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Профессору Валерию Николаевичу ЛУКАЧУ — 80 лет

Валерий Николаевич Лукач родился 25 октября 1942 г. в Щербакульском районе Омской области. После окончания в 1968 г. Омского государственного медицинского института им. М. И. Калинина он начал свою трудовую деятельность в качестве анестезиолога-реаниматолога в ГКБ № 2 г. Перми. Через 8 лет защитил кандидатскую диссертацию на тему «Интенсивная терапия массивных кровопотерь». С 1982 г. и по настоящее время Валерий Николаевич — преподаватель, ассистент, доцент, профессор Омского медицинского института, медицинской академии и медицинского университета. В 2001 г. он успешно защитил докторскую диссертацию на тему «Интенсивная терапия септических осложнений в акушерстве-гинекологии и хирургии». С этого же года Валерий Николаевич возглавил, и возглавлял до 2012 г., созданную им кафедру анестезиологии, реаниматологии и скорой медицинской помощи.

Работая внештатным главным анестезиологом-реаниматологом г. Омска с 1985 по 2010 гг., В. Н. Лукач проявил незаурядный талант организатора и клинициста, принимал активное участие в работе Федерации анестезиологов-реаниматологов России, многократно был участником всемирных конгрессов анестезиологов-реаниматологов в Европе, Африке, Австралии. Как признание медицинских заслуг профессора и врача Лукача В. Н. в области анестезиологии-реаниматологии город Омск неоднократно становился центром проведения важных мероприятий анестезиологов-реаниматологов Российского и международного значения. В 1997 г. Валерий Николаевич был организатором Российского Пленума правления Федерации анестезиологов-реаниматологов России, а в 2002 г. — VIII съезд анестезиологов-реаниматологов России, на котором профессор В. Н. Лукач был избран, и в дальнейшем неоднократно переизбирался, вице-президентом Федерации анестезиологов и реаниматологов России. В 2009 г. в г. Омске, также при его непосредственном участии, была организована Всероссийская Международная конференция и Пленум правления Федерации анестезиологов-реаниматологов России, что позволило внедрить в практику работы врачей анестезиологов-реаниматологов не только Омской области, но и многих регионов нашей страны, последние достижения этого важного раздела медицины.

Под руководством профессора В. Н. Лукача успешно защищены 3 диссертации на соискание ученой степени доктора и 11 — на соискание ученой степени кандидата медицинских наук. Валерий Николаевич является автором и соавтором 190 публикаций, нескольких монографий и учебных пособий по оказанию помощи при сепсисе, массивных кровопотерях, политравме, лечения болевого синдрома, которые стали руководством к действию не только во всех городских медицинских учреждениях, но и в районах Омской области и Сибирском регионе.

Профессор В. Н. Лукач уделяет огромное внимание и время подготовке молодых кадров. Ежегодно на кафедре проходят первичную подготовку более 30 ординаторов по специальностям «Анестезиология и реаниматология» и «Скорая медицинская помощь», не только для Омска и Омской области, но и других регионов страны. Ежегодно на кафедре повышают свою квалификацию более 300 врачей анестезиологов-реаниматологов и врачей скорой медицинской помощи, врачей различных специальностей, обучающихся в системе НМО. Ученики профессора Лукача работают в различных регионах России и возглавляют научные и врачебные коллективы в Москве, Екатеринбурге, Сургуте, Ханты-Мансийске, Нижнем Новгороде и в других городах.

Его многолетняя плодотворная врачебная, научная и организаторская деятельность в 2002 г. отмечена Почетной грамотой Министерства здравоохранения и социального развития РФ, в 2008 г. ему был вручен отраслевой нагрудной знак «Отличник здравоохранения». В 2012 г. за заслуги в охране здоровья населения, организации и оказании лечебно-профилактической помощи Валерию Николаевичу Лукачу присвоено почетное звание «Заслуженный работник высшей школы». Длительное время Валерий Николаевич входил в редакционный совет журналов «Общая реаниматология», «Анестезиология и реаниматология».

Дорогой Валерий Николаевич! Члены Правления ФАР, коллектив кафедры анестезиологии и реаниматологии ДПО ОмГМУ, ученики, коллеги, студенты и Ваши многочисленные друзья анестезиологи-реаниматологи, а также редакция журнала «Общая реаниматология» от всего сердца поздравляют Вас с юбилеем, желают Вам крепкого здоровья, творческого долголетия, талантливых учеников, удачи и успехов в профессиональной деятельности!

Научному руководителю Федерального научно-клинического центра реаниматологии и реабилитологии (ФНКЦ РР) профессору Виктору Васильевичу Морозу исполнилось 85 лет

14 октября 2022 г. исполнилось 85 лет Виктору Васильевичу Морозу — члену-корреспонденту РАН, заслуженному деятелю науки Российской Федерации, доктору медицинских наук, профессору, полковнику медицинской службы.

Виктор Васильевич Мороз родился 14 октября 1937 года в городе Ростове-на-Дону. В 1961 году окончил Военно-медицинскую академию им. С. М. Кирова, а в 1965 году — ординатуру при кафедре госпитальной хирургии Военно-медицинской академии им. С. М. Кирова. Говоря о научной деятельности, необходимо начать с первых исследований молодого ординатора, принявшего решение посвятить свой творческий поиск и энергию изучению механизмов формирования критических и терминальных состояний, поиску адекватных диагностики и лечения критических состояний.

В 1969 году он защитил кандидатскую диссертацию на тему «Объем циркулирующей крови и его компоненты при хирургических заболеваниях легких и их оперативном лечении». С 1967 по 1996 годы работал в Главном военном клиническом госпитале им. Н. Н. Бурденко, где прошел путь от старшего ординатора отделения анестезиологии до начальника отделения реаниматологии. В 1994 году он защитил докторскую диссертацию на тему «Пути коррекции гипоксии при критических состояниях».

В 1995 году Виктор Васильевич был избран профессором кафедры анестезиологии и реаниматологии Московской медицинской академии им. И. М. Сеченова. В 1996 году ему было присвоено звание профессора. В этом же году по предложению академика РАМН В. А. Неговского Виктор Васильевич избирается директором НИИ общей реаниматологии Российской академии медицинских наук, а в 2005 году — заведующим кафедрой Московского государственного медико-стоматологического университета.

Вся творческая жизнь Виктора Васильевича связана с анестезиологий-реаниматологией. Круг научных проблем, которые решает член-корреспондент РАН В. В. Мороз со своими многочисленными учениками, отличается широтой и глубиной научного поиска. Это касается фундаментальных и прикладных аспектов патогенеза, клиники, диагностики, лечения и профилактики критических, экстремальных и терминальных состояний, различных форм шока и гипоксии, сепсиса, эндотоксикоза и полиорганной недостаточности, использования перфторуглеродов для медико-биологических целей, патогенеза боевой травмы.

Виктор Васильевич разработал и внедрил в клиническую практику длительную внеорганную малопоточную оксигенацию, применив впервые в мире фторуглеродный оксигенатор, новый класс препаратов с газотранспортной функцией на основе перфторуглеродов. Профессор В. В. Мороз является одним из пионеров исследования роли генетической предрасположенности, роли биоритмов в течении различных критических состояний, исследований и внедрения в клиническую практику сорбционной детоксикации, плазмафереза, ультрафильтрации, методов лечения острой дыхательной недостаточности, алгоритмов инфузионно-трансфузионной терапии, парентерального и энтерального питания при критических и терминальных состояниях.

Под руководством и при непосредственном участии В. В. Мороза созданы фторуглеродные оксигенаторы, кровезаменитель с газотранспорт-

ной функцией на основе перфторуглеродов — «Перфторан», аппарат и устройство для гемосорбции. За фундаментальные исследования «Создание перфторуглеродных сред для управления жизнедеятельностью клеток, органов и организма» В. В. Морозу в составе авторского коллектива в 1999 году присуждена премия Правительства Российской Федерации, а в 2002 году он стал Лауреатом первой национальной премии лучшим врачам России «Призвание».

Неоценимый вклад профессор В. В. Мороз внес в исследования и разработку организационных и анестезиолого-реанимационных проблем военной медицины и медицины катастроф как непосредственный участник ликвидации последствий событий в Афганистане, Армении, Чечне, Чернобыле и других катастроф.

В сложные годы перестройки Институт реаниматологии удалось сохранить благодаря научному авторитету, организаторским способностям и бойцовским качествам Виктора Васильевича Мороза.

В. В. Морозом опубликовано более 900 научных работ, 12 томов трудов НИИ общей реаниматологии РАМН, 9 тематических сборников научных трудов.

Виктор Васильевич Мороз — председатель Диссертационного совета ФНКЦ РР, принимающего к защите диссертации по специальностям «Анестезиология и реаниматология» и «Патологическая физиология». Под руководством и при консультации В. В. Мороза выполнено 19 докторских и 44 кандидатских диссертаций.

В 2000 году В. В. Мороз был избран членом-корреспондентом РАМН, членом бюро Отделения медико-биологических наук РАН. Он также является академиком и членом Президиума Академии медико-технических наук России с 1999 года. В течение многих лет В. В. Мороз работал в президиуме Всесоюзного, Всероссийского обществ анестезиологов и реаниматологов России, членом правления Московского научного общества анестезиологов и реаниматологов (МНОАР), являясь сегодня Почетным членом всех этих обществ. В 1987 году на альтернативной основе МНОАР избрало его первым председателем МНОАР. На этом посту он проработал более 10 лет.

В 2014 году профессор В. В. Мороз выступил инициатором и организатором создания российского Общества по изучению шока, ставшего частью Международной федерации обществ по изучению шока. В. В. Мороз был избран и по настоящее время остается Президентом российского Общества по изучению шока.

Виктор Васильевич является одним из основателей и главным редактором рецензируемого научно-практического журнала «Общая реаниматология», который входит с 2005 года, включен в перечень ВАК при Минобрнауки России и индексируется в отечественных и международных базах данных, таких как РИНЦ, RSCI, Scopus, DOAJ и многих других. В. В. Мороз — член редакционного совета журналов «Неотложная медицинская помощь», «Журнал им. Н. В. Склифосовского» и «Политравма», член редколлегии журналов «Анестезиология и реаниматология» и редсовета «Вестник интенсивной терапии им. А. И. Салтанова», журнала «Journal of Critical Care». В настоящее время является президентом Национального Совета по реанимации, почетным членом Президиума Европейского Совета по реанимации, почетным членом словацкого научного медицинского общества анестезиологов.

Награжден 14 медалями, знаком «Отличник здравоохранения». В 1999 году В. В. Морозу присвоено звание «Заслуженный врач Российской Федерации», в 2008 году — «Заслуженный деятель науки Российской Федерации». Распоряжением Правительства Российской Федерации от 25 февраля 2011 года Виктору Васильевичу Морозу вместе с группой исследователей присуждена премия Правительства Российской Федерации в области науки и техники «За повышение эффективности диагностики и лечения острого респираторного дистресс-синдрома на основе разработки и внедрение новейших медицинских технологий». В 2020 году В. В. Мороз награжден Орденом Почета за большой вклад в развитие науки и многолетнюю плодотворную деятельность.

Виктор Васильевич — человек широчайшей эрудиции. С ним интересно работать, дискутировать, обсуждать научные проблемы. Он сразу же и охотно включается в разговор, старается понять проблему до конца.

В настоящее время Виктор Васильевич Мороз является научным руководителем Федерального научно-клинического центра реаниматологии и реабилитологии (ФНКЦ РР). В этой должности он продолжает успешно руководить несколькими направлениями российских научных исследований в области реаниматологии.

Глубокоуважаемый Виктор Васильевич! Коллектив ФНКЦ РР и редакция журнала «Общая реаниматология» поздравляют Вас с юбилеем и желают крепкого здоровья, долгих плодотворных лет жизни.

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Регионарная церебральная оксигенация у пациентов с тяжелым течением COVID-19

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Summary

The aim of the study was to assess regional cerebral oxygenation ($rScO_2$) in patients with acute respiratory distress syndrome (ARDS) associated with COVID-19.

