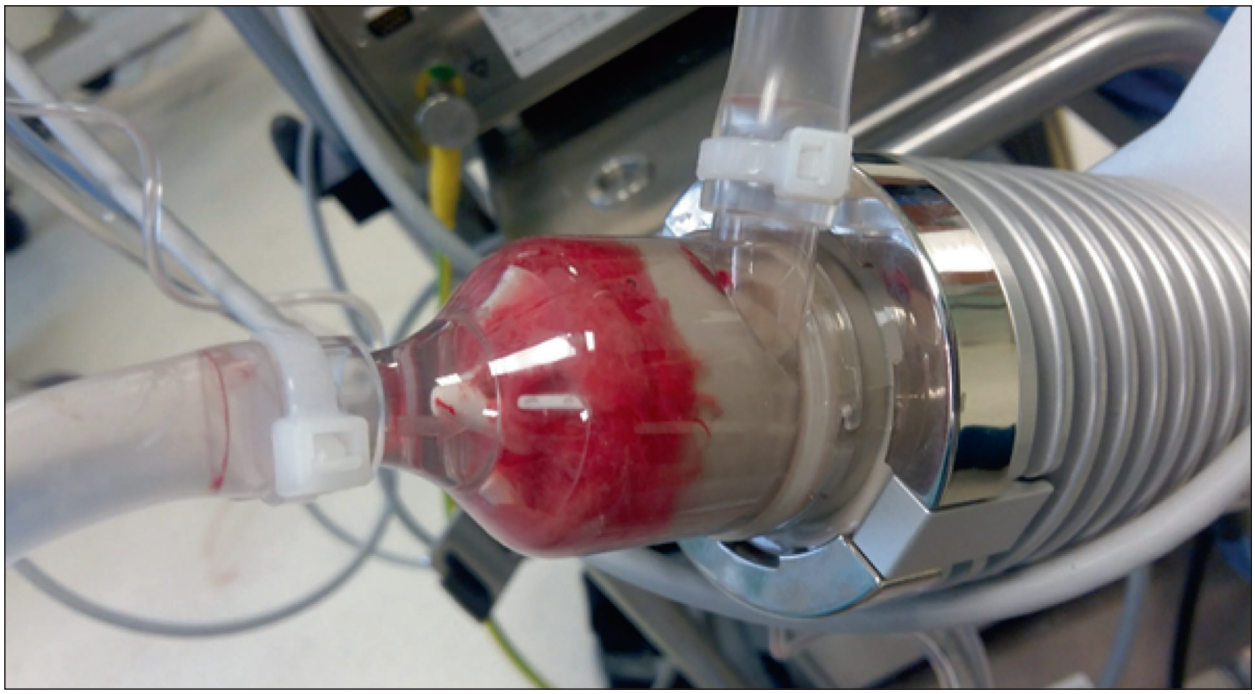

Fig. 1. Thrombosis of the centrifugal pump head of ECMO device, after circuit change.

Fig. 2. View of the extracorporeal circuit. View of centrifuged plasma before and after the first session of hemoadsorption.

to 36.7 μmol/l, and blood electrolytes returned back to normal. The P/F ratio more than doubled (from 92.1 to 200 mm Hg). The patient's clinical condition remained stable during the whole procedure (HR, BP, SpO_2, ECMO flow, blood gas parameters are given in the table below), there were no adverse effects. After ECMO flow stabilization, definition and setting of alarm limits on the renal replacement therapy (RRT) machine, the patient was put in a prone position to ensure consistency of lung ventilation.

The duration of ECMO was 19 days. Continuous veno-venous hemodialysis in the ECMO circuit was maintained for 7 days. The patient was decannulated on the 3rd day after ECMO disconnection. Urinary

Changes in clinical and laboratory parameters at different stages of treatment.

Parameter	Day									
	1	3	4	11	12	13	21	23	24	25
			ECMO start, tracheostomy	Hemoadsorption				ECMO stopped		Decannulation
				Start	Continuation					
Heart rate, bpm	62	68	89	70	68	60	59	68	76	62
Blood pressure, mm Hg	121/78	134/77	128/77	168/92	114/69	110/60	131/75	130/72	128/78	120/68
SpO_2, %	96/81	90	87	90	98	98	98	98	98	98
HFOT parameters: flow, l/min / O_2, %	50/70	50/90	50/95	60/60			50/50	40/45	60/65	60/55
NIV parameters: FiO_2, % / PEEP, cm H_2O		95%/8	95%/8							
MV parameters: FiO_2, % / PEEP, cm H_2O H_2O / P_{insp}, cm H_2O			95/10/30	50/15/15	50/8/24	50/8/24	50/8/20			
Lung involvement, CT	50/45%		75/75%	90/95%						75/80%
ECMO initiation/ ECMO circuit replacement			1	1				Stopped		
ECMO flow, l/min			3.6	4	4	3.6	3.6	3.3		
ECMO pump speed, rpm			6000	6000	6000	5600	5900	5600		
ECMO sweep gas flow, l/min			3	5	4	3	2	0		
RRT mode				CVVHD	CVVHD	CVVHD			CVVHD	
Ultrafiltration, ml/24 h				1200	600	2700			1800	
CytoSorb, h				24	24	24				
Urine output, ml/day	300	1240	2000	3400	1000	400	1100	2500	2400	1300
Laboratory values										
pH		7.293	7.278	7.338	7.365	7.454	7.283	7.244	7.268	7.152
pCO_2, mm Hg		41.6	38.1	24.1	39.8	37.9	50	51.1	44.7	49.9
pO_2, mm Hg		53.8	53.5	56.9	104	99.8	PvO_2 33	PvO_2 39	PvO_2 38.1	PvO_2 41.8
Hb, g/l		137	121	94	76	65	99	87	60	70
SpO_2, %		86.2	85.4	87.5	98.1	98.6	SvO_2 46.8	SvO_2 62.6	SvO_2 58.8	SvO_2 62.9
Lactate, mmol/l		1.8	1.2	1.5	0.9	1	1.1	0.8	1.2	0.7
HCO_3, mmol/l		19.1	17.5	19	22.4	26.8	20.9	19.5	19	15.3
Base excess, mmol/l		–5.9	–8.3	–6.8	–2.3	2.6	–2.8	–4.9	–6	–10.5
P/F ratio, mm Hg		59.7	53.5	94.8	208	200		86.7		
A-a, mm Hg		507.3	574.2	323.9	197.5	208.8		213.8		
ALT, U/l	42.9	38.40			47.5	41	38.9		21.6	
AST, U/l	30.5	29.1			93.7	25	22.7		14.2	
CRP, mg/l	41.2		98.8	21.2						
Bilirubin, mmol/l	9.6	18		55.2	36.7	17.2	18.6		11.5	12.1
Creatinine, mmol/l	60	75	60	223	190	148	173		389	175
Urea, mmol/l	6.6	6.1	5	15.3	14.3	11.6	16.5		39.9	19
LDH, U/l	1179	939	1144	7099		2510			732	
Leukocytes, $\times 10^9$	10.7	17.2	14.5	31.2	29.5	23.3	10.9	16.1	16.1	17.8
Platelets, $\times 10^9$	273	320	309	145	120	112	90	92	80	67
D-dimer, ng/ml	1485		6266	32653				7740		
Hemolysis				++++	++	—				
APTT, sec	24.4		26.3/68.3	error	error	44.5	31.6	220	error	55.1

Note. HFOT — high flow oxygen therapy; NIV — non-invasive ventilation; PEEP — positive end-expiratory pressure; P_{insp} — inspiratory pressure; CT — computed tomography; ECMO — extracorporeal membrane oxygenation; RRT — renal replacement therapy; CVVHD — continuous veno-venous hemodialysis; Hb — hemoglobin; A-a — alveolar-arterial difference in oxygen pressure; ALT — alanine aminotransferase; AST — aspartate aminotransferase; CRP — C-reactive protein; LDH — lactate dehydrogenase; APTT — activated partial thromboplastin time.

output rate gradually increased during 7 days, however, creatinine and urea levels rose again, which required continuation of hemodialysis sessions. The patient received intermittent procedures (two hemodialysis sessions were performed). The total duration of the patient's stay in ICU was 27 days.

Renal functions were restored with fluid therapy in combination with protein-free diet (Peptoproten Nephro, Protenfarma, Russia). Full mobility returned within 2 weeks after discharge from ICU during rehabilitation in the infectious disease unit. The serial chest CT scans demonstrated reduced involvement down to 35% on both sides (Fig. 3).

The patient was discharged from the hospital on day 54 and did not require oxygen therapy or hemodialysis thereafter.

Discussion

Two extracorporeal treatments for the hemolytic complications were reported in the liter-

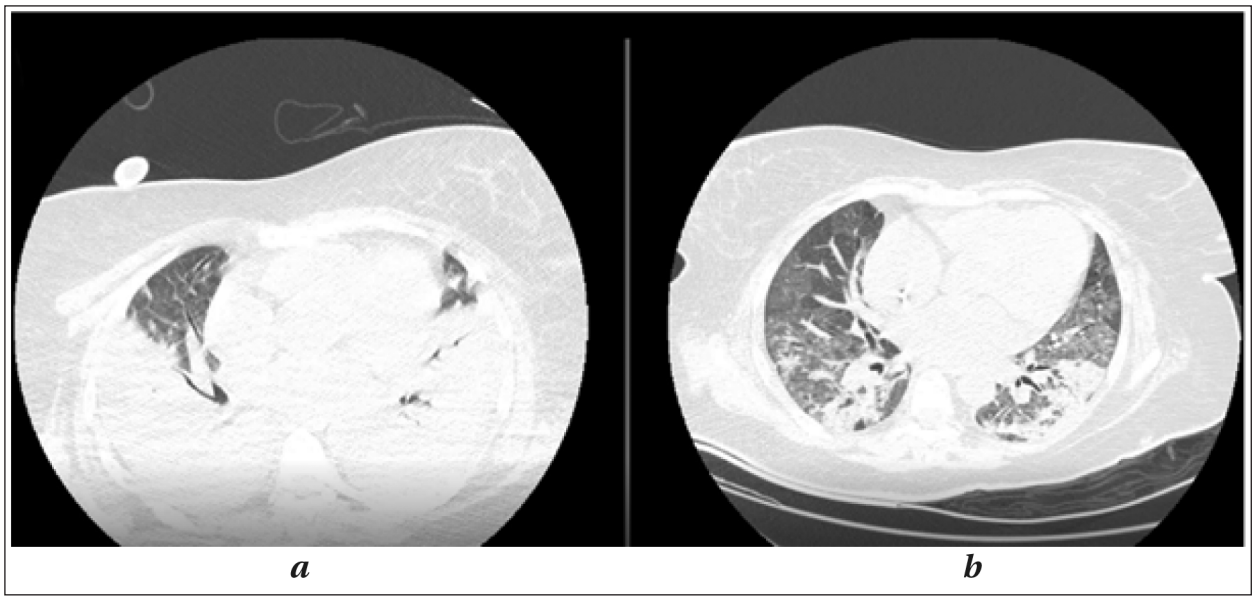

Fig. 3. The evolution of CT before (*a*) and after (*b*) the ECMO session lasting 19 days.

ature. They include therapeutic plasma exchange and hemoadsorption [16, 17]. Plasma exchange allows non-selective removal of toxic substances together with plasma. This technique is often used in autoimmune diseases therapy [18]. During the COVID-19 pandemic there were reports of the use of plasma exchange in the treatment of patients with coronavirus infection [19]. Hemoadsorption accomplishes two goals simultaneously: reduces the severity of the immune response by removing inflammatory mediators from whole blood and lowers the free hemoglobin level. Both effects occur without plasma separation [20, 21]. Publications describe the use of hemoadsorption in the treatment of hemolysis [17] and hemoglobinemia [22]. According to the results of a multicenter randomized controlled trial investigating the effectiveness of CytoSorb hemoadsorption for reducing free plasma hemoglobin during the cardiopulmonary bypass, there was a significant reduction in free hemoglobin concentration in the hemoadsorption group compared with the control one [14]. The choice of extracorporeal therapy of hemolysis in our clinical case was based on the following considerations.