Material and methods. The cross-sectional study was conducted. Twenty-eight patients with severe COVID-19 who were admitted in the intensive care unit were enrolled. Regional cerebral oxygenation was assessed using near-infrared spectroscopy, laboratory markers of cerebral damage, clinical and laboratory characteristics.

Results. Median age of patients was 65 years, of whom 50% were men. Three (11%) patients had severe ARDS, 8 (29%) patients had moderate ARDS, and 17 (60%) patients had mild ARDS. Mechanical ventilation was performed in 20 (71%) patients, vasopressors were used in 14 (50%) patients. The median levels of cerebral saturation were normal and did not differ between the left ($rScO_{2l}$) and right ($rScO_{2r}$) hemispheres (68 (58–75) and 69 (59–76), respectively). The level of S-100 protein was increased (0.133 (0.061–0.318) μg/l) in contrast to the normal level of neuron-specific enolase (12.5 (8.0–16.5) μg/l). A correlation was found only between $rScO_2$ and hemoglobin level (rho=0.437, P=0.02) and between $rScO_2$ and lymphocyte count (rho=–0.449, P=0.016). An increase in S-100 negatively correlated with a decrease in Glasgow Coma Scale score (rho=–0.478, P=0.028).

Conclusion. Near-infrared spectroscopy did not reveal a decrease in $rScO_2$ among patients with ARDS associated with COVID-19. The S-100 protein is a useful marker for the assessment of impaired consciousness. Further study of the causes of cerebral dysfunction in patients with severe COVID-19 and methods for its early identification is warranted.

Keywords: cerebral oxygenation; neurological dysfunction; COVID-19; S-100 protein

Conflict of interest. Authors declare no conflict of interest.

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Introduction

The outbreak of the novel coronavirus infection (COVID-19) has swept over 140 countries in a short period of time and has become a global public health problem [1]. In addition to the high incidence of acute respiratory distress syndrome (ARDS) [2]

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and cardiovascular complications [3], neurological complications [4] have been considered common in patients with COVID-19, making their early rehabilitation very difficult.

Underlying diseases of the central nervous system, multiple organ failure, use of sedatives and muscle relaxants make early diagnosis of COVID-19-related brain dysfunction difficult [5]. We suggested that screening of regional cerebral oxygenation ($rScO_2$) using near-infrared spectroscopy in patients with severe COVID-19 would not only allow noninvasive assessment of cerebral perfusion in ARDS, but also reveal its relationship with prognostic markers of disease severity.

The aim of the study was to assess the regional cerebral oxygenation ($rScO_2$) in patients with acute respiratory distress syndrome (ARDS) associated with COVID-19.

Material and Methods

A cross-sectional study assessed the $rScO_2$ values of 28 randomly selected patients with severe COVID-19 who were hospitalized in the intensive care unit within one day. There were no exclusion criteria. Diagnosis of COVID-19, evaluation of disease severity, and treatment, including respiratory therapy for acute respiratory failure, were performed according to the temporary guidelines of the Ministry of Health of the Russian Federation on prevention, diagnosis and treatment of the novel coronavirus infection (COVID-19) [6]. Mechanical ventilation was performed using Hamilton G5 and Hamilton C2 (Hamilton Medical, Switzerland) devices. Bilateral $rScO_2$ monitoring was performed using INVOS® 5100C cerebral oxymeter (Somanetics, Troy, Michigan, USA) until stable cerebral oscillation values (difference between values less than 10%) were achieved within 30 min. During $rScO_2$ measurement, mean arterial pressure (MAP), gas exchange indices (SpO_2, PaO_2, PaO_2/FiO_2, $PaCO_2$) and blood count (hemoglobin (Hb), lymphocytes (LYM)) were taken in all patients, as well as the levels of inflammatory markers (procalcitonin (PCT), C-reactive protein (CRP), interleukin-6 (IL-6), D-dimer, and markers of neuronal damage (protein S-100 (S-100), neuron-specific enolase (NSE)). Patients who did not receive sedatives and muscle relaxants were additionally divided into subgroups with impaired consciousness (n=7) and with clear consciousness (n=14). The Richmond Agitation-Sedation Scale was used to assess the depth of hypnosis in patients who were ventilated. The Glasgow Coma Scale (GCS) was used in patients with impaired consciousness.

Quantitative data were presented as medians (*Me*) and quartiles (25%; 75%), categorical data as absolute numbers (n) and proportion (%). Mann–Whitney test was used to evaluate significance of differences in quantitative variables between subgroups. Spearman's correlation coefficient (ρ) was used to identify correlations. The missing data percentage did not exceed 10% for each parameter. When testing statistical hypotheses, differences were considered significant at P<0.05. The data were analyzed using the SPSS 28.0.0.0 software package (IBM SPSS Statistics, Chicago, IL, USA).

Results

The median age of the patients was 65 years, half of them were male. Twenty (71%) patients were ventilated for 12 to 72 hours during $rScO_2$ measurement, with 50% of all patients sedated with dexmedetomidine until a target sedation level of –5 to 0 on the Richmond Excitation-Sedation Scale was achieved, depending on the clinical situation. After discontinuation of sedation, 7 (33%) patients were observed to have impaired consciousness (7 to 14 points on the Richmond Arousal-Sedation Scale). Neuroimaging (computed tomography or magnetic resonance imaging) revealed brain damage in only one of these patients, while in the remaining patients the changes were limited to the enlargement of the CSF spaces. In 7 patients, a reliable assessment of wakefulness level was impossible due to muscle relaxation and deep sedation. 50% of all patients received vasopressor support (norepinephrine) during $rScO_2$ measurement to maintain MAP ⩾60 mm Hg. Due to severe respiratory failure, 6 (21%) patients were in a prone position (Table 1).

Cerebral saturation values of the left ($rScO_{2l}$) and right ($rScO_{2r}$) hemispheres did not differ and averaged 68% and 69%, respectively, P=0.819. The $rScO_2$ values were generally normal (there were no episodes of $rScO_2$ falling below 45%), despite the fact that in 8 (29%) patients the PaO_2/FiO_2 ratio corresponded to moderate ARDS (according to the Berlin criteria for ARDS [7]), and in 3 (11%) patients, to severe. In subgroup comparisons, $rScO_{2l}$ (P=0.488) and $rScO_{2r}$ (P=0.322) scores did not differ between patients in full and impaired consciousness.

In the general patient cohort, we found a moderate increase in protein S-100 levels with normal NSE ones. When comparing subgroups, S-100 protein levels were higher in patients with impaired consciousness than in patients in full consciousness (0.154 (0.122–0.424) vs 0.095 (0.044–0.128), P=0.025, respectively), NSE level did not differ between subgroups (14.1 (9.9–42.2) vs 11.2 (6.0–15.4), P=0.11, respectively).

We found weak correlations of $rScO_2$ values: a direct one with hemoglobin level (rho=0.437, P=0.02) and an inverse one with lymphocyte count (rho=–0.449, P=0.016). S-100 level was negatively correlated with the GCS score (rho=–0.478, P=0.028), and NSE level had a significant positive moderate correlation with

General patient characteristics, *n*=28.

Parameter	Values
Age, years	65 (57–75)
Males, *n* (%)	14/28 (50%)
Mechanical ventilation	20/28 (71%)
On vasopressors	14/28 (50%)
Sedated	14/28 (50%)
Prone position	6/28 (21%)
GCS, points	15 (13–15)
Impaired consciousness	7/21 (33%)
MAP, mm Hg	88 (82–95)
SpO_2, %	96 (94–99)
PaO_2, mm Hg	90.8 (70.9–113)
$PaCO_2$, mm Hg	40.9 (35.7–46.2)
PaO_2/FiO_2	218 (155–269)
Hb, g/L	119 (91–136)
LYM, $\times 10^3/\mu L$	1.02 (0.66–1.46)
PCT, ng/mL	0.87 (0.32–2.10)
CRP, mg/mL	137 (53–209)
IL-6, pg/mL	111 (40–625)
D-dimer, μg/mL	1.46 (0.93–2.71)
S-100 protein, μg/mL	0.133 (0.061–0.318)
NSE, μg/mL	12.5 (8.0–16.5)
$rScO_{2l}$, %	68 (58–75)
$rScO_{2r}$, %	69 (59–76)

Note. GCS — Glasgow Coma Scale; MAP — mean arterial pressure; SpO_2 — arterial blood oxygen saturation according to pulse oximetry; PaO_2 — arterial blood oxygen pressure; $PaCO_2$ — arterial blood carbon dioxide pressure; FiO_2 — oxygen fraction in inhaled gas mixture; Hb — hemoglobin level; LYM — absolute number of lymphocytes; CRP — C-reactive protein; IL-6 — interleukin-6; NSE — neuron-specific enolase; $rScO_{2l}$ — regional cerebral oxygenation of the left cerebral hemisphere; $rScO_{2r}$ — regional cerebral oxygenation of the right cerebral hemisphere.

IL-6 level (rho=0.546, *P*=0.035). No relationship of $rScO_2$ with the severity of ARDS, frequency of vasopressor support and sedation was found.

Discussion

Currently, the putative mechanisms of neurological dysfunction in COVID-19 include hypercoagulation, vascular damage, hypoxia, immune dysregulation, electrolyte disturbances, and direct viral brain damage [8-11] and have been brought into focus. Laboratory markers of neurological dysfunction, such as lymphocytopenia, elevated concentrations of D-dimer, IL-6 and procalcitonin, also predict disease severity and adverse outcome [12–14], which may indicate the multifactorial nature of CNS damage in the context of COVID. The lack of correlation of $rScO_2$ with the levels of these laboratory markers in our study did not allow us to pinpoint the specific cause of cerebral dysfunction in COVID-19. The wide range of neuroimaging changes in the brain in severe disease and low detection rate of SARS-CoV-2 coronavirus in cerebrospinal fluid [11, 15, 16] make direct viral damage to the brain less likely to be the leading pathogenetic mechanism. Focusing on endothelial changes and consequences of abnormal immune response could help explain the mechanisms of CNS dysfunction in COVID-19.

The small sample size (which was not predetermined) and the lack of correlation of clinical results with the histological findings are the main limitations of our study. In addition, an assessment of changes in cerebral oxygenation and laboratory parameters at different stages of the disease is necessary.

Conclusion

Cerebral oxygenation parameters in patients with severe COVID-19 remained within the reference range despite hypoxemia. Increased S-100 in patients with severe COVID-19 has more diagnostic value than NSE and correlates with the depth of hypnosis. Cerebral dysfunction in COVID-19 is likely to be multifactorial and depends on the severity of cerebral damage requiring further scrutiny and investigation.

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Hemoadsorption in Patients with Various Types of Respiratory Support for Severe COVID-19

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Гемосорбция у пациентов с различными видами респираторной поддержки при тяжелом течении COVID-19

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Summary

Study aim. To evaluate the efficacy of hemoadsorption in patients with severe COVID-19 on mechanical lung ventilation (MLV) and noninvasive respiratory support.

Material and methods. We retrospectively analysed longitudinal clinical and laboratory parameters of 49 patients with severe coronavirus infection who were treated in the First Intensive care unit of Grodno University Hospital from September 2020 to November 2021 and underwent hemoadsorption using the Hemo-Proteasosorb sorbent. All patients were divided into two groups: Hemo-Proteasosorb + MLV (22 patients who underwent hemoadsorption while being on MLV) and Hemo-Proteasosorb without MLV (27 patients who had hemoadsorption while receiving the low- and high-flow oxygen therapy or noninvasive lung ventilation).

Results. In the Hemo-Proteasosorb + MLV group a decrease in procalcitonin (PCT) (from 0.27 [0.12–2.08] down to 0.14 [0.05–1.77], *P*=0.027), C-reactive protein (CRP) (from 135.4 [10.6–303.0] down to 64.3 [1.2–147.0], *P*=0.003), fibrinogen (from 11.7 [4.9–19.49] to 8.2 [3.7–14.7], *P*=0.00004), and D-dimer (from 1432.0 [443.0–6390.0] to 1087.0 [415.0–3247.0], *P*=0.006) was seen on day 3 after the hemoadsorption session. The Hemo-Proteasosorb without MLV group also demonstrated a reduction in the levels of CRP (from 4 [10.6–303.0] to 64.3 [1.2–147.0], *P*=0.003), fibrinogen (from 11.7 [4.9–19.49] to 8.2 [3.7–14.7], *P*=0.00004), D-dimer (from 1432.0 [443.0–6390.0] to 1087.0 [415.0–3247.0], *P*=0.006) on day 3 after the hemoadsorption session. The Hemo-Proteasosorb without MLV group also showed a decrease in PCT (from 0.29 [0.14–21.25] to 0.14 [0.04–11.91], *P*=0.002), CRP (from 132.6 [30.7–183.0] to 28.55 [5.3–182.0], *P*=0.0002), fibrinogen (from 10.2 [4.41–15.5] to 6.5 [2.8–11.9], *P*=0.00005), D-dimer (from 1445.0 [365.0–4830.0] to 1049.0 [301.0–3302.0], *P*=0.005), while an increase in SpO_2/FiO_2 (from 238 [88–461] up to 320 [98–471], *P*=0.011) was registered. On days 5–7, positive changes in SpO_2/FiO_2 index (238 [88–461] vs 320 [96–471], *P*=0.0020) were observed in the Hemo-Proteasosorb without MLV group, as well as a trend toward further reduction in the levels of CRP (132.6 [30.7–183.0] vs 23.85 [2.2–200.0], *P*=0.0001) and fibrinogen (10.2 [4.41–15.5] to 5.11 [2.3–11.5], *P*=0.0017). The patients were assessed using the NEWS2 score at all the stages of the study. On days 2–3 of the study, a reduction in the mean NEWS2 score was noted in the Hemo-Proteasosorb + MLV group (8.0 [4.0–11.0] vs 6.0 [2.0–10.0], *P*=0.0002), whereas on days 5–7 its increase was seen vs stage 2 of the study with its values still lower than those prior to hemoadsorption (8.0 [4.0–11.0] vs 7.0 [2.0–9.0], *P*=0.011). On day 3 of treatment, in the Haemo-Proteasorb without MLV group we observed a decreased mean NEWS2 score (7.0 [3.0–9.0] vs 5.0 [1.0–9.0], *P*=0.00002), on days 5–7, this trend was still present (7.0 [3.0–9.0] vs 3.0 [1.0–8.0], *P*=0.00002).

Conclusion. Hemoadsorption was beneficial for patients with severe COVID-19 during both oxygen therapy and mechanical ventilation due to decreased levels of inflammatory markers, hypercoagulation, and reduced NEWS2 scores.

Keywords: Sars-CoV-2; COVID-19; cytokine storm; hemoadsorption; Hemo-Proteasosorb; mechanical lung ventilation; ventilatory support; noninvasive respiratory support

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

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Introduction

The COVID-19, which emerged in December 2019, was a real challenge for researchers and physicians around the world, despite enormous efforts to control the infection was proclaimed pandemic in April 2020 and still was a serious public health threat as of September 2021. The severity of the pandemic is due to the high mortality rate in severe cases. Since patients with severe disease are treated in an intensive care unit and usually have complications such as massive lung injury, respiratory failure, and, in most cases, multiple comorbidities, effective management of these patients is crucial. Given the high overall mortality (42–62%) in severe infection, special attention should be focused on patients who require mechanical lung ventilation due to severity of their disease. Mortality in this category of patients ranges from 75 to 90% [1, 2]. Some large epidemiological studies have reported a high rate of invasive mechanical ventilation among all patients with COVID-19 admitted to intensive care units, from 29% in China to 89.9% in the USA [3, 4].

Even before the pandemic, mortality among patients aged 80–90 years with severe comorbidities who underwent mechanical ventilation was high. For example, an epidemiological study conducted in the United States in 2010 has demonstrated a 50% mortality in ventilated patients aged 85 years and older [5].

The ARDS associated with lung injury and severe respiratory failure, which causes 70% of deaths in ICU patients, is the first challenge facing physicians. The second important factor of mortality seen in 28% of severe COVID-19 is the «cytokine storm» resulting from an inadequate immune response to the SARS-CoV-2 virus. While the mechanism of this response has still been unclear, the virus is known to integrate its RNA into the cell through interaction with angiotensin-converting receptor type 2 (ACE-2), which leads to activation of the interferon system and formation of new ACE-2 receptors, and consequently creates new route for the infection [6]. Direct viral damage occurs due to its replication in the respiratory tract, leading to pyroptosis (inflammation-associated programmed cell death) and capillary leakage syndrome. The inflammatory response arising from pyroptosis results in hypercytokinemia, which turns the protective physiological cytokine response of the body into an abnormal one («cytokine storm») [7].

Another mechanism of lung tissue damage is diffuse alveolar lung injury resulting from release of proteases and reactive oxygen species and leading to pulmonary edema [8]. In addition to lung damage, the «cytokine storm» in COVID-19 infection is characterized by cardiovascular, renal, and hepatobiliary impairment and multisystem organ dysfunction [9–11].

Currently, drug suppression with the interleukin-6 receptor inhibitor tocilizumab is a widely used method for blocking the cytokine storm [12]. However, in several patient categories such as those on a long-term immunosuppression or at risk of a generalized bacterial infection or having this infection, etc., the use of this drug is contraindicated [13]. The use of tocilizumab associates with a high risk of generalized bacterial infection or invasive candidiasis which can dramatically worsen the outcome in patients with severe COVID-19 [14].

Alternative strategies for combating the «cytokine aggression» include the use of extracorporeal blood purification methods such as cascade hemofiltration, high-volume hemofiltration, plasmapheresis, hemoperfusion, extracorporeal liver support, high-adsorption hemofiltration and membrane perfusion with selective filtration of intermediate mass molecules to remove cytokines and chemical mediators from blood of patients with severe COVID-19 [15]. Even before the pandemic, C. Ronco et al. proved the efficacy of various methods of extracorporeal detoxification (ECD) and provided a pathophysiological rationale for their use to restore «immune homeostasis» in sepsis-associated «cytokine storm» [16].

Among ECD methods, anticytokine hemoadsorption demonstrated significant efficacy in treating patients with COVID-19. The use of this technique has been shown to enable extracorporeal elimination of key cytokines (IL-6, IL-10, TNF), which play a significant role in the «cytokine storm» development [17, 18]. The use of extracorporeal purification in patients with severe COVID-19 is reasonable because the elimination of inflammatory mediators from circulation reduces the severity of inflammation causing organ failure and death.

As early as in April 2020, the FDA concluded that selective hemoadsorption using the CytoSorb sorbent is effective in the treatment of patients with severe COVID-19 infection and approved its use in this category [19]. The effectiveness of this ECD in severe COVID-19 infection was confirmed by the studies conducted in the United States and Germany (using Cytosorb) as well as China and Russia (using the HA-330 selective hemosorbent). The results of all studies showed a significant decrease in serum levels of proinflammatory cytokines after the procedure and increased survival rate after hemoadsorption [20–23]. In a series of cases at Noorafshar Hospital in Iran between May 1 and May 31, 2020, hemoadsorption using the HA 380 sorbent (Jafron Biomedical) proved effective in patients with severe disease requiring mechanical ventilation. All the patients who underwent hemoadsorption demonstrated improvement in respiratory

function manifested by increased blood pO_2 and SpO_2 with 5 out of 6 patients subsequently extubated and discharged from the intensive care unit [24].

The benefits of hemoadsorption also include lack of absolute contraindications and significant side effects, as well as efficacy confirmed by the studies conducted in the USA, Germany, Italy, China, and Russia.

Aim of the study. To evaluate the effects of hemoadsorption on clinical and laboratory parameters in patients with severe COVID-19 who required mechanical lung ventilation (MLV) or receiving noninvasive respiratory support.

Material and Methods

We retrospectively studied the longitudinal clinical and laboratory parameters of 49 patients with severe coronavirus infection and «cytokine storm» hospitalized in the First ICU of the Grodno University Hospital from September 2020 to November 2021, who underwent hemoadsorption using the domestic Hemo-Proteasosorb sorbent.

All patients were divided into two groups. The first one, «Hemo-Proteasosorb + MLV», included 22 patients, of them 14 men (64%) and 8 women (36%), with the mean age of 56 (19.0–89.0) years, Charlson comorbidity index of 4.0 (1.0–8.0) points. The other group, «Hemo-Proteasosorb without MLV» comprised 27 patients, of them 16 men (59%) and 11 women (41%) with the mean age of 61 (35.0–86.0) years and Charlson comorbidity index of 4.0 (1.0–9.0) points.

Inclusion criteria were laboratory and clinically confirmed COVID-19 infection complicated by a «cytokine storm». Exclusion criteria were pregnancy, acute cerebrovascular accident, advanced cancer at the time of inclusion, HIV infection, chronic active viral hepatitis B or C with elevated transaminases, pulmonary or extrapulmonary tuberculosis, generalized epilepsy, alcohol or drug abuse, decompensated liver cirrhosis, acute pancreatitis, sepsis.

This study determined 14-day and 30-day survival of patients underwent hemoadsorption. and changes in blood inflammation markers, coagulation parameters, SpO_2/FiO_2 index and the patient's status assessed by NEWS2 scoring at different time points of the study.

All patients in both study groups received standard therapy according to the current guidelines of the Ministry of Health of the Republic of Belarus (Orders No. 393, 690, and 900).

For low-flow oxygen therapy, intranasal cannulas and facial masks were consistently used in all patients with the oxygen flow of 15 l/min. Noninvasive lung ventilation, if necessary, was done using the Mindray SynoVent E3 device (China) in the NIV mode with FiO_2 from 30 to 100%. The invasive lung ventilation was performed using Mindray SynoVent E3 (China) in P-SIMV mode with FiO_2 from 30 to 100%. The criteria for initiating the next stage of respiratory support included respiratory rate >22/min, $SpO2/FiO_2$<60%, SpO_2<90% with the ongoing oxygen therapy.

Invasive ventilation was performed in 22 patients (45%), while 27 patients (55%) required oxygen therapy or noninvasive ventilation. Indications for the extracorporeal purification included progressive rise of inflammatory markers (interleukin-6, C-reactive protein, procalcitonin, leukocyte count), D-dimer, and fibrinogen.

The efficacy of the treatment was evaluated using the changes in proinflammatory cytokines (CRP, procalcitonin) levels. Respiratory system assessment in hyperimmune inflammation was performed by monitoring the SpO_2/FiO_2 index. The coagulation system was evaluated by measuring the levels of fibrinogen, which also reflected the severity of inflammation, and D-dimer. The patients' status during hemoadsorption was serially evaluated using the NEWS2 score. Hemoadsorption was performed in all patients using the «Hemo-Proteasorb» antiproteinase biospecific hemosorbent (Republic of Belarus) according to the following procedure. A central vein was punctured and catheterized prior to the start of hemoperfusion. Before the procedure, the extracorporeal circuit was flushed with 5,000 units of unfractionated heparin. The extracorporeal circuit was connected in sterile conditions. Before hemoperfusion, the mass exchangers were flushed with fivefold volume of sterile 0.9% NaCl solution. Thereafter, blood was drawn from a vein into the MCA 0/330-MKV01 single-use hemoperfusion line using a BP-742 roller pump (Fresenius, Germany). Blood was passed through the Hemo-Proteasosorb sorbent column and then returned to the previously catheterized peripheral vein. Blood perfusion rate in the line was 80–90 ml/min. The procedure duration was 60 minutes. The average number of sessions was 4.5 (3.0–6.0).

Blood sampling for the study was done 6 hours prior to the procedure of extracorporeal blood purification. Follow-up tests were carried out on days 3 and 5–7 in both groups.