During plasma exchange large volumes of blood products obtained from different donors are used, and the massive transfusion itself increases the immune burden on the recipient's body. Plasma exchange is performed once a day, on average, three sessions are required. During this time, the patient receives from 18 to 27 units of blood components from different donors. These significant volumes promote further complications, while treatment of patients without the use of donor plasma has a positive impact on clinical outcome [23]. When plasma exchange is performed along with ECMO, a frequent replacement of extracorporeal RRT circuit is required (for three sessions the circuit of plasma exchange should be connected to ECMO system three times, moreover, continuous hemodialysis needs to be restarted after the end of plasma exchange). Each circuit replacement can cause an air embolism. The human factor which could also cause serious complications cannot be neglected. The procedure is rather labor-intensive as well. Thus, we considered inappropriate the use of plasma exchange due to the higher immune burden on the patient's body and poorly studied impact of this technique on free hemoglobin concentrations in blood plasma (during 2015–2021, only 2 clinical observations were published in the available scientific literature [24, 25]).

Activation of the immune response, increased levels of damage-associated molecular patterns and elevated blood free hemoglobin as a result of the ECMO are direct indications for the use of hemoadsorption using the CytoSorb adsorber. The reduction of free hemoglobin concentration was claimed by the manufacturer of the column and confirmed in a multicenter RCT [14]. The effects of reduction of inflammatory mediators have been confirmed by an extensive body of evidence (more than 370 papers in international peer-reviewed journals) [26].

In our clinical observation, using hemoadsorption for the management of negative effects of ECMO-associated mechanical hemolysis, the reduction of hemolysis severity was confirmed by a more than 4-fold decrease in LDH, stabilization of renal function, an increase in P/F ratio by more than 2 times after the first session of hemoadsorption.

Conclusion

In this clinical observation, the use of hemoadsorption in the treatment of ECMO-associated mechanical hemolysis was safe and technically feasible, and allowed rapid and safe resolution of ECMO pump head thrombosis, as well as fast improvement of kidney function. Timely, appropriate and clinically relevant use of a complex combination therapy resulted in the patient's recovery.

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Pathogenesis, Prognosis and Outcomes of Multiple Organ Failure in Newborns (Review)

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Summary

Multiple organ failure (MOF) is the leading cause of neonatal mortality in intensive care units. The prevalence of MOF in newborns is currently unclear, since its incidence varies in asphyxia, sepsis, prematurity, and comorbidity, and depends on the level of development and funding of health care in different countries. Sepsis and acute respiratory distress syndrome prevail among the causes of MOF in this category of patients.

Aim of the review. To summarize the available literature data on the pathogenesis, therapeutic strategies and outcomes of MOF in newborns.

Material and methods. We searched PubMed, Scopus, Web of Science, and RSCI databases using the following keywords: «newborns, multiple organ failure, etiology, pathogenesis, premature, diagnosis, treatment, respiratory support, cardiotonic support», without language limitations. A total of 144 full-text sources were selected for analysis, 70% of which were published in the last five years and 50% were published in the last three years. Criteria for exclusion were low information value and outdated data.

Results. The prevalence of MOF in neonates is currently unclear. This could be due to common association of neonatal MOF (as well as the adult one) with various diseases; thus, its incidence is not the same for asphyxia, sepsis, prematurity, and comorbidities. There is no precise data on neonatal mortality in MOF, but according to some reports, it may be as high as 13–50%.

In newborns, MOF can be caused by two major causes, intrapartum/postnatal asphyxia and sepsis, but could also be influenced by other intranatal factors such as intrauterine infections and acute interruption of placental blood flow.

The key element in the pathogenesis of neonate MOF is cytokinemia, which triggers universal critical pathways. Attempts to identify different clinical trajectories of critical illness in various categories of patients have led to the discovery of MOF phenotypes with specific patterns of systemic inflammatory response. This scientific trend is very promising for the creation of new classes of drugs and individual therapeutic pathways in neonates with MOF of various etiologies.

The pSOFA scale is used to predict the outcome of neonatal MOF, however, the nSOFA scale has higher validity in premature infants with low birth weight.

Central nervous system damage is the major MOF-associated adverse outcome in newborns, with gestational age and the timing of treatment initiation being key factors affecting risk of MOF development in both full-term and premature infants.

Conclusion. The study of cellular messengers of inflammation, MOF phenotypes, mitochondrial insufficiency, and immunity in critically ill infants with MOF of various etiologies is a promising area of research. The pSOFA scale is suggested for predicting the outcome of MOF in full-term infants, while the nSOFA scale should be used in premature infants with low birth weight.

Keywords: multiple organ failure; newborns; critical illness phenotype

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

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Introduction

Multiple organ failure (MOF) syndrome has been studied in all areas of contemporary health care, but the issue is particularly relevant for neonatology [1, 2]. The MOF is one of the leading causes of neonatal death in intensive care units (ICU) and carries a huge financial burden for the healthcare system and the parents, e.g., in the United States, the cost of treatment of these patients is estimated to be $20 billion annually [3].

The MOF syndrome is a relatively «new» complication, which appeared due to the evolution of critical care. Advances in transfusion medicine, respiratory support, adsorption methods of treatment, inotropic and fluid therapy made it possible to prolong the life of critically ill patients, which resulted in the

emergence of novel clinical patterns leading to identification of MOF. The earliest studies were focused on the study of MOF in adults, and only afterwards the issue came to attention of pediatric and neonatology specialists J. J. Skillman (1969), who described a new syndrome consisting of respiratory failure, hypotension, sepsis and jaundice in a patient with acute bleeding from a stress gastric ulcer, is considered the pioneer of MOF research [4]. Later in 1973, N. L. Tilney showed a stereotyped sequential organ involvement in patients with abdominal aortic aneurysm rupture [5]. The detailed description of MOF was given by A. E. Baue in 1975, who highlighted the sequential pattern of critical symptoms and showed the inevitable development of respiratory and hepatorenal failure during the first three days in a series of dead patients who have undergone extensive and aggressive surgical intervention [6]. The term «multiple organ failure» was first proposed by B. Eiseman in 1977, whereas definitions and pathogenesis of systemic inflammatory response in this condition were formulated by D. E. Fry (2012) [7]. The main focus of scientific research concerning MOF was first placed on both adults and children, but in the last decade began to shift towards the newborns. As a result, a lot of new data were obtained for this category of patients. Our review discusses the latest data on diagnosis, definition, etiology and pathogenesis of MOF syndrome in newborns, as well as the current ways of its management.

The aim of the review is to summarize the available literature data on the prevalence, pathogenesis, treatment and outcomes of MOF syndrome in newborns.

Material and Methods

The information was searched through PubMed, Scopus, Web of Science, and RSCI databases using the following keywords: newborns, multiple organ failure, etiology, pathogenesis, premature, diagnosis, treatment, respiratory support, cardiotonic support, with no language limitations. A total of 144 full-text sources were selected for analysis, 70% of which were published within the last five years and 50% within the last three years. The exclusion criteria were low relevance and outdated content.

Definitions of MOF in neonates

To summarize the available definitions of MOF, it can be defined as a severe nonspecific stress response characterized by failure of two or more organs and systems seen separately or sequentially, requiring partial or complete replacement of the function of the affected organs, with a mutual enhancement effect and a high likelihood of persistence and death [8–10].

Currently, there is no unified definition of neonatal MOF, so neonatologists use criteria accepted in pediatrics [11, 12]. The first set of criteria for pediatric MOF was proposed by J. D. Wilkinson in 1987 [13]. In 1996, the proposed criteria were modified by F. Proulx, who defined pediatric MOF as simultaneous dysfunction of at least two of seven organ systems including respiratory, cardiovascular, neurological, hematological, renal, hepatic and gastrointestinal ones [14]. In 2005, the International Pediatric Sepsis Consensus Conference developed and introduced into clinical practice a set of diagnostic criteria for MOF that includes dysfunction of two of the six organ systems [15, 16].

Prevalence of MOF in Newborns

No precise data of prevalence of MOF in the newborns are available to date. This could be due to various underlying diseases: similarly to adults, the frequency of MOF in neonates is different in asphyxia, sepsis, prematurity, and multiple comorbidities [17–19]. Thus, S. L. Weiss (2021) reports that the frequency of MOF in children with respiratory-associated asphyxia requiring mechanical ventilation can be as high as 73%. Development of MOF on day 1 of ventilation occurred in 63% of patients, while in others MOF was diagnosed on days 2–28 of ventilation [20]. In sepsis, the frequency of MOF varies from 19% to 68% [21, 22], In newborns who had fetal inflammatory response syndrome (FIRS), the frequency of MOF was 38.2% and even greater in premature infants [23]. The frequency and outcomes of MOF significantly vary depending on country income and healthcare expenditures. Thus, in high-income countries, the neonatal mortality rate from MOF due to intrapartum asphyxia is 10%, while in developing countries it is as high as 28% [24].

There is no exact data on neonatal mortality in MOF; only several reports show mortality in the range of 13–50% [25–27]. The wide variation in mortality rate of neonates is due to dependence of MOF on numerous factors including availability of health care resources, presence of malformations in the neonate, gestational age and weight at birth, mode of delivery, etc. [28–30]. Nevertheless, MOF is considered an independent factor of neonatal death, increasing the likelihood of an adverse outcome by 6-fold and more, whereas surviving children have a higher risk of developing organic and functional failure [31–33].

Etiology and Pathogenesis of Neonatal MOF

The pattern of causes of MOF in children and newborns differs from that in adults. The causes of pediatric MOF have been thoroughly analyzed in the J. S. Upperman (2017–2018) series «Specific etiologies associated with the multiple organ dysfunction syndrome in children» [34, 35]. Sepsis and acute respiratory distress syndrome (ARDS) are the

most frequent and studied causes of pediatric MOF. Sepsis is usually caused by respiratory infections (37%), bacteremia (25%), urinary tract infections, surgical conditions, brain disorders (12%), etc. In pediatric patients, the incidence and mortality of MOF is lower than in adults: the former averages 2–2.8 per 100,000 person-years, while the latter ranges from 18 to 27%. At the same time, in this age group MOF can also develop in organ transplantation, acute kidney injury, trauma, burns, etc.

In newborns, the etiology of MOF is distinct: as in children, it is most often initiated by two main causes which are intrapartum asphyxia and sepsis. However, MOF is often influenced by intrapartum factors, most often, intrauterine infections and acute placental circulation disorder [36–39]. This causes fetal inflammatory response syndrome, which worsens MOF in newborns who, in E. Jung's apt words (2020), have been «rescued by birth» [40]. Another mechanism of MOF, unique for newborns, is due to therapeutic hypothermia used to prevent brain damage in neonatal asphyxia, which does not occur in older children and adults [41, 42]. This procedure reduces the risk of death from asphyxia but increases the risk of MOF and adverse outcomes [43].

The pathogenesis of MOF in neonates is poorly understood, therefore, many ideas about its key events were extrapolated from older patients. At the same time, despite assumptions about the uniformity of the pathogenesis of MOF, there is evidence that immune system reactivity varies not only among neonates, children and adults, but also within the same age group. All this has prompted the study of critical illness phenotypes in different diseases and age groups.

The involvement of cellular messengers of inflammation was clearly shown in the experimental model of aseptic MOF developed by S. Steinberg (1989) when injection of combination of mineral oil and zymosan activated pathogen-associated molecular patterns (PAMPs) initiating inflammatory response to infectious agent, which in turn triggers cytokine-mediated epithelial, endothelial, mitochondrial, immune cellular and systemic organ dysfunction [44]. The universal endogenous protective factor in this model is the cytochrome-P450 system reducing inflammation, which has been demonstrated in «adult» and «child» models [45, 46]. The findings suggested that an imbalance between cellular messengers of inflammation and cytochrome-P450 metabolism is a key factor in the pathogenesis of MOF in all age groups. Experimental data were confirmed in clinical studies in critically ill children with different conditions. In such patients, a decrease in cytochrome-P450 activity was inversely correlated with the severity of cytokinemia and organ dysfunction, and increased levels of danger signals (PAMP, MAMP, DAMP, SAMP, TAMP) and cytokines initiating the cascade of systemic inflammatory reactions were observed in the blood [47–50].

Cytokinemia is the leading factor of self-injury in MOF in adults, children and newborns. It triggers the universal mechanisms of the critical condition including epithelial cell dysfunction and apoptosis, clinically presenting as ARDS, hepatobiliary dysfunction and/or acute renal tubular dysfunction; endothelial cell dysfunction and apoptosis, clinically presenting as thrombotic microangiopathy with loss of microvascular homeostasis; mitochondrial autophagy (mitophagy) and dysfunction manifested as catabolism, hibernation and impaired autonomy; immune cell dysfunction and apoptosis, clinically manifested as lymphoid organ depletion with ineffective pathogen removal and tissue regeneration [51–53].

In the last decade, antimicrobial peptides (AMPs), the molecules composed of 12–50 amino acid residues, exhibiting antimicrobial, antifungal and antiviral effects and potent chemoattractant activity, have been shown to impact pathogenesis of MOF. A 2017 meta-analysis revealed age-related patterns of AMPs involvement in the pathogenesis of MOF. Thus, in adults, severe sepsis was associated with impaired dynamic expression of cathelicidin and defensin, and in neonates, with that of hepcidin and presepsin [54, 55].

The search for new signaling pathways and inflammatory messengers opens up new possibilities in the prediction of MOF in neonatology. The most promising biomarkers of MOF are shown in Table 1.

The immune system plays a key role in the pathophysiology of neonatal MOF, but it is unclear when the immune system is suppressed and when it is overreactive. Activity of thymus gland and capability to generate immune responses are changing with age that impacts the complexity of the pathophysiology of MOF in different age groups [70, 71]. Attempts to identify different clinical trajectories of critical illness in various categories of patients led to the discovery of MOF phenotypes with specific systemic inflammatory response [72]. The phenotype of MOF refers to the pattern and timing of organ dysfunction that affect the risk of adverse outcome, are universal for a particular phenotype and can be seen in adults, children and neonates [73, 74]. For example, the NPMODS phenotype develops in 26% of children with sepsis and is accompanied by a high risk of death regardless of the presence of MOF at the time of seeking medical care [75]. However, the suitability of a concept to distinguish critical illness phenotypes in children is still a controversial issue, since the literature contains data questioning this scientific direction. In particular, M. M. Pollack (2020) in a study that included 681 patients, mean age 2.4 years, failed to identify the reported clinical trajectories of MOF in critically ill children [76].

Table 1. Promising inflammatory biomarkers in the prediction of MOF.

Inflammatory biomarker	Potential for use
Endocan (endothelial cell-specific molecule-1 or ESM-1)	The biomarker level correlates with the severity of sepsis, but its threshold level having high sensitivity and specificity is still to be determined [56].
Cluster of differentiation 64 (CD64)	It is expressed by inflammatory cells in response to bacterial infection and is not affected by transient neonatal tachypnea, ARDS or other noninfectious factors, usually occurring within the first 72 hours after birth. Its high values in premature infants and other infectious conditions often associated with MOF are a shortcoming [57, 58].
Differentiation molecule 11b (CD11b) cluster	The marker level increases within 5 minutes after exposure to an infectious agent, making it a more accurate biomarker in predicting MOF [59].
Pancreatic stone protein (PSP)	It belongs to the class of C-type lectins and is secreted by the pancreas in response to systemic stress and organ damage associated with critical illness. This biomarker has demonstrated 100% sensitivity and specificity in clinical studies with preterm and premature infants [60, 61].
Soluble intercellular adhesion molecule-1 (sICAM-1)	A protein factor used in the transport of neutrophils to the site of inflammation *in vivo* [62]. When endothelial cells are activated by cytokines, there is a rapid increase (within 1-6 hours) in the serum level of sICAM-1, which makes it a marker of systemic inflammation. Currently, there is debate about the usefulness of this marker for diagnosing EOS, as some authors have suggested sICAM-1 as a useful marker only in the first 4 days of life, while others have noted similar or even higher values in healthy neonates during the first 5 days after the birth [63, 64].
Progranulin	Autocrine growth factor of 593 amino acids, which regulates the TNF/TNFR signaling system, can predict sepsis and MOF in neonates after 34 weeks' gestation [65]
Neopterin	Biomarker of immune activity, which increases in the cell-mediated immune response [66].
Resistin (FIZZ3)	Cysteine-rich protein, which plays a controversial physiological role in obesity and insulin resistance and is elevated in systemic inflammatory response in neonates, children, and adults, but its diagnostic value remains to be known [67,68]
Presepsin (PSP)	The protein is the N-terminal fragment of the macrophage CD14 receptor. The mechanism for the production of PSP is associated with bacterial phagocytosis and cleavage of membrane-bound CD14 by lysosomal enzymes. PSP showed comparable performance with procalcitonin in predicting neonatal sepsis at threshold value of 706.5 pg/mL having a sensitivity of 85.7%, a specificity of 68.8%, a positive predictive value of 85.7%, and a negative predictive value of 68.8%. However, the performance of this biomarker in various age groups and in other causes of MOF remains unknown [69].

The study of MOF phenotypes in different illnesses could be potentially useful for revealing new treatment options for critically ill newborns. E. K. Stroup (2019) based on a study in 5,297 critically ill children identified 4 phenotypes that developed in the first 72 hours of disease and manifested as the following clinical and laboratory syndromes: 1) severe encephalopathy with moderate organ dysfunction; 2) moderate resolving hypoxemia; 3) severe persistent hypoxemia and shock; 4) persistent cytopenia, hepatobiliary dysfunction and shock [77]. These results were echoed by a larger cohort study by L. N. Sanchez-Pinto (2020), which conducted a six-year evaluation of 20827 children admitted to the ICU in critical condition [78]. Based on the most distinctive features of MOF (type of organ dysfunction, severity of disease and clinical trajectory of ICU stay on day 3), 4 main phenotypes were identified. They include Phenotype 1, manifesting as severe persistent encephalopathy (19.2%), Phenotype 2, manifesting as moderate resolving hypoxemia (34.5%), Phenotype 3, manifesting as severe persistent hypoxemia and shock (19.1%), and Phenotype 4, presenting as moderate persistent thrombocytopenia and shock (22.6%). The lowest mortality rate was registered in phenotype 2, while risk-adjusted mortality ratios (aHR) on day 28 of ICU stay for other phenotypes were as follows: phenotype 1, 3.0 (IQR, 2.1–4.3); phenotype 3, 2.8 (IQR, 2.0–4.1); phenotype 4, 1.8 (IQR, 1.2–2.6). The findings prove the feasibility of different therapeutic approaches to the management of critically ill children.

Each phenotype in SARS exhibits unique pathogenesis and therefore differs significantly from the others. Thus, in some cases there is an overreaction of the immune system, in others, on the contrary, its inhibition. As an example, the three most studied phenotypes of MOF in children can be discussed. The first of them is AHUS (atypical hemolytic-uremic syndrome), manifested by thrombocytopenia, low ADAMTS13 activity, acute kidney injury, extensive endotheliosis and systemic thrombotic microangiopathy [79–81]. The pathogenesis of this phenotype includes deficiency of genes involved in the synthesis of complement inhibitors and ADAMTS13, resulting in an overreactive immune response [82]. The disease is successfully treated with monoclonal antibodies (eculizumab) that block the terminal activity of human complement [83–89]. Another phenotype is caused by insufficiency of the Fas receptor-Fas ligand system [86, 87]. The hyperinflammation in

Table 2. Sequential Assessment of Organ Failure in Newborns (nSOFA) scale [110].

Respiratory score					
Points	0	2	4	6	8
Criteria	not intubated	intubated			
	$SpO_2/FiO_2 \geqslant$ 300 mm Hg	$SpO_2/FiO_2 <$ 300 mm Hg	$SpO_2/FiO_2 <$ 200 mm Hg	$SpO_2/FiO_2 <$ 150 mm Hg	$SpO_2/FiO_2 <$ 100 mm Hg
Cardiovascular score					
Points	0	1	2	3	4
Criteria	No inotropes, no systemic steroids	No inotropes, systemic steroid treatment	One inotrope, no systemic steroids	Al least two inotropes or one inotrope and systemic steroids	At least two inotropes and systemic steroids
Hematological score					
Points	0	1	2	3	
Критерии	Platelets $\geqslant 150\times10^9$/л	Platelets $100–149\times10^9$/л	Platelets $<100\times10^9$/л	Platelets $<50\times10^9$/л	

this phenotype is associated with the inability to undergo the activation-induced cell death. The latter is mediated by two molecular signals which are the Fas receptor (Fas, CD95) and Fas ligand (FasL, CD178) signaling pathway and the CTL/NK cell signaling pathway [88]. A defect in these signaling pathways triggers the process of immune overreaction and systemic self-damage [89]. Fas ligand known as «death factor» binds to Fas receptor and induces cell death. Mutations in Fas-FasL genes lead to FasL-mediated T-cell apoptosis and «immune escape mechanism», which is crucial for the pathophysiology of MOF, autoimmune lymphoproliferation and oncogenesis [90–92]. MOF in this phenotype can be easily reproduced experimentally in knockout mice with an inactivated gene located on chromosome 19 (in humans on chromosome 10) [93]. Another phenotype is manifested by the «immune paralysis» phenomenon [94, 95]. The child's immune response in critical illness is very dynamic, with systemic inflammation often accompanied by suppression of leukocyte count and function and clinically manifested by the compensatory anti-inflammatory response syndrome (CARS) [96]. Normally, it is a time-limited syndrome and prevents systemic inflammation, but when CARS is excessive, it is considered an acquired immunodeficiency, which can significantly compromise the patient's recovery [97]. The «immune paralysis» always associated with high mortality was reported in children and newborns with sepsis, viral infections, trauma and asphyxia [98–100]. External and intrinsic factors contributing to this phenomenon include family history, use of steroids, chemotherapy, and immunosuppressive medications [101, 102].

The role of mitochondrial failure in neonatal MOF has not been studied, but studies in children show promise for this research area. In addition to ATP production, mitochondria play important roles in cell homeostasis and intercellular interactions, including gene expression, inflammation, immune function, oxidative stress, calcium homeostasis, cell motility, heat production, hormone synthesis, and apoptosis [103, 104]. There is evidence proving the role of mitochondria in the pathogenesis of MOF. First, decreased mitochondrial oxygen consumption, low ATP levels, and mitochondrial gene suppression correlate with the severity of MOF and death [105]. Secondly, mitochondrial abnormalities in all vital organ systems have been reported in experimental models of sepsis and MOF [106, 107]. Finally, both spontaneous and pharmacological recovery of mitochondrial function improves critical illness survival. In particular, enhancing mitochondrial biogenesis to produce new mitochondria and mitophagy to remove defective mitochondria restores organ function and positively affects the outcome of MOF [108, 109].

Prediction of MOF Outcomes in Neonates

Several systems for predicting death in children with MOF hospitalized to ICU have now been proposed, but the best one suited for neonates remains unknown. In children, the prediction of death in MOF is based on the Pediatric Sequential Organ Failure Assessment (pSOFA) Scale [110], which is also valid for preterm infants (Table 2). The neonatal SOFA scale (nSOFA) has been proposed for low birth weight preterm infants, but its validation for different variants of MOF is still under development. In a study by James L Wynn (2020, 679 neonates), the nSOFA demonstrated high accuracy in preterm infants at 0, 6, and 12 hours (AUC 0.77 with 95% CI 0.62–0.92, P=0.001, AUC 0.78 with 95% CI 0.66–0.92, P<0.001 and AUC 0.93 with 95% CI 0.86–0.997, P<0.001) [111]. At the same time, the authors emphasize that nSOFA needs further development and inclusion of additional parameters to improve the accuracy of the prediction. The high validity of nSOFA has been repeatedly confirmed: the high discriminatory ability of the nSOFA scale (0.891) in sepsis-associated MOF has been reported by Russian and international researchers in large

populations, and the endpoint of patient death (9 points) was comparable in all studies [112, 113].