Complete blood count was done using ABX analyzer «Micros» (Roche, France). Levels of fibrinogen and D-dimer were measured by biochemical method on «Architect®c8000 System» (USA). The levels of C-reactive protein (CRP) and procalcitonin (PCT) were determined by enzyme immunoassay on the Abbott Axsym® system (USA) machine. For a comprehensive assessment of respiratory function, the SpO_2 (pulse oximetry index) to FiO_2 (% of oxygen in the inhaled gas mixture) ratio was calculated.

The results were analyzed using the Statistica 10.0 software (Statsoft Inc., USA). Normally distributed variables were reported as means (*M*). Medians

Table 1. Changes in the studied parameters in the patient groups, *Me* (25%, 75%).

Parameter	Study stage	Parameter values in groups			
		Hemo-proteasosorb + MLV, *n*=22	*P-value*	Hemo-proteasosorb without MLV, *n*=27	*P-value*
CRP, mg/l	Baseline	135.4 (10.6–303.0)		132.6 (30.7–183.0)	0.911#
	On day 3 after hemoadsorption	64.3 (1.2–147.0)	0.003*	28.55 (5.3–182.0)	0.0002* 0.142#
	On days 5–7 after hemoadsorption	107 (19.6–253.0)	0.249*	23.85 (2.2–200.0)	0.0002* 0.003#
PCT, ng/ml	Baseline	0.27 (0.12–2.08)		0.29 (0.14–21.25)	0.499#
	On day 3 after hemoadsorption	0.14 (0.05–1.77)	0.028*	0.14 (0.04–11.91)	0.002* 1.0000000#
	On days 5–7 after hemoadsorption	0.27 (0.08–0.45)	0.285*	0.22 (0.05–9.29)	0.721* 0.866#
Leukocyte count, $\times 10^9$/l	Baseline	15.18 (6.7–26.56)		11.64 (2.1–29.0)	0.031#
	On day 3 after hemoadsorption	12.78 (8.17–26.97)	0.502*	9.13 (2.75–20.9)	0.0008* 0.002#
	On days 5–7 after hemoadsorption	19.6 (6.17–38.4)	0.093*	12.1 (1.34–26.1)	0.677* 0.010#
SpO_2/FiO_2, %	Baseline	183 (87–448)		238 (88–461)	0.067#
	On day 3 after hemoadsorption	169 (85–471)	0.615*	320 (98–471)	0.012* 0.039#
	On days 5–7 after hemoadsorption	161 (84–467)	0.852*	320 (96–471)	0.002* 0.011#
Fibrinogen, g/l	Baseline	11.7 (4.9–19.49)		10.2 (4.41–15.5)	0.011#
	On day 3 after hemoadsorption	8.2 (3.7–14.7)	0.00004*	6.5 (2.8–11.9)	0.00005* 0.141#
	On days 5–7 after hemoadsorption	9.6 (4.6–17.9)	0.003*	5.11 (2.3–11.5)	0.00006* 0.002#
D-dimer, μg/ml	Baseline	1432.0 (443.0–6390.0)		1445.0 (365.0–4830.0)	0.718#
	On day 3 after hemoadsorption	1087.0 (415.0–3247.0)	0.006*	1049.0 (301.0–3120.0)	0.006* 0.849#
	On days 5–7 after hemoadsorption	1114.0 (481.0–10000.0)	0.650*	1335.0 (335.0–3302.0)	0.179* 0.968#

Note. CRP — C-reactive protein; PCT — procalcitonin; MLV — mechanical lung ventilation; * — *P-value* vs the baseline (Wilcoxon test); # — *P-value* vs the same time point in the MLV group (Mann–Whitney test).

(*Me*) and interquartile ranges (values of the 25th and 75th percentiles) were used for parameters with non-normal distribution. The variables not having «close to normal» distribution were reported as Median (*Me*) with upper and lower quartiles. The significance of the results was assessed using the Wilcoxon nonparametric test. Mann–Whitney U-test was applied to compare independent groups with one or two quantitative variables with non-normal distribution. The differences were considered significant at $P<0.05$.

Survival rates in the study groups were assessed by Kaplan–Meier method using the SPSS Statistics software. To identify independent factors influencing mortality in the studied cohort of patients, we performed multivariate analysis using Cox regression method.

Results

The baseline laboratory parameters of patients in both study groups demonstrated a severe inflammatory response associated with a rise in the levels of CRP, PCT, and leukocyte count. On day 3 after hemoadsorption, a decrease in the levels of CRP and PCT was seen in the studied groups. Interestingly, the patients receiving noninvasive respiratory support were found to have a significant decrease in the leukocyte count post-hemoadsorption, whereas in those from the MLV group difference between groups was non-significant. On days 5–7, a trend toward a further decrease of CRP and a slight increase in the leukocyte count was seen in the latter group. Meanwhile, in the «Hemo-Proteasosorb + MLV» group, the opposite was observed with the CRP level higher than in the previous time point and the leukocyte count exceeding the baseline (Table 1).

After calculating the baseline SpO_2/FiO_2 index in both study groups, it was found to be lower in the «Hemo-Proteasosorb + MLV» group than in the «Hemo-Proteasosorb without MLV» one, which suggests a more severe patient condition in this group due to more serious respiratory failure. In the same group, there was a trend towards progressive reduction of the index during all the stages of the study, which was considered as worsening respiratory failure. On the contrary, in the «Hemo-Proteasosorb without MLV» group, a significant increase of SpO_2/FiO_2 index was observed on days 3 and 5–7 as compared to the baseline (Table 1).

Respiratory function assessment was also performed by monitoring the changes in the types of

Table 2. The changes in types of respiratory support and clinical condition of patients in the groups, *Me* (25%, 75%).

Parameter	Study stage	Parameter values in groups			
		Hemo-proteasosorb + MLV, *n*=22	*P-value*	Hemo-proteasosorb without MLV, *n*=27	*P-value*
Type of respiratory support	Baseline	2.5 (1.0–3.0)		1.0 (1.0–2.0)	0.00003#
	On day 3 after hemoadsorption	3.0 (1.0–3.0)	0.441*	1.0 (0.0–2.0)	0.686* 0.00004#
	On days 5–7 after hemoadsorption	3.0 (1.0–3.0)	0.169*	1.0 (0.0–2.0)	0.016* 0.000001#
NEWS 2, points	Baseline	8.0 (4.0–11.0)		7.0 (3.0–9.0)	0.0129#
	On day 3 after hemoadsorption	6.0 (2.0–10.0)	0.0002*	5.0 (1.0–9.0)	0.00002* 0.002#
	On days 5–7 after hemoadsorption	7.0 (2.0–9.0)	0.011*	3.0 (1.0–8.0)	0.00002* 0.0001#

Note. * — *P-value* vs the baseline (Wilcoxon test); # — *P-value* vs the same time point in the lung ventilation group (Mann–Whitney test). For statistical analysis, each type of ventilatory support was assigned a numerical value from 0 to 3 depending on the level: 0, no oxygen support or support up to 5 l/min; 1, oxygen support up to 15 l/min using nasal cannulas and/or face mask; 2, noninvasive lung ventilation in CPAP mode; 3, invasive ventilation in P-SIMV mode. The data were included in the table accordingly. The value of 1 at different stages in the group with mechanical ventilation is due to the fact that some patients were switched to a less invasive support, while the others had deteriorated. For example, Patient #2 in the group with MLV required only oxygen support up to 15 l/min using nasal cannulas and/or a face mask at the baseline, while on days 5–7, the MLV was required corresponding to deterioration from 1 to 3. In contrast, some patients had the opposite situation: prior to hemoadsorption, they required invasive or noninvasive lung ventilation, and during hemoadsorption, a lower level of respiratory support was required, which corresponded to a positive trend from 3 to 2 or from 2 to 1. For this reason, the range of values in the groups was from 1.0 to 3.0.

respiratory support. The results of this monitoring are shown in Table 2.

The effect of hemoadsorption on hemostasis was evaluated by analyzing the results of coagulation tests (D-dimer, fibrinogen, prothrombin time, APTT, INR) and the platelet count. There were no changes in the levels of prothrombin time, APTT, INR, platelet count during the hemoadsorption, that is why we only analyzed the serial changes of D-dimer and fibrinogen levels universally considered to be markers of disease severity in COVID-19. In both groups, a significant decrease in fibrinogen was seen on day 3 after hemoadsorption and a trend to its reduction was observed on days 5–7. On day 3, both in patients on mechanical ventilation and in those on noninvasive respiratory support, D-dimer level dropped significantly as compared with the baseline values, but on day 3, it rose in both groups (Table 1).

In addition to laboratory parameters, we assessed clinical condition of patients during different periods of the study using the NEWS2 score. In the noninvasive respiratory support group there was a significant decrease of NEWS2 scores on day 3. On days 5–7, the trend towards their further decrease persisted indicating the improvement of the patients' condition. On day 3 after hemoadsorption, the values of the NEWS2 score decreased, while on days 5–7, they increased as compared with the results obtained on day 3, but still remained lower versus baseline (Table 2).

The Kaplan-Meier survival curve was plotted to determine the survival rate in patients receiving hemoadsorption (Fig. *a, b*). The 14-day survival rate in the «Hemo-Proteasosorb+MLV» group was 64%, while in the «Hemo-Proteasosorb without MLV» group it was 85% (Fig. *a*).

The 30-day survival rate was 41% in the MLV group and 73% in the noninvasive respiratory support group (Fig. *b*).

To identify independent factors influencing mortality in the studied cohort, a multivariate Cox proportional hazards regression model was performed. Age, gender, comorbidity did not afferct mortality in patients receiving hemoadsorption. However, the impact of invasive ventilation was predictably evident (Table 3).

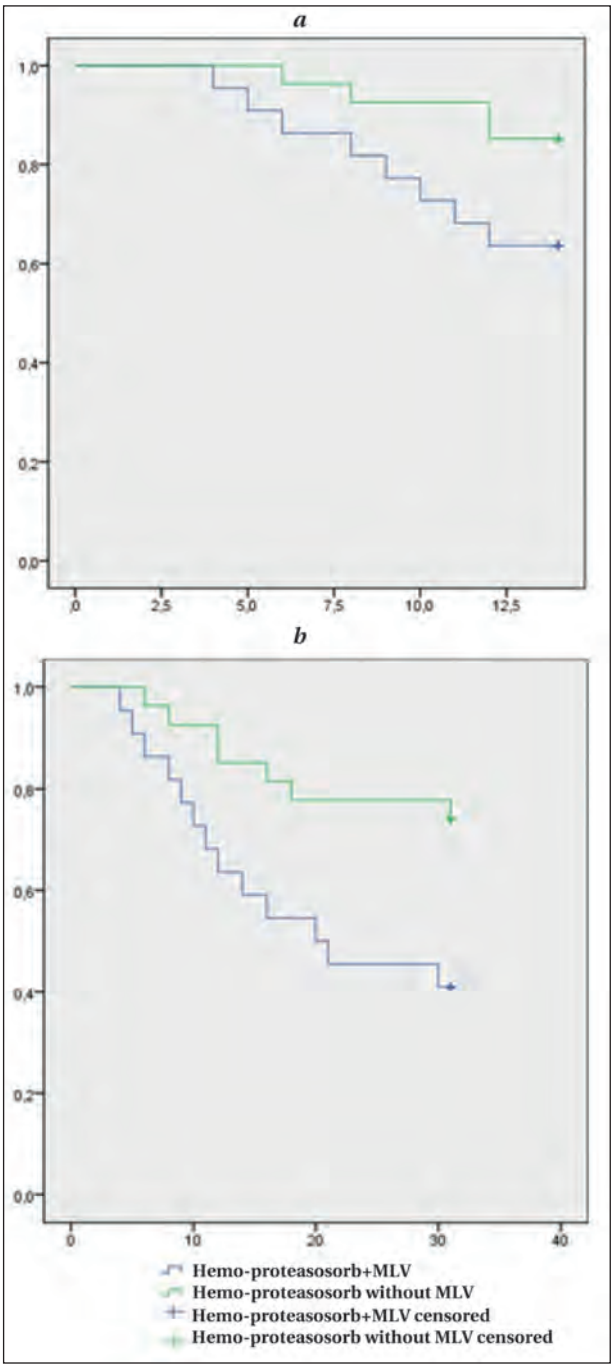
Table 3. Assessment of risk factors for combined endpoint (mortality) in patients with severe COVID-19 who underwent hemoadsorption.

Parameter	HR	95% CI	*P-value*
Lung ventilation	4.282	1.62–12.05	0.004
Sex	0.78	0.30–2.05	0.61
Age	0.23	0.29–1.89	0.17
Comorbidity	0.54	0.88–3.37	0.51

Note. The results of Cox multiple regression analysis are shown. HR — hazard ratio; CI — confidence interval.

Discussion

Our findings are consistent with the results of a randomized study conducted by Liang Yu (China) on the use of HA-330 hemosorbent in patients with severe COVID-19 which demonstrated higher oxygenation index 72 hours after hemoadsorption (rise from 74.0 to 222.2 mm Hg) vs the control group (rise from 83.0 to 122.9 mm Hg), decrease of APACHE score from 16 to 13.5 (in the control group its increase was seen from 13 to 18), and almost a twofold reduction of pneumonia severity index as



Kaplan–Meier survival curve on day 14 (*a*) and day 30 (*b*).

compared with the control group (from 126.5 to 83 points vs increase from 125 to 164 points in the control group). Mortality of patients in the hemoadsorption group, as compared with the control group, appeared to be three times lower (15.4% vs. 47.6%, respectively) [21].

Another retrospective study conducted by Ruiz-Rodrigues J.C. between March 3, 2020, and June 22, 2020, which included 343 patients with severe COVID-19 infection, six of whom underwent hemoadsorption using the CytoSorb® anti-cytokine sorbent while being on mechanical ventilation, significant reductions in D-dimer (from 17,868 μg/mL down to 4,488 μg/mL), C-reactive protein (from 12.9 mg/dL down to 3.5 mg/dL), ferritin (from 1539 μg/L down to 1197 ng/mL), and interleukin-6 (from 17,367 pg/mL down to 2,403 pg/mL) were found as compared to the baseline. After the procedure, an improvement in oxygenation (PaO_2/FiO_2 rose from 103 to 222 mm Hg) and a decrease in the SOFA score (from 9 at the baseline to 7.7 post procedure) were revealed. The mortality in the intensive care unit was 33.7% [25].

Thus, our results demonstrate the effectiveness of hemoadsorption using the domestic Hemo-Proteasosorb sorbent in patients with severe COVID-19 both on noninvasive respiratory support and on mechanical ventilation. The effectiveness of hemoadsorption, though, was lower in the group of patients who required invasive ventilatory support. Therefore, the start of hemoadsorption may be considered more appropriate during the period when invasive respiratory support is not required.

Conclusion

The use of hemoadsorption in COVID-19 has demonstrated clinical effectiveness in patients on both noninvasive and invasive respiratory support. Positive effects of hemoadsorption manifesting as increase in SpO_2/FiO_2 index were more significant in the group of patients without mechanical ventilation. The procedure was associated with a reduced NEWS2 score in both study groups with the changes being more significant in the noninvasive respiratory support group.

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Acute Myocardial Infarction Complicating Coronavirus Infection (Case Report)

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Острый инфаркт миокарда как осложнение коронавирусной инфекции (клиническое наблюдение)

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Summary

Coronavirus infection caused by the SARS-CoV-2 virus is a multifaceted disease due to generalized vascular endothelial damage. Endothelial damage also underlies COVID-associated coagulopathy.

The paper presents a case of coagulopathy causing myocardial infarction in a 43-year-old patient with no history of coronary disease. We have reviewed the available literature for the pathophysiological rationale of the assumed possibility of coronary thrombosis resulting from coagulopathy with the intact intima of the coronary arteries.

Conclusion. The present observation of coronary thrombosis with radiographically intact coronary artery intima confirms the important role of coronavirus infection in triggering endothelial dysfunction. Currently, the most effective strategy for this type of coronary lesions is the use of anticoagulants and antiplatelet agents along with ECG, echocardiography and troponin level monitoring.

Keywords: COVID-19; covid-associated coagulopathy; myocardial infarction

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

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Introduction

Coronavirus infection is primarily a respiratory disease, therefore the new coronavirus was named SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) [1]. However, unlike «classic» community-acquired pneumonia, COVID-19 has many other targets, including cardiovascular system [2]. In particular, endothelial dysfunction and coagulation disorders are considered among the most frequent complications of coronavirus infection [3].

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In patients with COVID-19, severe manifestations such as viral pneumonia and systemic inflammation often coexist with coagulation disorders [4–6].

Proteins, glycoproteins and proteoglycans on the surface of host cells, including serine transmembrane protein 2 (TMPRSS2) and heparan sulfate proteoglycans (HSPG), are important for the initial interaction between viruses and cells [7–13]. Other proteins acting as viral receptors, such as sialic acid receptors [14, 15], matrix metalloproteinase inducer CD147 [16] and angiotensin-converting enzyme ACE2, mediate viral entry into the host cell [17]. ACE2, which is part of the renin-angiotensin-aldosterone system [18, 19], is currently the most studied receptor in the context of SARS-CoV-2 [19] and is considered one of the crucial cellular target proteins for viral infection [20]. There is evidence that the virus interacts with ACE2 through its transmembrane spike glycoprotein, which is essential for determining host cell tropism and viral diversification [5, 17, 18, 21]. The HSPG binding has also been demonstrated to cause significant conformational changes in the spike protein structure, whereas the receptor-binding domain of the spike subunit contains an HSPG binding site [22, 23]. The HSPG is a co-receptor of the cell surface proteoglycan with the ACE2 protein for recognition of the spike protein of SARS-CoV-2 [24–26]. The SARS-CoV-2 spike protein has been experimentally found to have high affinity for human ACE2 [9, 27]. The density of ACE2 in each tissue can correlate with the severity of tissue damage [28–32].

Regardless of the specific ACE2 expression loci, SARS-CoV-2 binds to the corresponding ACE2 sites wherever there is an endothelium, as it is the endothelial cells that express ACE2 [33]. Endothelial cells are fundamental to vascular endothelial function and regulate aggregation, thrombosis, fibrinolysis, and vasodilation [5, 17, 34].

ACE2 has the most extensive expression pattern in the heart, lungs, gastrointestinal system, and kidneys [32, 35]. In addition, ACE2 plays an important role in the neurohumoral regulation of the cardiovascular system. The expression of ACE2 in the brain has been suggested to contribute to the development of neurogenic hypertension [36, 37]. Binding of SARS-CoV-2 to ACE2 causes acute myocardial and lung damage by disrupting alternating ACE2 signaling pathways [35]. On the one hand, elevated ACE2 receptor density increases the viral load, but on the other hand, it can reduce the extent of cardiac damage because ACE2-induced conversion of angiotensin II to angiotensin (1–7) is a protective factor for the heart against the effects of the renin-angiotensin-aldosterone system [38]. Viral entry into the cell causes suppression of ACE2 regulation and increases systemic angiotensin II levels, resulting in increased cardiac damage [39]. Infection affects important pathways of biochemical regulation of the heart, such as ACE2 signaling pathway, fibrinogen pathway, redox homeostasis, causes stent-related plaque rupture, and finally worsens myocardial damage and dysfunction [40, 41]. Myocardial damage without direct plaque rupture can also occur due to cytokine storm, hypoxic damage, coronary spasm and endothelial or vascular damage [42, 43].

Thus, COVID-19 increases the risk of heart disease in patients with cardiovascular comorbidities [44].

Clinical case report

Patient K., 43 years old, having obesity and hypertension, was urgently admitted to Moscow City Clinical Hospital No. 52 on November 20, 2021, with a preliminary diagnosis of COVID-associated pneumonia and clinical presentation of acute coronary syndrome. On November 6, 2021, he developed a fever of up to 38°C and an impaired sense of smell. COVID-19 PCR (+) dated November 10, 2021, computer tomography (CT) of the chest dated November 20, 2021 (Fig. 1) has shown CT grade 1 pneumonia, before hospitalization he took Eliquis 2.5 mg once a day, Ibuclin, Dexamethasone, and antiviral med-

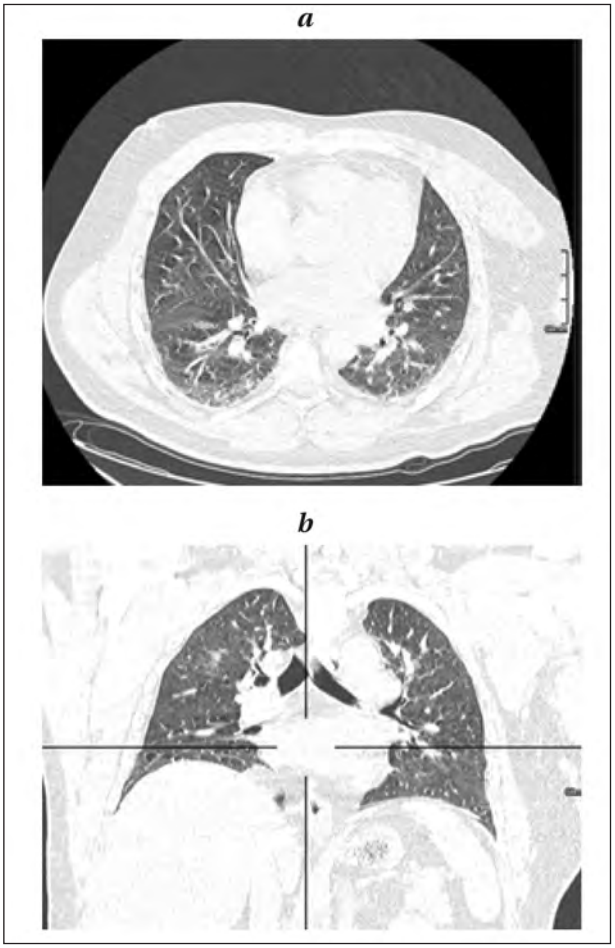

Fig. 1. Chest computed tomography dated November 20, 2021.

ications. On November 19, 2021, in the evening, the patient felt transient discomfort behind the sternum at rest, in the morning of November 20, 2021, his condition worsened, he had squeezing central chest pain and tried oral non-steroidal anti-inflammatory drugs with no effect.

On the evening of the same day, amidst persisting symptoms, he called an ambulance. The electrocardiogram (ECG) (Fig. 2, *a*) showed sinus rhythm, ST elevation in I, AVL, V2-V6, QS in V3-V6. He was diagnosed with ST-elevation acute coronary syndrome, COVID-19 infection confirmed by PCR. On admission, troponin I was 107.00 ng/L.

The patient was admitted to the intensive care unit for coronary angiography (CAG). On CAG done November 20, 2021 (Fig. 3, *a*), parietal thrombosis of left anterior descending artery (LAD) with reduced coronary blood flow was found.

Due to the parietal thrombus in LAD with reduced coronary blood flow (TIMI-II), without coronary atherosclerosis but with evidence of embolism in the terminal portion of LAD in the apical area, myocardial damage was considered due to the type 2 myocardial infarction with the underlying coagulopathy and endothelial dysfunction. We suggested that the spontaneous fibrinolysis developed after

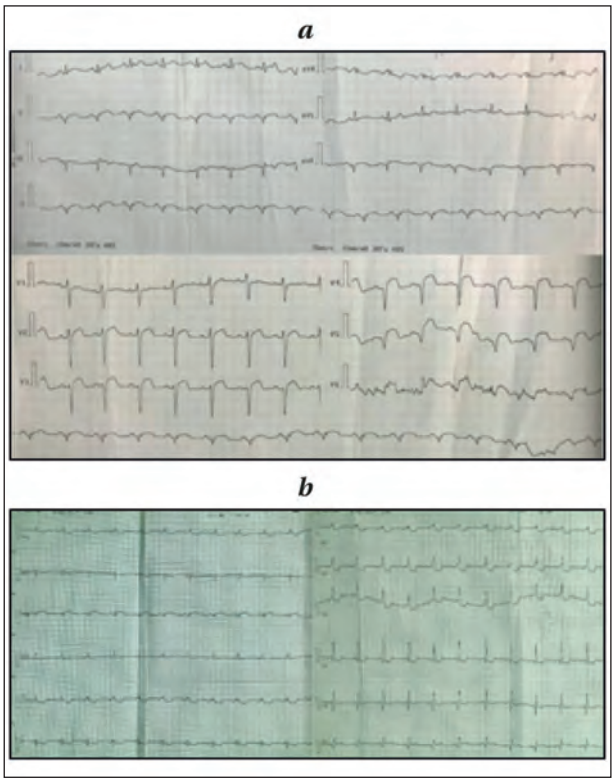

Fig. 2. ECG dated November 20, 2021 (*a*) and after rhythm restoration of November 23, 2021 (*b*).