Basic Principles of Neonatal MOF Treatment

The treatment of neonatal MOF is based on the same principles as in adults, i. e., hemodynamic and respiratory support [114].

Considering the specifics of neonatal physiology, the main scientific research regarding hemodynamic support in MOF is focused on the most effective regimens and dosages of inotropic therapy. Today, dopamine, dobutamine and adrenaline remain the most studied drugs in neonatology, and dopamine remains the most frequently prescribed drug in neonates with MOF, even with low gestational age [115]. Meanwhile, their efficacy with respect to perfusion of organs and systems in neonatal MOF remains poorly documented [116], hence, other drugs with good clinical potential such as milrinone, norepinephrine, vasopressin, and levosimendan, have been introduced in neonatology.

Milrinone is a phosphodiesterase-3 inhibitor with positive inotropic, peripheral vasodilator and lusitropic effects [117]. In the last decade, milrinone has been prescribed in neonatology for the treatment of cardiopulmonary dysfunction in the context of pulmonary hypertension and low cardiac output in cardiovascular and respiratory anomalies, asphyxia, perioperative period during cardiac surgery and congenital diaphragmatic hernia [118]. At the same time, the authors of the Cochrane review (2015, 8 RCTs) emphasize the need for better quality studies, as the available data are insufficient to identify the advantages of milrinone compared to placebo, levosimendan or dobutamine with regard to mortality, duration of ICU stay, hospital stay, and ventilatory support [119].

Norepinephrine is an endogenous sympathomimetic amine that acts primarily on α-1 vascular and myocardial receptors with mild β-1 stimulation and minimal effect on β-2 adrenoreceptors. Because of this, norepinephrine is effective for constriction of peripheral vessels with minimal inotropic effect [120]. There is data on the use of norepinephrine in hypotensive preterm infants with refractory shock or low cardiac output, especially in severe septicemia, cardiac surgery or right ventricular «stress» [121]. In combination with dobutamine or milrinone, norepinephrine maintains vascular tone and can enhance coronary perfusion and support right ventricular myocardium in cases of asphyxia with severe pulmonary hypertension and right ventricular failure [122].

Vasopressin is a hypothalamic peptide hormone that increases vascular smooth muscle tone and peripheral resistance through V1A receptors, except in the pulmonary circulation, where the drug increases nitric oxide release, causing vasodilation [123]. Vasopressin is well established in the therapy of neonatal refractory shock, but further studies are needed to assess its efficacy, as a 2017 meta-analysis (8 RCTs, 224 patients) showed no impact of the drug on neonatal survival (RR=1.19; 95% CI: 0.71–2.00) [124]. Moreover, some studies have reported side effects of vasopressin that included significant hyponatremia, transient thrombocytopenia, liver and limb necrosis [125, 126]. Therefore, the use of vasopressin in the therapy of neonatal MOF requires further clarification.

Levosimendan is a cardiotonic agent that increases cardiac calcium sensitivity and has positive inotropic and vasodilatory effects, reducing pre- and postload for the heart [127]. Levosimendan is mainly used in neonates with heart failure and pulmonary hypertension [128]. Despite the promising use of levosimendan in neonates with MOF, there are currently no large studies of its effectiveness in this category of patients.

A high-potential area of respiratory support for neonates with MOF is the use of inhaled pulmonary vasodilators for severe hypoxemia due to neonatal respiratory failure. For this purpose, inhaled nitric oxide and prostacyclin (epoprostenol, iloprost, treprostinil) are used. Inhaled pulmonary vasodilators, in addition to their pulmonary vasodilatory effects, can potentially be employed to improve oxygenation, control local inflammation, and provide alveolar protection [129]. In a 2019 meta-analysis (9 RCTs, 856 patients), the use of nitric oxide in neonates with hypoxemia reduced neonatal mortality (OR 0.66, 95% CI: 0.57–0.77, P<0.00001) and the need for ECMO (OR 0.89, 95% CI: 0.50–0.71, P<0.00001) [130]. Nevertheless, currently there is still insufficient data on the efficacy and safety of nitric oxide in MOF, therefore its use is marked as «based on expert consensus» in the draft Russian guidelines for the treatment of pediatric sepsis [131]. Prostacyclin and its synthetic analogues, as well as milrinone and levosimendan may be cheaper alternatives to nitric oxide, but evaluation of their effectiveness and safety in neonatology is still under way.

The efferent therapies in neonatology have not been widely used and therefore are also in the process of investigation of their effectiveness. Several small retrospective studies of low quality showing promising results are available in the literature. Inclusion of adsorption technologies in standard therapy of MOF was associated with positive effects in 81% of neonates. These included an increase in the oxygenation index and a significant decrease in the dose of inotropic drugs after 6 hours, improvement of acid-base balance, creatinine and urea values after 12 hours, and an increase in urine output and stabilization of blood pressure after 24 hours. The incidence of complications was relatively low: thrombocytopenia was observed in 6 children, one patient had occlusive disorders [132].

The efficacy and appropriateness of ECMO in neonates with respiratory disease remain unclear today, since the literature data are quite contradictory. In a study of the effectiveness of ECMO in severe adenovirus pneumonia in 542 patients of different ages (adults, children and newborns), significantly higher mortality was observed in the neonates (OR 10.9; 95% CI=3.2–37.3; *P*<0.001) [133]. An independent factor of increasing survival rate during ECMO in critically ill neonates was absence of intraventricular hemorrhage and acute renal failure in patients [134]. Promising results were obtained with advanced ECMO technologies and creation of «artificial placenta» (extracorporeal life support, ECLS) for extremely premature infants, which is now in clinical trial phase [135].

Outcomes of Neonatal MOF

Multiple organ failure is associated with negative long-term outcomes for children and newborns [136–139].

A retrospective study by N. P. Pinto (2017) evaluated the functional status of 303 children during three years after MOF. The clinical trajectory of these children was as follows: cumulative mortality increased from 3.9% to 7.8% from discharge to 6 months later (*P*=0.08), and to 10.4% after 3 years (*P*=0.03); overall morbidity increased from 5.2% to 6.5% and 10.4%, respectively. The number of children with worsening functional status or death was comparable to that of patients who survived with no change in functional status (38% and 44%, respectively). The study showed that long-term functional status in children was associated with parameters characterizing MOF such as need for invasive therapy, ventilator use, number of days on ventilator, use of vasopressor therapy, and length of stay in the ICU [140].

Brain damage is the leading adverse outcome associated with MOF in newborns, with gestational age and timing of treatment initiation being the key factors influencing its risk in both full-term and premature infants [144]. In a retrospective cohort study of preterm infants who lived more than 7 days (2021, 3940 infants, 22–26 weeks) with MOF caused by sepsis, necrotizing enterocolitis, or bowel perforation, timely antibiotic therapy in all children reduced the risk of brain damage, but did not influence the risk of death [145]. Similar data were obtained in full-term infants [143].

According to E. Serebryakova (2017), the course and outcomes of MOF in newborns significantly depend on gestational age and birth weight, so these parameters can be considered predictors of adverse outcomes [144]. In contrast to full-term infants, very low birth weight and extremely low birth weight newborns had higher incidence of respiratory distress syndrome, a longer stay in the ICU, and a high frequency of severe brain damage, bronchopulmonary dysplasia, and retinopathy.

Conclusion

The issue of neonatal MOF is urgent, but insufficiently studied. The study of different critical illness phenotypes in full-term and premature infants is the most promising area of pathophysiology of MOF, which makes it possible to personalize therapeutic trajectories. The pSOFA scale for full-term infants and nSOFA scale for premature infants with low birth weight should be used to predict the outcomes of MOF. The treatment of neonatal MOF is based on the same principles as in adults, i. e., hemodynamic and respiratory support, while the use of several promising drugs such as milrinone, noradrenaline, vasopressin, levosimendan, and inhaled pulmonary vasodilators, could potentially improve the therapy outcome.

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Selection of the End-Expiratory Pressure for Mechanical Respiratory Support (Review)

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Summary

End-expiratory pressure remains one of the few parameters of mechanical respiratory support whose values have not been strictly regulated using the evidence-based approach. The absence of «gold standard» for end-expiratory pressure optimization together with its obvious significant contribution to the efficiency and safety of respiratory support has driven the search for the optimal method of choosing its values for several decades.

Aim of the review: to identify the optimal methods for determining the values of end-expiratory pressure based on the analysis of its positive and negative effects in the used strategies of mechanical respiratory support.

Material and methods. We analyzed 165 papers from the PubMed, Scopus, and RSCI databases of medical and biological publications. Among them we selected 86 sources that most completely covered the following subjects: respiratory support, end-expiratory pressure, recruitment, ventilation-perfusion relationships, metabolography, and gas analysis.

Results. We outlined the main positive and negative effects of the end-expiratory pressure with regard to both lung biomechanical characteristics and pulmonary perfusion. The evolution of views on the methods of determining optimal values of the end-expiratory pressure was reviewed with the emphasis on a certain «fixation» of the scientific community in recent decades concerning the opening of the alveoli. The promising techniques based on the analysis of the diffusion capacity of the lungs were presented.

Conclusion. Focusing on mechanical lung opening prevents the scientific community from advancing in the optimization of the end-expiratory pressure. Dynamic assessment of pulmonary diffusion efficiency provides a new perspective on the issue, offering additional ways to the development of «gold standard».

Keywords: end-expiratory pressure; ventilation-perfusion relationships; shunt; alveolar dead space; compliance; gas analysis

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Introduction

Mechanical respiratory support (MRS) is one of the most powerful, radical, and widely used methods of life support in the anesthesiologist's arsenal. However, the great potential of mechanical ventilation in the treatment of the most severe patients with acute respiratory failure has always been associated with the understanding of the many risks and possible harm. Several decades of clinical use of MRS have forged a strategy underlying current approaches to selecting mechanical ventilation parameters based on the open-lung concept and pulmonary-protective ventilation concept [1, 2]. Generated by initially controversial and even opposing considerations, today both concepts are equally recognized as obligatory for effective and safe MRS [3].

Currently, the MRS concepts quite specifically determine the recommended values of respiratory cycle parameters and, most importantly, provide guidance for their management regardless of the selected mode of mechanical support [4]. Thus, the initial tidal volume should be equal to 8 ml per kg of ideal (predicted based on sex and height) body weight with subsequent reduction to 6–7 ml/kg. The respiratory rate should not exceed 35 per minute to achieve the target values of pCO_2 (end expiratory pressure as determined by capnography or arterial blood gas analysis). The ratio of inspiration time to exhalation time should ensure the initiation of the next inspiration at exhalation flow rate zero, controlled by the flow curve [2]. The inspiratory oxygen fraction should be sufficient to achieve a saturation (SaO_2 or SpO_2) of 88–95% followed by titration, if possible, to values <0.7. In these clear algorithms, however, there is a parameter, the positive end-expiratory pressure (PEEP), which values have not yet been so strictly regulated. The recommended PEEP values should be at least 5 cm H_2O but «probably greater than that» [5]. This unique uncertainty demonstrates not only the secondary role of this value in providing efficiency and safety of mechanical lung ventilation. In addition, it reflects high variability of the PEEP optimal value in different patients and

an absence of reasonable and generally accepted approach to its selection. In this paper, the main positive and negative effects of PEEP and the evolution of views on methods to determine its optimal values will be discussed.

The Effects of PEEP

Although the effects of PEEP were described by Alvan L. Barach et al. as early as in 1938 [6], the idea of its unfavorable effect on hemodynamics delayed its use. Only in 1967 David Ashbaugh, Thomas Petty and their colleagues described acute respiratory distress syndrome [7], and the term «residual positive pressure» was coined by John S. Inkster [8] at the IV World Congress of Anesthesiology in London (1968). The immediate purpose of PEEP is to counteract atelectasis, i. e., to compensate for the reduction of end-expiratory lung volume resulting from various disturbances of biomechanics of both lung tissue and chest wall structures [9, 10]. End of exhalation in MRS is the most critical period of the respiratory cycle in terms of possible alveoli collapse. Collapsed alveoli do not participate in gas exchange, the proportion of QS/QT shunt increases and, as a consequence, oxygenation decreases, while cyclic opening of collapsed alveoli leads to their mechanical damage (atelectotrauma) [11, 12]. Such changes can occur not only as a result of severe disease: an increased subphrenic pressure in the supine position is sufficient for their appearance [13, 14], which is commonly seen in obesity, pregnancy and other conditions causing abdominal hypertension [15–17], as well as in the use of hypnotics and myorelaxants [18, 19]. The potential harm and prevalence of such disorders have driven the use of positive end-expiratory pressure in almost all types and regimens of respiratory support.

In turn, excessively high PEEP causes several issues (leaving aside the effect on systemic and extrapulmonary organ hemodynamics manifesting in cardiopulmonary interactions and venous return, the effect of portocaval gradient on hepatic blood flow, and the impact of jugular vein drainage on intracranial pressure, as well as the other extrapulmonary effects). Firstly, PEEP shifts upwards the airway pressure curve, which at the same respiratory volume naturally increases peak pressure and the probability of alveolar barotrauma with the appearance of extra-alveolar gas in lungs [20, 21]. Secondly, it obviously affects pulmonary perfusion, and, as a consequence, blood oxygenation.

Perfusion in the pulmonary system occurs under relatively low pressure: normal pulmonary capillary pressure is 6–12 mm Hg, which is equivalent to 8–16 cm H_2O [22]. John West (1960) described gravitational pressure gradient in capillaries located at different heights of continuous fluid column in pulmonary vascular bed [23]. Vertical size of an adult lung varies from 20 to 30 cm depending on the size and position of the body [24]. Since the Swan-Ganz catheter enables to measure pressure in pulmonary capillaries usually in the West zone III, and less often in West zone II [22], 20 cm H_2O can be taken as approximate upper limit of hydrostatic addition to measured pulmonary capillary pressure, which prevents capillary collapse under intra-alveolar pressure. In spontaneous breathing, the latter fluctuates ±1 cm H_2O that does not interfere with blood flow even in the most «gravitationally impaired» zones [25]. However, in case of intra-alveolar pressure increase, e.g. during exertion, coughing, Valsalva test or mechanical ventilation, it may be high enough to compress the capillary system not only in «vulnerable» (upper with respect to the direction of gravity) areas [26].

In fact, the intra-alveolar pressure in mechanical ventilation reaches 30, and in some settings up to 40 cm H_2O. [27]. And if the maximum value of hydrostatic pressure in the pulmonary capillary, taking into account the hydrostatic gradient along the lung height, as shown above, can reach only 36 cm of water column, the recruitment maneuver according to the well-known «40×40» method ensures a rather long (40 s) episode of 40 cm H_2O pressure in all open alveoli with all the ensuing consequences. These consequences include «squeezing» of pulmonary blood flow into those parts of lungs, where it remains mechanically possible, i. e. where alveoli are not opened [28]: in mechanically heterogeneous lungs Pascal's law is valid only for continuous column of fluid in vessels.

From the point of view of pulmonary perfusion, low PEEP is beneficial, while its high values are associated with expanded West zones I and II zones and larger proportion of alveolar dead space (ADS) [29]. The rise of ADS affects external respiration not only by expanding the useless ventilation zone. Blood flow literally «squeezed out» from these zones becomes enhanced in the perfused areas [30]. Such increase in perfusion volume, according to the fundamental ideas of H. Rahn and W.O. Fenn [31] can exceed the possibilities of gas diffusion rate (first of all, of less soluble oxygen!), that will eventually result in venous shunting in lungs as well [32], though the characteristic «non-ventilated but perfused» alveoli are absent in this case. Apparently, this mechanism of local pulmonary circulation overperfusion underlies hypoxemia created by ground glass opacities in novel coronavirus infection COVID-19 [33]. The symmetric effect of such irregularity on blood desaturation in the systemic capillaries, underlying the concept of weak microcirculatory units and explaining the abnormally high venous saturation without participation of arteriovenous anastomoses, was shown in a rather illustrative model [34].

Methods for Determining The Optimal PEEP

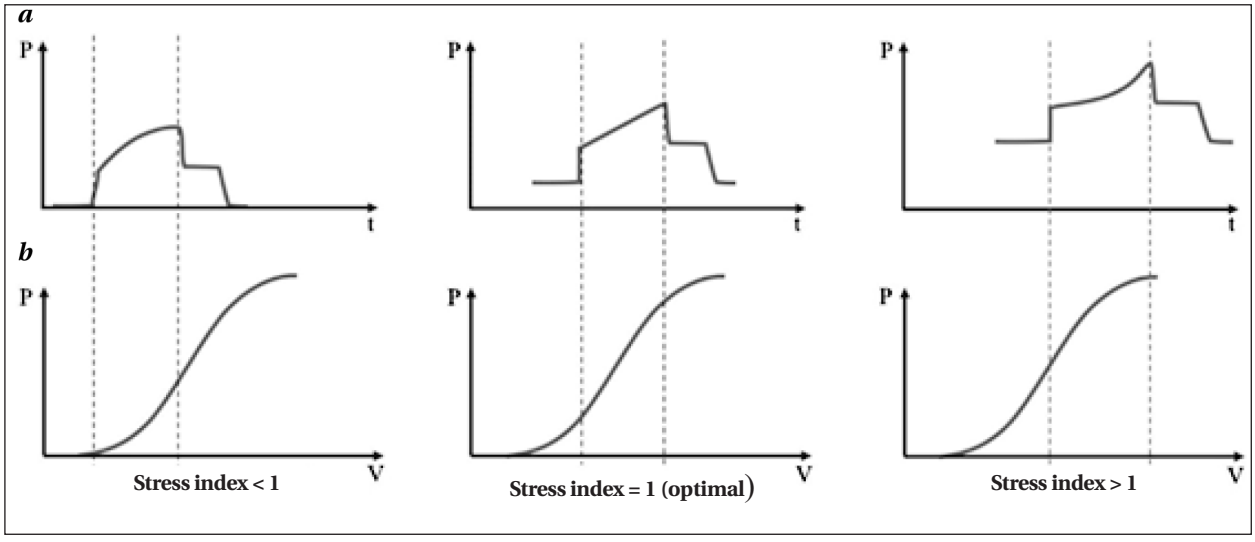
As for the methods for determining the optimal PEEP, one cannot avoid a historical overview here as well. Over more than half a century, dozens of different techniques have been proposed, reflecting a certain evolution of approaches [35–37]. The key indicator of the efficiency of ventilation is the diffusion rate of gases. This parameter cannot be assessed directly at the patient's bedside, so the arterial blood gas analysis which allows assessment of perfusion efficiency, took the leading place in selection of optimal parameters of respiratory support. Gas analysis has been used since the introduction of PEEP technique until now, e.g., as FiO_2/PEEP chart of ARDS.net project. However, the invasiveness of this approach and the need for regular blood sampling prompted the search for alternatives. The focus was placed on perfusion and ventilation, which matching directly affects diffusion, with blood gas analysis serving as a reference method.

Initially, the negative effect of positive end-expiratory pressure on perfusion was associated mainly with a decrease in cardiac output [38]. Improvement of oxygenation, in turn, was attributed to reduced shunt fraction [39]. The main parameter for determining the optimal PEEP level, in addition to blood oxygen level, was cardiac output. Meanwhile, biomechanical lung parameters, such as static compliance, were only a potential alternative at that time [40].

However, a number of key works underlying the modern concepts shifted the emphasis from perfusion to ventilation, defining the trend for decades to come. Thus, the study of J. Mead, T. Takishima and D. Leith, dealing with biomechanical characteristics of the lungs and the theory of atelectotrauma [41], was the basis of the «open lungs» concept by B. Lachmann [1], whereas the research of M. B. Amato [2] laid the foundation of a pulmonary-protective ventilation. In these papers, the emphasis was made on lung biomechanics, and the main goal was formulated as «to open alveoli, and while maintaining their patency, reduce damaging effects on lung tissue both from respiratory support device and from the lungs themselves». Recruitment of alveoli in ventilation became the leading purpose of PEEP, and the emphasis of damaging action had shifted towards barotrauma. This approach became the foundation of the modern paradigm of respiratory support, which was reflected in the methods of selecting the optimal values of PEEP.

Compliance, already a true biomechanical parameter, has become the key for most of them. Collapsed as well as overstretched alveoli have low compliance, showing high resistance to further stretching. In fact, several techniques are based on the avoidance of such low compliance. They differ only in the choice of an indicator for PEEP level setting: from direct analysis of static or dynamic compliance [42, 43], searching for inflection points on inspiratory or expiratory pressure-volume curves [44–46], to complex formulas for calculation of the moment of its maximal increase [47, 48]. The idea of finding the point of maximum compliance to set the PEEP level has evolved into the idea of estimating the damaging flow energy analysis. Thus, the so-called «stress index», based on pressure-time curve analysis, has been described [49, 50], and its target values, approximately equal to 1, are reached when most of the inspiration period lies in the zone of maximum compliance (Fig.).

Determination of the optimal pressure zone, in which the flow energy has the least damaging effect, naturally evolved into the concept of minimization of this energy. The driving pressure deter-



Pressure-time (*a*) and pressure-volume curves (*b*). The differences in the stress index are shown (author's illustration).

mined as a ratio of tidal volume to respiratory system compliance has become an integral indicator of dynamic stress caused by mechanical ventilation. In everyday practice the driving pressure is calculated as the difference between inspiratory plateau pressure and PEEP. Based on the above, achieving minimum driving pressure is possible both by maximizing compliance, as mentioned above, and by minimizing respiratory volume either directly or through reducing the difference of peak pressure and PEEP, which has become a modern trend in MRS [51].

In addition to the parameters measured inside the respiratory circuit, the assessment of intrapleural pressure is of great interest. As there is no acceptable way of direct assessment of this pressure today, the search went on around indirect approaches, the simplest and most reproducible of which turned out to be esophageal manometry [52–54]. The value of pressure in esophageal lumen, taken equal to intrathoracic (and intrapleural) pressure, enables to calculate transpulmonary pressure, which represents pressure gradient between intra-alveolar and intrapleural pressure. Some authors think that this pressure can reflect the real load on lung tissue, and serve as an indicator of PEEP level adjustment [55-58]. Volumes can also be analyzed: for instance, pulmonary volumes and capacities can be evaluated using the nitrogen washout method. This method is used to analyze end-expiratory lung volume (EELV) during the most dangerous phase of respiratory cycle in terms of atelectasis [59–61].

The physical characteristics of the lung can also be assessed through computed tomography (CT), dynamic bioimpedance measurement, and ultrasonography. CT in theory can allow to detect areas of atelectasis and overstretching and also to predict mechanical density using X-ray density and to estimate the weight of lung tissue to be resisted to open alveoli, thus selecting the optimal level of PEEP [62–65]. However, time-consuming character and potential harm of regular optimization of PEEP through CT scanning do not allow this method to be widely implemented in practice. Bioimpedance has shown to be very promising, although the geometric complexity of the thorax does not allow to precisely specify the conduction of electric current through the tissues [66, 67]. Ultrasound is a much simpler alternative to electromagnetic techniques, which allows assessing alveolar opening with high accuracy, but does not permit to determine the damaging energy of gas flow and alveolar overstretching [68–70].