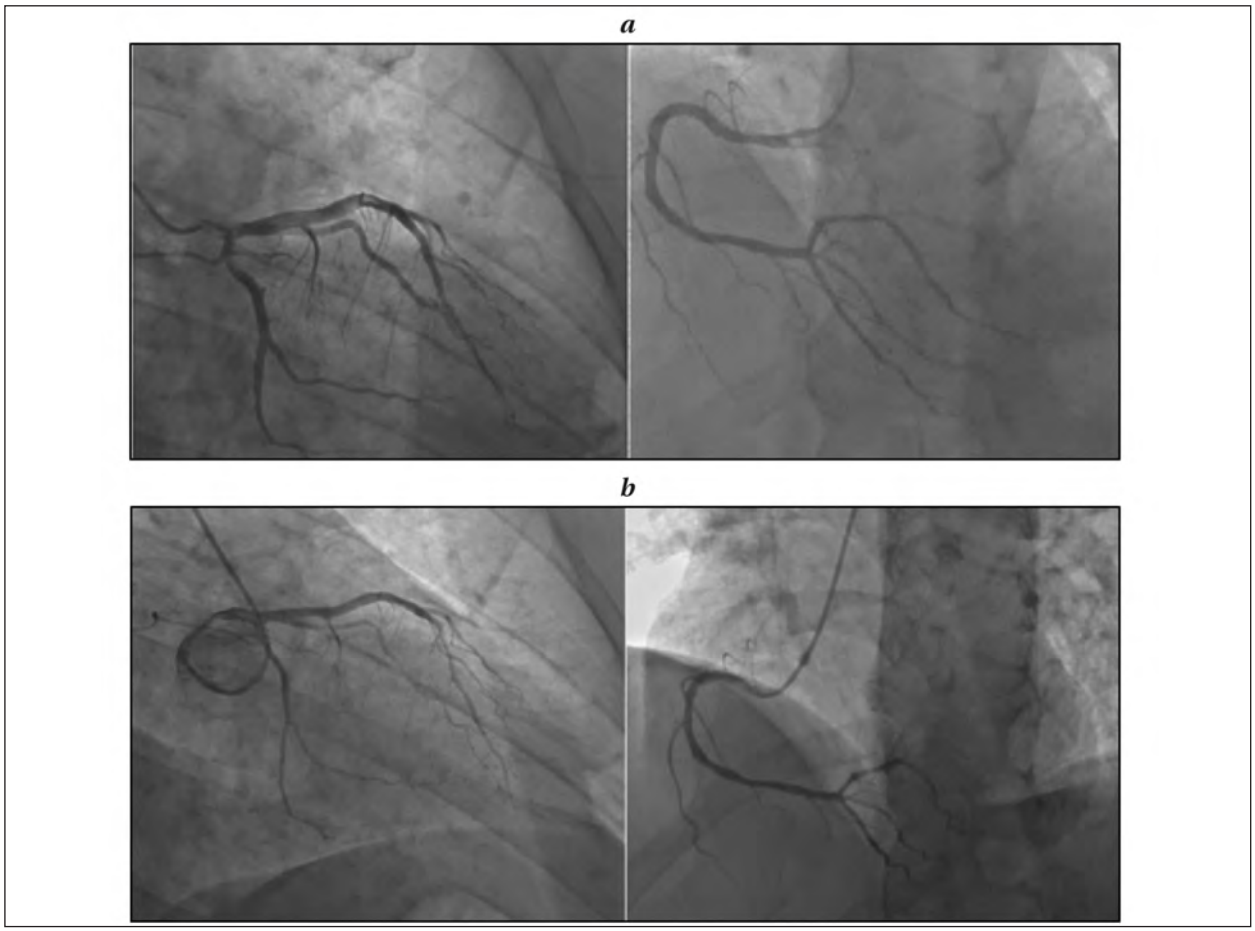

Fig. 3. Coronary angiography dated November 20, 2021 (*a*) and November 26, 2021 (*b*).

LAD thrombosis could promote embolic thrombosis with the major thrombus fragments in distal parts of LAD branches, while leaving the LAD itself relatively «intact» (angiographically seen as parietal thrombosis). This suggestion provided a rationale for administration of the IIb/IIIa receptor blocker Eptifibatide 0.75 mg/ml (100 ml) intravenously for 12 hours. In addition, dual antiplatelet therapy (acetylsalicylic acid 250 mg loading dose, then 100 mg + Ticagrelor 180 mg during percutaneous coronary intervention, Clopidogrel 600 mg loading dose, then 75 mg) was started. No coronary artery stenting was performed due to the absence of visible stenoses of the LAD. Thromboelastography (TEG) was also performed (Fig. 4) and showed normal plasma coagulation with normal clot density formation (R interval 12.6 min [reference range 9–27 min], MA 57.9 mm [reference range 44–64 mm], G 6.9 [reference range 3.6–8.5], CI 0.2 [reference range –3–+3]). The TEG results confirmed the suggested priority of endothelial dysfunction over coagulopathy per se in our case report.

The treatment was associates with improvement in patient's condition. No squeezing central chest pain was reported. Echocardiography dated November 21, 2021 has shown left ventricular ejection fraction (LVEF) ~60% with impaired local contractility of LV, circular akinesis of apex, hypo- and akinesis of middle and apical segments of septal wall, hypokinesis of basal and middle segments of lateral wall. ECG dated November 21, 2021 demonstrated ST elevation in I, II, V2-V6, abnormal Q wave in V3-V6 which was interpreted as acute myocardial infarction of anterior and lateral wall expanding to the LV apex. Troponin I of November 21, 2021 was 74.00 ng/L. 48 hours later, the ECG still showed ST elevation in I, AVL, V4-V6. Troponin I of November 22, 2021 was 36.00 ng/L.

On November 22, 2021, an atrial fibrillation paroxysm occurred, which was terminated by cardioversion within 48 hours of onset (Fig. 2, *b*). Further antiarrhythmic therapy with continuous intravenous amiodarone was administered. Antiviral and biological therapy was prescribed according to the Guidelines for prevention, diagnosis, and treatment of the novel coronavirus infection.

After stabilization, the patient was admitted to the cardiology department on November 24, 2021. A follow-up coronary angiography (Fig. 3, *b*) was performed on November 26, 2021 due to the presence of coronary heart disease, myocardial infarction, contraindications for exercise testing and to assess the coronary artery patency and determine the management strategy. Positive changes were noted compared to the one of November 20, 2021: the left coronary artery (LCA) was intact, the right main coronary artery (RCA) had no hemodynamically significant stenosis, in the distal part (apical region) there was a slight delay in contrast agent passage; the left circumflex artery (LCA), obtuse marginal artery (OMA), and right coronary artery (RCA) had no hemodynamically significant stenosis.

The follow-up Holter ECG monitoring of November 27–28, 2021 has shown sinus rhythm with episodes of rapid atrial fibrillation and short runs of ventricular tachycardia. The follow-up chest CT scan of November 29, 2021 showed improvement compared to the one made on November 20, 2021.

The patient was discharged from the hospital in a stable condition (normal temperature, reduced markers of systemic inflammation) on day 11 after admission.

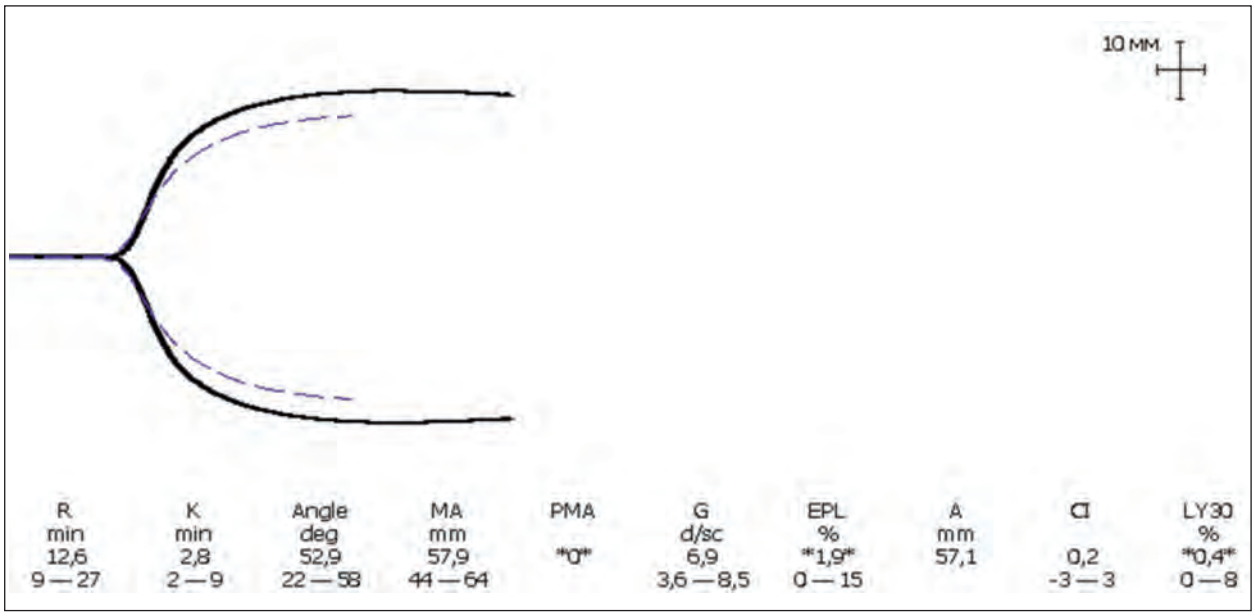

Fig. 4. Thromboelastography dated November 20, 2021.

Conclusion

This case report supports the important role of coronavirus infection in triggering endothelial dysfunction in coronary thrombosis with radiologically intact coronary artery intima. Currently, anticoagulant and antiplatelet therapy with ECG, echocardiographic and troponin level monitoring remain the most effective management strategy for this type of coronary lesion. Many issues of COVID-associated coagulation disorder and endothelial damage, which determine non-atherosclerotic coronary thrombosis, are still poorly understood. The phenomenon of spontaneous fibrinolysis with the underlying systemic COVID-associated hypercoagulation also remains unclear. These issues require further study.

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Respiratory Mechanics and Gas Exchange in Acute Respiratory Distress Syndrome Associated with COVID-19

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Механика дыхания и газообмен при остром респираторном дистресс-синдроме, ассоциированном с COVID-19

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Summary

Aim. To compare respiratory mechanics and gas exchange in patients with acute respiratory distress syndrome (ARDS) with and without COVID-19.

Material and methods. We examined 96 patients, who were divided into two groups. The main group included 48 patients with COVID-19-associated ARDS. The control group included 48 patients with ARDS not associated with COVID-19. Most characteristic patients were selected for the following baseline parameters: age, sex, SAPS II score, disease severity, plateau pressure (Pplateau), oxygenation index (PaO_2/FiO_2), and arterial-alveolar oxygen gradient ($A\text{-}aO_2$). Respiratory mechanics and gas exchange parameters assessed immediately after ARDS diagnosis and on days 1, 3 and 7 of treatment included arterial oxygen (PaO_2) and carbon dioxide ($PaCO_2$) pressure, tidal volume (Vt), respiratory rate (RR), respiratory minute volume (RMV), positive end expiratory pressure (PEEP), and $P_{plateau}$.

Results. Patients in the main group had higher Vt (9.7 vs. 5.1 ml/kg, $P<0.001$), RR (38 vs. 30 min^{-1}, $P<0.001$), and RMV (27.7 vs. 10.5 l/min, $P<0.001$). Control group patients showed hypercapnia ($PaCO_2$ 43 vs. 38 mmHg, $P<0.001$), lower respiratory compliance (30 vs. 48 ml/cm H_2O, $P<0.001$) and ventilation ratio (VR) (1.5 vs. 2.0, $P<0.01$). Lower PEEP values were required for patients in the main group. However, despite the higher rate of tracheal intubation in the control group (50% vs 16.7%) in the initial period of intensive care, the proportion of patients receiving invasive lung ventilation was significantly higher in the main group (33.3% vs.14.6%) by day 7.

Conclusion. The initial phase (the first 7 days) of ARDS associated with COVID-19 is characterized by higher values of Vt, RR and RMV, as well as lung compliance vs «typical» ARDS with almost identical PaO_2/FiO_2 values.

Keywords: COVID-19; ARDS; respiratory support; respiratory mechanics

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

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Introduction

The pandemic new coronavirus infection COVID-19 has led to a dramatic increase in the incidence of acute respiratory distress syndrome (ARDS) worldwide [1, 2]. As experience in the management of patients with COVID-19-associated ARDS accumulates, efforts are being made to develop its classification, according to the mechanical changes of the respiratory system, in order to optimize algorithms of respiratory therapy [3, 4]. To date, viral pneumonia was shown to be accompanied by a variety of clinical manifestations and disorders of respiratory mechanics with the underlying interaction between such major factors as viral load, patient reactivity, baseline physiological reserve and comorbidity as well as the patient's adaptive capacity for hypoxemia and the time from the onset of the disease to the beginning of intensive care [5–7].

Despite disease-specific differences in the pathogenesis of ARDS, most authors suggest using similar methods of respiratory support for its control. These include lung ventilation with low tidal volume (Vt) (4–8 ml/kg) and maintenance of plateau pressure below 30 cm H_2O. Individualized use of high levels of positive end-expiratory pressure (PEEP), 12–16-hour ventilation in the prone position, muscle relaxants, and recruitment maneuvers are recommended for patients with COVID-19 on mechanical lung ventilation (MLV) [8–10]. Recently, the personalized respiratory support with pulmonary protection has become the basis of ARDS treatment and was shown to reduce mortality. The ventilation strategy is also discussed in the context of recent debates about phenotypic heterogeneity in patients with COVID-19-related ARDS [2, 5, 11, 12]. Although early reports suggested that COVID-19-associated ARDS has mostly unique features, new data indicate that the respiratory mechanics of patients with or without COVID-19-associated ARDS are broadly similar [3, 6, 13, 14].

Large variations in mortality in different medical centers indicate that respiratory support can contribute significantly to the outcome of COVID-19-associated ARDS [15, 16]. The understanding of respiratory mechanics in COVID-19 pneumonia and the feasibility of involving the unstable alveoli in gas exchange can provide a background for adjustment of respiratory settings. While solid evidence supporting the paradigm change in ventilation control is still lacking, an individualized approach with respect to respiratory biomechanics of each patient has been proposed [4, 7, 15, 17].

The aim of the study was to compare parameters of respiratory mechanics and gas exchange in patients with acute respiratory distress syndrome (ARDS) associated with COVID-19 and not related to COVID-19.

Material and Methods

Forty-eight adult patients with COVID-19-associated ARDS hospitalized in the Republican Infectious Hospital Zangiota-1 (Tashkent, Uzbekistan) during the period July 1 to August 27, 2021 were included in the prospective study and comprised the first (main) group. SARS-CoV-2 was identified by reverse transcriptase-polymerase chain reaction of nasal swabs. The SARS severity was assessed by oxygenation index (RaO_2/FiO_2) according to Berlin definitions [14].

The second group (control) consisted of 48 adult patients with ARDS not related to COVID-19, hospitalized in the Vakhidov Republican Research and Medical Center of Surgery (Tashkent, Uzbekistan) from January 2017 to August 2021.

Inclusion criteria for patients in the study were age older than 18 years and diagnosis of ARDS (according to Berlin definitions).

Patients who underwent tracheal intubation immediately upon admission to the ICU were not included in the study.

The patients were selected according to the principle of initial characteristics representativity according to the following criteria: age, sex, SAPS II score, disease severity, plateau pressure (Pplateau), oxygenation index (RaO_2/FiO_2), and alveolar-arterial oxygen gradient ($A\text{-}aO_2$).

Invasive lung ventilation with sedation was started in the volume control mode with Vt of 6–8 ml/kg of predicted body weight and respiratory rate (RR) up to 35 min^{-1} (adjusted according to arterial blood pH). Oxygen fraction (FiO_2) was set to achieve an arterial blood oxygen saturation greater than 93%.

The PEEP parameters were set by the attending physician according to gas exchange and hemodynamic tolerance values with an upper limit of Pplateau of 28 cm H_2O.

During the first 12 hours of the patients' stay in ICU we analyzed the ventilator settings in the non-invasive ventilation mode (CPAP), including the patient's supine position. Respiratory mechanics and possibility of lung recruitment were assessed.

Initial measurements were made immediately after ARDS diagnosis with the patient being on non-invasive ventilation. The following parameters were measured from 6 to 12 am on days 1,3, and 7 of treatment: PaO_2, FiO_2, $PaCO_2$, Vt, RR, MV, PEEP, and Pplateau (with a breath hold of 0.2 to 0.3 s).

Alveolar-arterial oxygen gradient was estimated using the formula: $A\text{-}aO_2 = [(AP–PH_2O) \times FiO_2) – (PaCO_2/RQ)] – PaO_2$ (mm Hg),

Where AP is the atmospheric pressure, PH_2O, the partial pressure of water vapor, and RQ, the respiratory coefficient. AP, PH_2O, and RQ were considered to be 760 mmHg, 47 mmHg, and 0.8, respectively.

Table 1. Baseline parameters of non-invasive lung ventilation in the studied groups.

Parameters	Values in groups		*P-value*
	Main, *n*=48	Control, *n*=48	
Age, years (min–max)	53 (31–72)	56 (38–71)	0.216
SAPS II, points (min–max)	47 (37–58)	48 (37–59)	0.465
Sex (F/M), *n*	37/11	35/13	0.281
Moderate ARDS, *n* (%)	33 (68.8%)	35 (72.9%)	—
Severe ARDS, *n* (%)	15 (31.2%)	13 (27.1%)	—
Vt, ml/kg (min–max)	9.7 (6.1–14.2)	5.1 (3.9–6.9)	<0.001
RR, min^{-1} (min–max)	38 (25–45)	30 (25–35)	<0.001
MV, l/min (min–max)	27.7 (12–38)	10.5 (9.3–11.8)	<0.001
$PaCO_2$, mmHg (min–max)	38 (34–43)	43 (37–49)	<0.001
PEEP, cmH_2O (min–max)	10 (8–14)	8 (7–12)	0.072
Plateau pressure, cmH_2O (min–max)	24 (20–27)	25 (22–28)	0.655
CRS, ml/cmH_2O (min–max)	48 (28–70)	30 (23–40)	<0.001
PaO_2/FiO_2, mmHg (min–max)	128 (67–163)	136 (80–167)	0.105
A-aO_2 gradient, mmHg (min–max)	347 (242–514)	351 (271–485)	0.554
VR (min–max)	2.0 (1.6–2.6)	1.5 (1.3–2.0)	<0.001

Note. SAPS II — Simplified Acute Physiology Score; F — females; M — males; ARDS — acute respiratory distress syndrome; V_t — tidal volume; MV — minute volume; $PaCO_2$ — partial pressure of CO_2 in arterial blood; PEEP — positive expiratory end pressure; CRS — compliance of respiratory system; PaO_2/FiO_2 — oxygenation index; A-aO_2 gradient — alveolar-arterial oxygen gradient; VR — ventilation ratio.

Compliance of respiratory system (CRS) was calculated as the ratio of Vt to the difference between Pplateau and established PEEP.

Ventilation ratio (VR) was calculated as the ratio of [MV (ml/min) × $PaCO_2$ (mm Hg)] to [patient weight (kg) × 100 × 37.5].

PaO_2/FiO_2, A-aO_2 gradient, CRS, and VR were calculated on days 1, 3, and 7.

The study materials were analyzed using parametric and nonparametric statistical analysis methods, using STATISTICA 13.3 software (StatSoft Inc.). Accumulation, correction, and synthesis of the initial data as well as the visualization of the results were performed in Microsoft Office Excel 2019 electronic spreadsheets.

The normality of quantitative variable distribution was assessed using the Shapiro–Wilk test. All parameters had a normal distribution. The data were combined into variation series, where arithmetic mean values and standard deviations were calculated. Student's t-test was calculated to compare the mean values. The differences were considered significant at $P<0.05$.

Results

Initially, 164 patients with COVID-19-associated ARDS and 62 patients with non-COVID-19-associated ARDS were included in the study. During statistical analysis and comparison of patients baseline characteristics (age, sex, SAPS II score, disease severity, plateau pressure ($P_{plateau}$), RaO_2/FiO_2 and A-aO_2), 48 patients with COVID-19-associated ARDS were matched against the same number of patients with non-COVID-19-associated ARDS. The main baseline characteristics and ventilator parameters in the groups are shown in Table 1.

Patients with COVID-19-associated ARDS had higher tidal volumes (9.7 versus 5.1 mL/kg, $P<0.001$), respiratory rate (38 versus 30 min^{-1}, $P<0.001$), minute ventilation (27.7 versus 10.5 L/min, $P<0.001$), compliance of respiratory system (48 versus 30 ml/cm H_2O, $P<0.001$), and ventilation ratio (2.0 versus 1.5, $P<0.001$). Hypercapnia was more common in the control group patients ($PaCO_2$ 38 vs. 43 mmHg, $P<0.001$).

Ventilation parameters in patients of both groups on days 1, 3, and 7 of treatment are shown in Table 2. Within the first 24 hours from the study start, 8 (16.7%) patients in the study group were intubated, as were 24 (50%) patients in the control group. On day 3, 6 (12.5%) patients in the main group were intubated, and by day 7, another 2 (4.2%) did so, thus the percentage of intubation in the main group ($P<0.001$) was 33.3% (16 out of 48) within a week, whereas in the control group 3 (6.25%) patients were switched to noninvasive CPAP support on day 3. Only 12.5% (6 out of 48) patients in the study group were completely weaned off noninvasive ventilation, while in the control group this parameter was 20.8% (10 out of 48), with 3 of them (6.25%) were transferred to spontaneous respiration on day 3 of the study, and 17 out of 48 (35.4%) patients were extubated ($P<0.001$). Thus, 14.6% (7 of 48) of patients in the control group remained on invasive lung ventilation on day 7.

Indications for tracheal intubation included hypoxemia ($SpO_2<92\%$), RR over 30 per min, impaired consciousness, and, additionally, increased visible chest excursions and chest X-ray abnormalities. In 3 cases, invasive ventilation in group 1 patients was started due to circulatory failure with the underlying acute myocardial infarction, and in 2 cases it was due to septic shock.

The Vt and MV were almost equal in both groups throughout the study. Respiratory rate

Table 2. Parameters of invasive ventilation in the studied groups.