Chronologically, we can observe certain focusing of researchers first on systemic hemodynamics and then on «recruitment and derecruitment» of alveoli, characteristic for the last two or three decades [71]. Contemporary studies have just started to downplay the significance of total lung recruitment, speaking about physiological prospects of «moderate» opening [72, 73], proving once again that the ultimate goal of MRS is not the maximum number of opened alveoli, but an absolutely different result which is normal (or maximally close to normal!) pulmonary gas exchange, i. e., values of minute oxygen uptake (VO_2) and carbon dioxide elimination (VCO_2) [74, 75]. And this result is not obviously related to the proportion of open alveoli, especially considering the cost of «side effects» that often has to be paid for opening the alveoli and keeping them patent. Thus, PEEP may be unjustifiably high not in terms of alveoli overstretching or reduced venous return, but due to unfavorable redistribution of pulmonary capillary blood flow to the zones of collapsed yet perfused alveoli [76, 28].

Owing to this paradigm shift, the clinicians are able to focus on the clinical and physiological result of diffusion assessed by arterial blood gas analysis and by volumetric gas analysis of respiratory mixture. In this context, the situation partly resembles the evolution of ideas about cardiac preload, when the estimation of ventricular filling pressures in recent decades was supplemented by the possibility to estimate the result of end-diastolic volumes on cardiac chambers [22].

In recent years the technique of volumetric capnography, which helps assess the diffusion processes during the adjustment of PEEP level, has gained popularity [77, 78]. The transient increase in VCO_2 associated with changes in the PEEP level occurs due to an increase in the efficiency of diffusion, which can be globally considered as a positive effect. However, the transient increase in PEEP indicates a decrease in the shunt fraction, while its decrease suggests a reduced alveolar dead space fraction. A transient decrease in VCO_2 level, which can be caused by an increase in shunting or anatomical dead space, is considered negative [79–81].

In view of the recent studies on the interpretation of the VCO_2 to determine the optimal PEEP values [82], the changes of carbon dioxide production are worth noting. The duration of these changes is a major parameter. Variations in VCO_2 associated with altered proportion of alveolar dead space or shunt reflect instantaneous changes in the release of this gas, while they last only a few minutes. Longer variations rather reflect changes in minute alveolar ventilation or metabolic carbon dioxide production rate and are not directly related to PEEP level optimization. Besides an isolated estimation of VCO_2, it is also possible to estimate lung oxygen uptake (VO_2), which, according to E. V. Ruchina et al. (2013), can be even more sensitive to PEEP level changes compared to VCO_2 [83], probably due to a greater diffusivity of the first gas. Moreover, simultaneous estimation of the exchange of both gases would potentially increase the specificity of this technique.

The prevalence of techniques of respiratory support parameter selection that exclusively focus on alveolar opening reflects the established belief of both researchers and clinicians that optimization of ventilation is similar to optimization of lung gas exchange, which in turn exhaustively confirms the normal blood gas composition. Such an approach has been described in recent papers of leading international specialists and included in contemporary Russian clinical guidelines [71, 84–86]. However, the ultimate goal of both natural and mechanical lung ventilation is the most effective pulmonary gas exchange in the current clinical situation, which depends not on the optimization of ventilation and/or blood flow values, but on their proportional matching implying the maximum achievable value of the diffusion surface of the lungs. Based on the above, dynamic analysis of respiratory gas production and consumption with high time resolution is very promising, in our opinion. As an instrumental alternative to the volumetric capnography, the use of metabolic modules from various manufacturers, whose function is the continuous parallel calculation of the volumes of carbon dioxide produced and oxygen consumed for the realization of indirect calorimetry, can be proposed. Although their task is not to optimize ventilation, the data obtained with their help have a trend pattern, visually convenient for interpretation, and the simultaneous assessment of the diffusion intensity of the two main gases allows us to hope for greater sensitivity and specificity.

Conclusion

The ambiguity of parameters, methods and criteria for the selection of optimal end-expiratory pressure during mechanical respiratory support emphasizes high individual variability of this parameter in patients and limitation of most known approaches to its selection, focused on the involvement of alveoli in ventilation, but ignoring ventilation-perfusion relationships.

The possibility of dynamic assessment of pulmonary diffusion efficiency makes volumetric oxi- and capnometry a promising approach to the selection of optimal value of end-expiratory pressure, integrally reflecting ventilation-perfusion matching, which requires further study and practical implementation of the method.

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Competency-Based Approach in Teaching Cardiopulmonary Resuscitation

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Summary

Aim of the study: to develop an additional professional competence «Emergency care in cardiac arrest» and to evaluate a set of tools for its development among the graduating students majoring in general medicine (code 31.05.01).

Material and methods. The study was done in two stages. During the first stage, within the framework of PC (professional competence)-11 «Readiness to participate in providing first medical aid in conditions requiring urgent medical intervention» an additional professional competence «Emergency care in cardiac arrest» was developed with the definition of performance assessment. During the second one, the scientific research was conducted at the medical institute of the Immanuel Kant Baltic Federal University during the study of Anesthesiology, resuscitation, and intensive care, which has been included in the block 1 discipline (module) list, being a basic part of the General Medicine curriculum (code 31.05.01). The study involved 140 six-year students majoring in general medicine (code 31.05.01). The students were divided into two groups. The main group included 80 students who studied in 2021 (average age 25±1.5 years), while the control group comprised 60 participants who studied in 2019 (average age 25.9±1.6 years, retrospective analysis).

Results. An additional professional competence «Emergency care in cardiac arrest» and its stratified structure have been developed. Specific elements were elaborated for each component stratum. Based on the developed elements, which were mastered by the student in the process of training, the necessary competence was developed. The novel pedagogical technologies in the curriculum contributed to more effective learning and development of the competence. The levels of development of additional professional competence «Emergency care in cardiac arrest» differed between the groups. Most students in the control group had a threshold level of competence. The basic and advanced levels of competence were significantly higher among the students in the main group compared with the control group ($P<0.05$).

Conclusion. We have shown the necessity of developing an additional professional competence «Emergency treatment in case of cardiac arrest» within the «Readiness to participate in providing first medical aid in conditions requiring urgent medical intervention» PC-11. We have successfully implemented and validated in practice the system of development of additional professional competence using pedagogical innovations, including those based on advanced information and communication technologies.

Keywords: training; cardiac arrest; competence; simulation training; mind map; animated cartoons

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

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Introduction

In recent years the doctrine of medical education has been undergoing significant changes in the Russian Federation and worldwide. The global transformations were initiated by the World Federation for Medical Education and the Association for Medical Education in Europe. Today, higher medical education should provide training of specialists with certain competencies, who will be able to carry out their professional activities adapted to the requirements of ever-changing conditions of work [1–4]. Currently, the general provisions of the competence paradigm have become the basis for the implementation of the competence approach in medical education, and the main task of higher medical education institutions is to train a physician with certain professional competencies [5–8].

The Federal State Educational Standard of Higher Education, which formulates a competency-based approach aimed at improving the quality of professional education, serves as the main document regulating the organization of the education in General Medicine (code 31.05.01) [6, 9]. According to this document a gradual development of competences occurs at all stages of education, and the section «Requirements for the results of mastering the curriculum» contains a list of competences. There are 8 core cultural, 11 core professional and 22 professional competences (PC) [9].

The PC-11, which is «Readiness to participate in the emergency medical care in conditions requiring urgent medical intervention» deserves special attention and is developed after studying many

disciplines, included in the curriculum of the student's training. Each of the clinical disciplines explores aspects of specialized emergency medical care. However, all disciplines share the section «Care in cardiac arrest», because this condition can complicate any disease. In this regard, a special emphasis should be made on the development of competence of providing emergency care in case of cardiac arrest. This competence has a direct connection with the labor function «Providing emergency or urgent medical care to the patient», which is regulated in the Professional Standard for Medical Specialists. The unified labor function specifies the labor activities, as well as details of the necessary knowledge and skills that a physician must possess in order to provide professional care to a patient with circulatory and respiratory arrest [10].

The study of the discipline «Anesthesiology, resuscitation, and intensive care» is the final stage of development of PC-11 «Readiness to participate in the emergency medical care for conditions requiring urgent medical intervention», as it includes a full list of activities of providing advanced medical care for life-threatening conditions. However, within the framework of the discipline a need exists for in-depth training of students to provide emergency care specifically in cardiac arrest within PC-11, which, in our opinion, confirms the necessity of developing appropriate additional professional competence «Emergency care in cardiac arrest».

Aim of the study: to elaborate an additional professional competence «Emergency care in cardiac arrest» and to test a set of tools promoting its development among the graduating students of General Medicine (code 31.05.01).

Material and Methods

The study was conducted in two stages.

Stage I. Within the framework of PC-11 «Readiness to participate in the provision of emergency medical care in conditions requiring urgent medical intervention», an additional professional competence «Providing emergency care in cardiac arrest» was elaborated, and the level of its development was assessed.

Stage II. The research was carried out at the medical institute of the Immanuel Kant Baltic Federal University during the study of the «Anesthesiology, resuscitation, and intensive care» subject included into the Block 1 Core Disciplines (modules) of the General Medicine curriculum (code 31.05.01). The curriculum was based on the Federal state educational standard of higher education in General Medicine (specialist level, code 31.05.01), approved by the Ministry of Education and Science of the Russian Federation, order No. 95 dated February 9, 2016, and the syllabus approved by the Academic Council of Immanuel Kant Baltic Federal University.

The study involved 140 6th-year (graduating) students of the medical institute specializing in General Medicine (code 31.05.01). The students were divided into two groups. The study group included 80 participants with the average age of 25±1.5 years, who studied the subject in 2021. The control group included 60 physicians with the average age of 25.9±1.6 years who were trained in 2019. Their data were analyzed retrospectively.

The conditions of education were identical for both groups. Seminar classes were held in line with the schedule in the classrooms of the medical institute, practical training and simulation course took place in the simulation center. The duration of the «Anesthesiology, resuscitation, intensive care» rotation, which aims at developing the competence of emergency care in cardiac arrest, was identical in the study groups. The curriculum comprised two mandatory courses, theoretical and simulation. Figure 1 shows the set of tools used to develop competencies in the groups.

The academic course differed between the groups. In the control group, it included lectures, student's recitation, preparing a topical essay, and group discussion. In the study group, it was supplemented by novel pedagogical technologies such as mind maps, «abstract-Interview» method, and thematic animation. The criteria for assessing the level of theoretical knowledge are shown in Table 1.

Simulation training in the control group comprised two blocks including basic cardiopulmonary resuscitation/automatic external defibrillation and advanced CPR. In the study group role-play was added to the above-mentioned blocks. The clinical situation «Circulatory arrest due to cardiac causes» was used as the basic training model. Training and assessment of practical skill in the simulation training on basic cardiopulmonary resuscitation was conducted on a manikin with computer software allowing real-time training in chest compressions and ventilations.

The first session included baseline assessment of basic knowledge in the fundamental and clinical disciplines. The results of assessment are shown in Fig. 2. We found that the trainees of both groups had the same level of theoretical knowledge acquired during the training. No significant differences between the groups were found ($P>0.05$).

Most students in both groups had an advanced or basic level of knowledge, whereas 15% of students had a threshold level. The obtained results allow us to consider the groups equivalent in the experiment.

Statistical analysis of the results. Statistical analysis was performed using Statistica 10.0 software package (StatSoft Inc., USA). The groups were compared using χ^2 criterion or Fisher's exact test. Statistical results were presented as percentages. Differences were considered significant at $P\leqslant 0.05$.

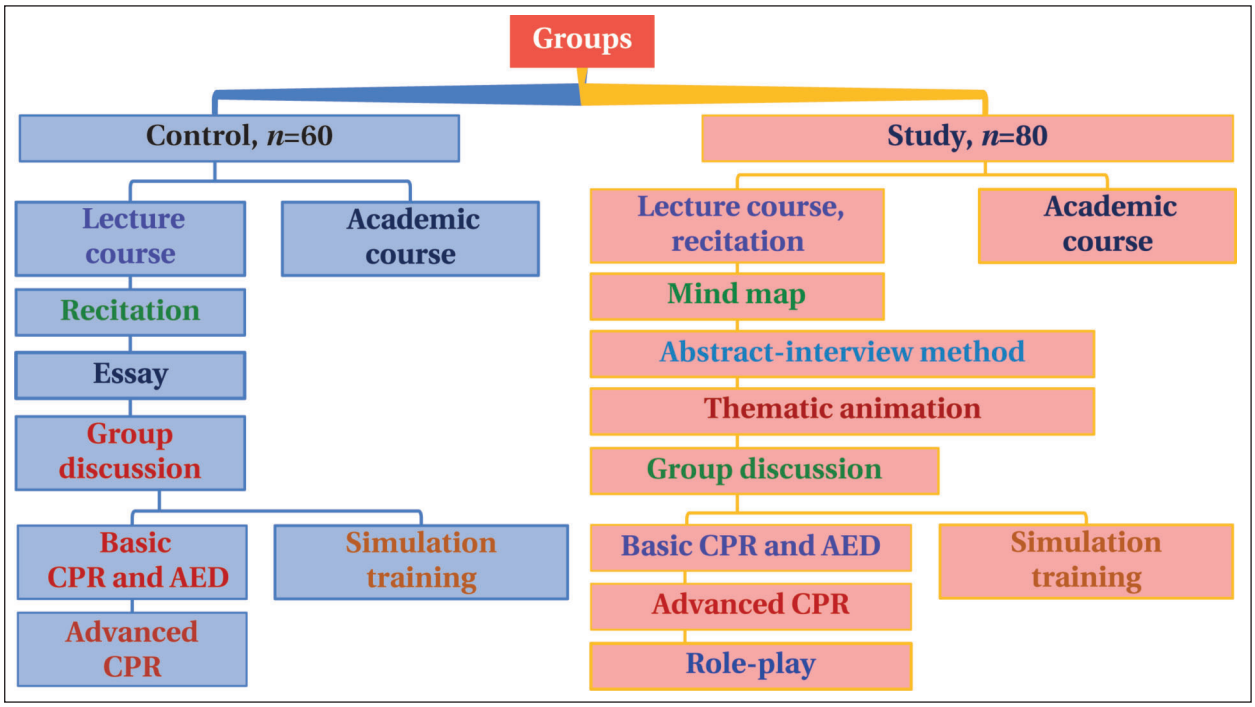

Fig. 1. Groups and set of tools used to develop competencies.

Table 1. Assessment of the level of basic and novel theoretical knowledge (adapted from the curriculum of the «Anesthesiology, resuscitation, intensive care» discipline).

Criteria	Assessment scale, points
The answer is logical, the student shows knowledge of professional terms, concepts, categories, and theories. He/she argues extensively and gives convincing examples. Demonstrates analytical approach in covering various concepts. Draws meaningful conclusions. Demonstrates confident knowledge of regulatory legal acts and special literature. Speech is competent and professional vocabulary is used.	Advanced level — 5
The answer presents various approaches to the problem, but their rationale is not complete enough. The conclusions are correct. Arguments and examples of law enforcement practice, but there is inconsistency in the analysis. Demonstrates knowledge of regulatory legal acts and special literature. Speech is competent, predominantly professional vocabulary is used.	Basic level — 4
The answer is not logically structured enough. The student reveals poor disclosure of professional concepts. The points made are declared, but not supported by evidence. The answer is mostly theoretical, no examples are given. There is only a general idea about regulatory legal acts. Knowledge of special literature is missing. Professional vocabulary is used sporadically.	Threshold level — 3

Results and Discussion

Development of the model of competence development in emergency care in cardiac arrest. For successful development of the competence of providing emergency care in cardiac arrest, we developed a model, which provides a detailed elaboration of all supposed stages of training medical students (Fig. 3.).

The elaborated model of developing competence in emergency care of cardiac arrest makes it possible to move the project forward as quickly and successfully as possible. Detailed elaboration allows to exclude ineffective methods and to choose technologies with high efficiency of training.

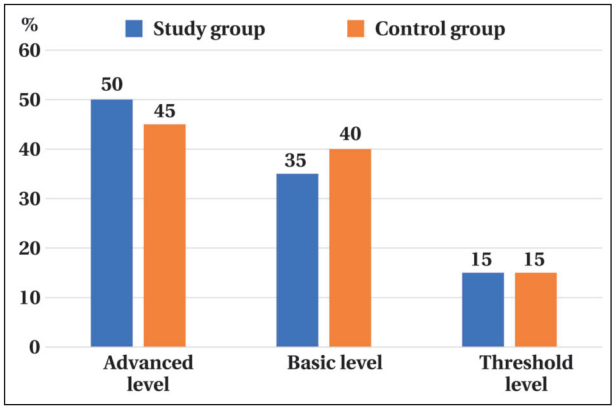

Fig. 2. The results of baseline assessment.

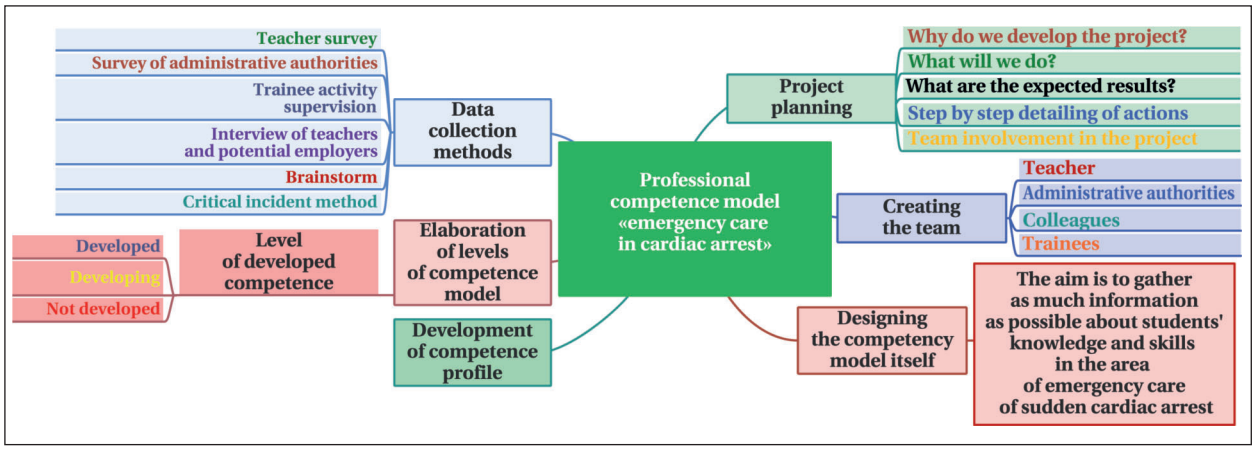

Fig. 3. Model of developing the competence of emergency care in cardiac arrest.

Sources of information at the planning stage are Federal State Educational Standard of Higher Professional Education for General Medicine, survey of fellow teachers, administrative staff, employers, who may have participated in this type of training, have experience in teaching and have an opinion on the project being developed. Interviewing the trainees themselves is quite important for obtaining their opinion on the level of their own training and the experience of previous students.

The critical incidents method makes it possible to anticipate unusual psychological and physical reactions, in response to a certain «critical situation», which cardiac arrest is. Conducting a structured interview enables the instructor to identify trainees who have already had positive or negative experiences with CPR in real-life situations. Any information obtained by the instructor during the training phase can contribute to the success of the project.

The participants of the model of developing additional professional competence are the students and the instructor. The main condition for achieving the set goal is the student's active attitude towards the education. The student acts as a consumer of knowledge, abilities and skills required to develop the competence, he/she is a conscious participant of learning. An instructor organizes and coordinates the educational process, serves as a source of information, technical and other resources. The set goal is achieved by creating certain pedagogical conditions, which are implemented in this model.

The model of competence development consists of three blocks.

1. The goal-oriented block is necessary to develop a bank of learning materials and manuals for the discipline of Anesthesiology, Resuscitation, and Intensive Care which include mind maps, the «Abstract-Interview» methodology, thematic animation, set of clinical cases for simulation training, preparing dummies and highly realistic robots to work, as well as development of assessment tools.

2. Activity block includes practical classes in «Anesthesiology, resuscitation, intensive care» with the use of mind maps, «abstract-interview», thematic animation, set of clinical cases for simulation training.

3. Reflexive block includes assessment of the level of competence development, stratified structure of additional professional competence «Emergency care of cardiac arrest» and levels of its development.

Thus, the additional professional competence «Emergency care of cardiac arrest» and its stratified structure have been produced (Fig. 4).

In the starting stratum a specific property of an individual, his/her capabilities for purposeful professional activity, were determined. In the second stratum the two most important aspects of competence development were pointed out, i. e., ability and readiness to carry out professional activity. Two components were distinguished in the «Ability» stratum: cognitive («I know», knowledge) and functional («I know how», skill). In the «Readiness» stratum two components were also distinguished: motivational («I want», willingness) and personal («I can», capability) [1]. Specific elements were developed for each component stratum. Based on the designed elements, which the student learns in the process of training, the development of the necessary competence occurred.

The proposed structure of the competence of medical students for emergency care in cardiac arrest corresponded to the content requirements of the Federal State Educational Standards of Higher Education and the list of labor functions of a medical specialist, as defined by the professional standard «General medicine».

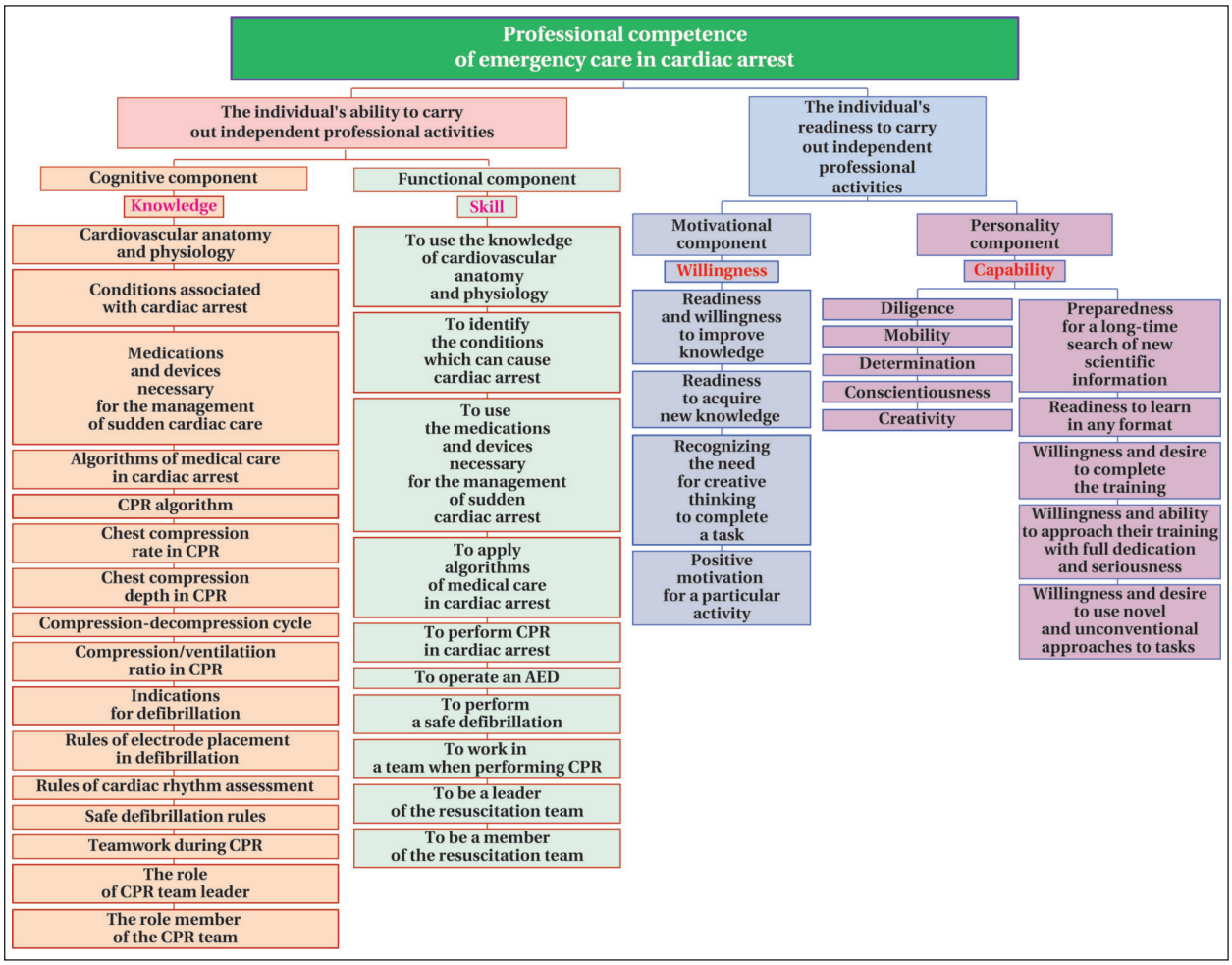

Fig. 4. Stratified structure of professional competence «Emergency care in cardiac arrest».

Assessment of competence completion was the final stage and took place at the end of mastering the discipline, when all theoretical aspects were studied, the simulation course on cardiopulmonary resuscitation and automatic external defibrillation was completed, game training with practicing the role of the leader of the resuscitation team was conducted. All stages of mastering theoretical knowledge and practical skills were taken into account.

Three levels were determined to assess the development of competence.

Threshold level was minimally sufficient to carry out professional activities.

Basic level implied fully developed components of professional competence, allowing both independent performance of certain activities and interdisciplinary interaction, and readiness to actively expand one's labor functions.

Advanced level comprised confident possession of all components of professional competence, allowing to actively use in practice both standard and innovative methods (see Table 2).

Assessment of academic knowledge of the new topics. Assessment of the level of mastering the new academic knowledge necessary to develop a competence is demonstrated in Fig. 5. In the study group, 80% of students had an advanced and

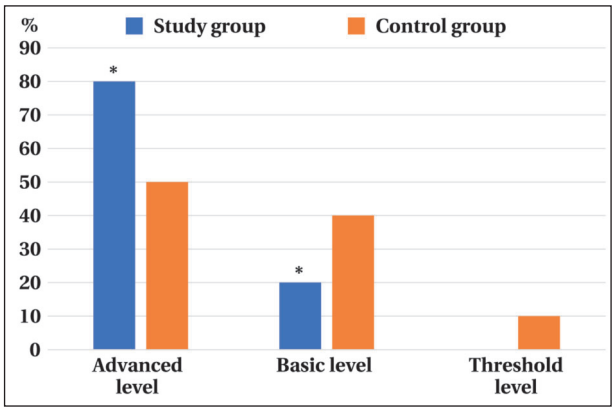

Fig. 5. Results of the current assessment of theoretical knowledge on the new subjects.
Note. * — $P<0.05$ — significant differences between the groups.

Table 2. Levels of development of professional competence «Emergency care in cardiac arrest».

Criteria	Assessment scale, points
The answer is logical, the student shows knowledge of professional terms, concepts, categories, and theories. He/she argues extensively and gives convincing examples. Demonstrates analytical approach in covering various concepts. Draws meaningful conclusions. Demonstrates confident knowledge of fundamental and related clinical disciplines. Speech is competent and professional vocabulary is used. Demonstrates an algorithm of care of sudden cardiac arrest during the cardiopulmonary resuscitation simulation. Confidently plays the role of «Leader» of the resuscitation team. Knows the roles of team members and creates effective communication to achieve the global goal of providing expert medical care in sudden cardiac arrest. Consistently manages patient care, prioritizes, encourages and supports the team.	Advanced — 5
The answer contains various approaches to the problem, but their rationale is not complete enough. The conclusions are correct. Arguments are supported by examples of law enforcement practice, but analysis is inconsistent. Demonstrates knowledge of basic and related clinical disciplines. Speech is competent, using predominantly professional vocabulary. Demonstrates the algorithm of care in sudden cardiac arrest during the cardiopulmonary resuscitation simulation. Confidently plays the role of «Leader» of the resuscitation team. Knows the roles of team members and creates effective communication to achieve the global goal of providing expert medical care of sudden cardiac arrest. Consistently manages patient care, prioritizes, encourages and supports the team.	Basic — 4
The answer is not logically structured enough. The student demonstrates uncertainty in the disclosure of professional concepts. The points made are declared, but not argued. The answer is mostly theoretical, no examples are given. Has basic knowledge of fundamental and related clinical disciplines. Knowledge of special literature is missing. Professional vocabulary is used sporadically. During CPR simulation, demonstrates the algorithm of care in sudden cardiac arrest. Is unsure of the role of the «Leader» of the CPR team. Does not fully know the roles of team members, partially creates effective communication to achieve the global goal of providing expert medical care in sudden cardiac arrest. Consistently manages patient care, fails to prioritize, does not always encourage and support team.	Threshold — 3

20% had a basic level of mastering the new material ($P<0.05$ vs the control group), which favored the development of the necessary competence.

Assessment of practical skills development. After completing the academic course, the classes continued in the simulation center, where during the simulation course on basic CPR and AED the students consistently mastered the necessary practical skills and developed the additional professional competence of emergency care in cardiac arrest. During the simulation the student will demonstrate his or her knowledge of the algorithm of care in sudden cardiac arrest, perform quality chest compressions and ventilations, and operate the automatic external defibrillator.

Objective assessment of the studied parameters with the help of dummy computer software is an important component. It accurately determines the hand position, each cycle of compressions and decompressions, calculates the frequency and depth of compressions, i. e., shows an objective view of what is happening. The instructor sees all data online. An exam card is created for each trainee, where all the parameters of the trainee and total score are automatically displayed (Fig. 6). After completing an assignment, the instructor individually reviews the trainee's score. They discuss the reasons for possible failures and develop an individual learning plan. This method of reading the results increases the motivation to learn, because it eliminates any bias in the assessment.

The list of skills and results of training in basic cardiopulmonary resuscitation and automatic external defibrillation are shown in Table 3.

During training all students in the study group developed the necessary skills. In the control group, the skill of correctly positioning the hands to perform chest compressions, performing compressions and breathing in a 30:2 ratio was fully developed. The remaining practical skills were fully developed in 90% of the trainees in this group and were in the process of developing in 10% of the trainees. All identified differences were significant ($P<0.05$). The skill of safe handling of automatic external defibrillator was developed in 100% of students in the study group and in 80% in the control group ($P<0.05$).

Thus, the study results showed significant differences in the degree of development of cardiopulmonary resuscitation skills between the groups. The students in the study group with good academic background showed high results of ac-

Fig. 6. An exam card of a trainee in simulation training on basic cardiopulmonary resuscitation.

Table 3. Assessment of practical skills in cardiopulmonary resuscitation.

Skills	Frequency of developed skills				*P*-value
	1 Developed		2 Not fully developed		
	Study, *n*=80	Control, *n*=60	Study, *n*=80	Control, *n*=60	
Cardiopulmonary Resuscitation Algorithm					
Knowledge of cardiopulmonary resuscitation algorithm	80 (100%)*	54 (90%)	0 (0%)*	6 (10%)	0.004
Safety assessment	80 (100%)*	54 (90%)	0 (0%)*	6 (10%)	0.004
Assessment of consciousness	80 (100%)*	54 (90%)	0 (0%)*	6 (10%)	0.004
Airway patency and assessment of normal breathing	64 (80%)	54 (90%)	16 (20%*)	6 (10%)	0.108
Correct hand positioning	80 (100%)	60 (100%)	0 (0%)	0 (0%)	1.0
Compression depth 5–6 cm	80 (100%)*	54 (90%)	0 (0%)*	6 (10%)	0.004
Compression rate 100–120 per minute	80 (100%)*	54 (90%)	0 (0%)*	6 (10%)	0.004
Equal compression–decompression	80 (100%)*	54 (90%)	0 (0%)*	6 (10%)	0.004
Performing 2 ventilations	80 (100%)*	54 (90%)	0 (0%)*	6 (10%)	0.004
Compression/ventilation ratio 30:2	80 (100%)	60 (100%)	0 (0%)	0 (0%)	1.0
Handling of automatic external defibrillator					
Safety when analyzing rhythm	80 (100%)*	48 (80%)	0 (0%)*	12 (20%)	<0.001
Safety during defibrillation	80 (100%)*	48 (80%)	0 (0%)*	12 (20%)	<0.001

Note. * — $P<0,05$ — significant differences between the groups.

quiring the skill of qualified medical care in sudden cardiac arrest.

Assessment of development of additional professional competence in emergency care of cardiac arrest. The final stage of the research was the assessment of the level of development of additional professional competence of emergency care in cardiac arrest. The summarized assessment of theory section and practical skills for the development of the necessary competence was performed. We found that the levels of development of additional professional competence differed between the groups (Fig. 7).

In the control group, the threshold level prevailed, 60% of students in this group had minimally sufficient knowledge and skills to perform inde-

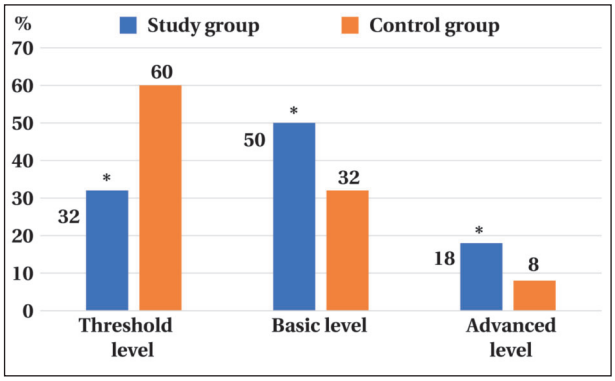

Fig. 7. Results of the development of additional professional competence.
Note. * — $P<0.05$ — significant differences between the groups.

pendent work activities in cardiac arrest. In the study group the threshold level was achieved in 32% of students ($P<0.05$). The basic level was observed in 32% of students in the control group and 50% in the study group ($P<0.05$), which confirms the confident mastery of all elements of the competence not only to carry out purposeful activity, but also to develop new types of labor functions and interdisciplinary interaction. The advanced level, confirming the creative mastery of all elements of the competence, was achieved by 18% of students in the study group and 8% in the control group ($P<0.05$).

Development of additional competence of emergency care of cardiac arrest and training of students on its basis have shown positive results. The level of development of cardiopulmonary resuscitation skill, team organization and mastery of the leadership role determine the physician's readiness for his/her professional activity. A specialist with the basic and advanced levels of competence is competent not only for independent work, but also for interprofessional communication [12–14], as well as in management of the resuscitation team. This person has a global perspective of treatment for a patient with cardiac arrest, and is able to diagnose and manage it using state-of-the-art techniques.

Making changes in the training curriculum, the use of new pedagogical technologies allowed to improve the results of training in the study group. After conducting a retrospective analysis of the training of the control group, we decided to develop a competence of emergency care in cardiac arrest, and to introduce new pedagogical technologies in the curriculum of the «Anesthesiology, resuscitation, intensive care» discipline, both in the academic section and in simulation training. The study group studied in an upgraded «Anesthesiology, resuscitation, intensive care» rotation.

Conclusion

This study supports the necessity of developing additional professional competence of emergency care in cardiac arrest within the framework of PC-11 «Readiness to participate in the emergency medical care in conditions requiring urgent medical intervention». We have successfully implemented and validated in practice the system of developing additional professional competence using new pedagogical tools, including those based on modern information and communication technologies.

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