Parameter	Values in groups					
	Day 1		Day 3		Day 7	
	Main	Control	Main	Control	Main	Control
Spontaneous breathing, *n* (%)	—	—	—	3 (6.25%)	6 (12.5%)	10 (20.8%)
	—		*P*<0.001		*P*<0.001	
Non-invasive ventilation, *n* (%)	40 (83.3%)	24 (50%)	34 (70.8%)	21 (43.75%)	26 (54.2%)	14 (29.2%)
	P<0.001		*P*<0.001		*P*<0.001	
Intubated, *n* (%)	8 (16.7%)	24 (50%)	14 (29.2%)	21 (43.75%)	16 (33.3%)	7 (14.6%)
	P<0.001		*P*<0.001		*P*<0.001	
Extubated, *n* (%)	—	—	—	3 (6.25%)	—	17 (35.4%)
	—		*P*<0.001		*P*<0.001	
V_t, ml/kg	6.1 (5.9–6.8)	6.0 (6.0–6.0)	6.1 (5.9–6.9)	6.0 (6.0–6.1)	6.4 (5.9–7.4)	6.0 (6.0–6.8)
	0.0321		0.210		0.758	
RR, min^{-1}	32 (24–40)	26 (18–35)	28 (25–33)	29 (24–33)	31 (26–35)	26 (20–32)
	P<0.001		*P*=0.884		*P*=0.007	
MV, l/min	11.9 (9.8–13.0)	10.9 (9.3–1.6)	11.5 (10.3–14.2)	11.6 (10–13.2)	12.3 (10.4–14.6)	12.5 (10.4–14.0)
	P=0.059		*P*=0.553		*P*=0.954	
PEEP, см H_2O	8 (6–12)	14 (8–16)	10 (6–12)	10 (7–16)	12 (6–16)	7 (5–14)
	0.004		0.489		<0.001	
P_{lateau} pressure, cm H_2O	24 (21–28)	32 (22–36)	25 (21–28)	26 (20–28)	27 (23–28)	23 (19–28)
	0.007		0.784		0.016	
FiO_2, %	75 (50–100)	60 (50–70)	70 (50–100)	55 (40–70)	60 (40–100)	50 (40–60)
	P=0.021		*P*=0.026		*P*=0.079	

Note. For quantitative parameters, minimal and maximal values are shown. V_t — tidal volume; RR — respiratory rate; MV — minute volume; PEEP — positive expiratory end pressure; FiO_2 — oxygen fraction in the oxygen-air mixture.

among patients on noninvasive ventilation was different between 2 groups: in the main one it was 32 (from 24 to 40), while in the controls it was 26 (from 18 to 35) (*P*<0.001). On day 3 of treatment, the values were equal, and on day 7 increased again in the main group (31 vs 26, respectively, *P*=0.007).

During day 1, the PEEP values were adjusted in the range between 6 and 12 cm H_2O with a mean of 8 cm H_2O in patients from the main group. They were higher in the control group patients due to their specific response to recruitment maneuvers. Further, due to the initiation of invasive lung ventilation with sedation and myoplegia in most patients and adjustment to higher PEEP values, these values demonstrated no differences between the groups (*P*=0.489), but their range (from 7 to 16 cm H_2O) was wider in the control group than in the main one (from 6 to 12 cm H_2O). With progressing COVID-19 pneumonia and decreasing of ventilated lung tissue volume, PEEP values were to be increased and became higher in the study group (12 [6–16] cm H_2O) than in the control one (7 [5–14] cm H_2O) (*P*<0,001).

The PaO_2/FiO_2 values were different between patient groups as early as on day 1 of the study, reaching 170.8 mm Hg in the control group versus 153.5 mm Hg in the main group (*P*<0.001), as they were on day 3 (217.91±68.26 versus 175.0±73.45 mm Hg, *P*<0.001), and on day 7 (268.54±65.23 versus 240.0±63.94 mm Hg) (Fig., *a*).

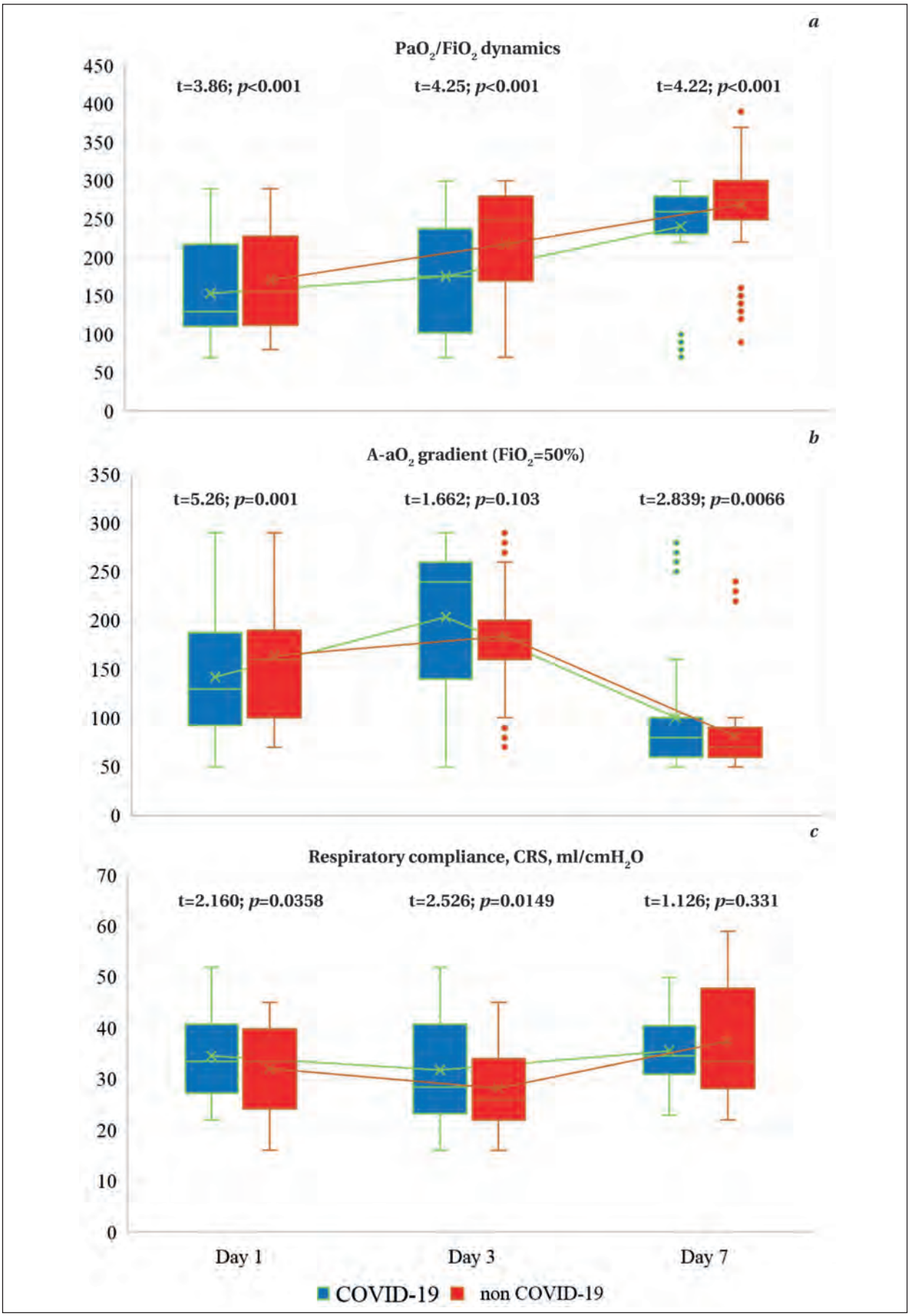
The Figure (*a*) shows that during respiratory therapy there was an increase in PaO_2/FiO_2 both in the control group (from 170.8 to 268.54±65.23 mmHg) and in the main group (from 153.5 to 240.0±63.94 mm Hg), i. e. the parameter was higher on day 3 than on day 1 of the study.

The alveolar-arterial gradient values in the main group were lower on the first day of mechanical lung ventilation than in the control group (142.0±65.75 versus 163.75±68.31) (*P*<0.001), (Fig., *b*). On the third day of mechanical ventilation, this parameter increased in both groups with no significant differences, and on the 7th day, it dropped in both groups, which was probably due to a decrease in the oxygen fraction used, being higher in the main group than in the control one (100.417±62.09 and 81.875±41.95, respectively, *P*=0.0066).

CRS values in the main group were higher than those in the controls on both the 1st and 3rd days of mechanical ventilation (34.521±8.53 versus 32.000±8.61 (*P*=0.0358) and 31.83±10.32 versus 28.125±8.01 (*P*=0.0149), respectively) (Fig., *c*). On day 7, the differences were absent.

Ventilation rate (VR) values were higher in patients in the main group than in the control one on days 1 and 3, but also did not differ between the groups on day 7 of treatment. A decrease in RR during CPAP support could be associated with an increase in Vt and cause higher VR in patients with COVID-19 on the first day of noninvasive lung support.

COVID-19-associated ARDS was initially characterized by higher values of Vt, MV, RR and CRS than non-COVID-19-associated ARDS. Later, during respiratory therapy, patients with COVID-19-associated ARDS, due to higher CRS, required lower



Changes in the studied parameters in the groups of patients.
Notes. PaO_2/FiO_2 – oxygenation index (*a*); A-aO_2 — alveolar-arterial oxygen gradient (*b*); CRS — compliance of respiratory system.

PEEP settings than those with non-COVID-19-associated ARDS, while V_t and MV were almost identical.

It should be emphasized that patients with ARDS associated with COVID-19 required tracheal intubation less frequently at the initial stage of treatment, but on day 7, the proportion of patients receiving invasive ventilation in the study group was higher than in the control group, and no extubation was observed in the main group.

Discussion

Our observations show that the initial (1–5 days) characteristics of COVID-19-associated ARDS change over time and approach those of «typical» ARDS.

L.Gattinoni et al. suggested that relatively high CRS correlating with low PaO_2/FiO_2 can identify a separate subgroup of patients with ARDS associated with COVID-19 requiring a specific algorithm of respiratory support [3, 15]. In contrast, other authors argue that this pattern of respiratory mechanics is just a clinical phenotype which is also seen in patients with ARDS of other etiologies and is determined by severity and stage of the disease [16, 18, 19].

According to the study by O. Voennov et al., two types of clinical hypoxia phenotypes depending on SpO_2 level and dyspnea severity can be distinguished among COVID-19 patients. The first type is characterized by a decrease in saturation down to 93% and an increase in RR up to 25 per minute, and does not require lung ventilation. The second phenotype with RR over 25 and SpO_2 under 93% can associate with arterial hypoxemia and tissue hypoxia with acidosis and requires mechanical ventilation [20].

The H-/L-phenotyping system suggested by L. Gattinoni et al. in patients with ARDS associated with COVID-19 was not confirmed in the studies of LDJ Bos et al. who concluded that lung compliance itself does not correlate with the extent of affected lung tissue, and most patients can be classified neither to H-, nor to L-subphenotype, but have mixed characteristics. Patients were often found to have extensive pulmonary damage and diffuse changes on chest CT, which could indicate potentially recruitable lung tissue. CRS was similar to that in other cohorts of patients with COVID-19 and with non-COVID-19-related ARDS [15, 21–23].

Different pulmonary compliance with initially equal values of blood oxygenation were observed in patients with and without COVID-19, both at baseline and on days 1 and 3 of respiratory support. These differences decreased as the disease progressed, with hypoxemia becoming more severe in patients in the main group, indicating its «discordance» with the lung compliance. The V_t reduction is known to be beneficial mainly in patients with low CRS, therefore, individual adjustment of respiratory support taking with respect to disease severity, airway pressure and lung compliance parameters, and in a continuous mode rather than based on the initial values, is necessary [16, 17, 24, 25].

Our results also argue in favor of systematic assessment of respiratory mechanics and personalization of ventilator settings in patients with COVID-19-associated ARDS.

Previously published studies evaluating COVID-19-associated ARDS respiratory mechanics have shown inconsistent results. For example, pulmonary compliance has been shown to decrease with lung injury volume greater than 50%, as in ARDS of other etiology, but the possibility of alveolar recruitment still exists [8, 9, 15, 16]. The results of our study show that even with more than 50% lung damage, CRS can be both high and low, with respiratory mechanics studied in the early disease, i. e., up to 10 days from onset of the first symptoms of respiratory failure. Patients with varying severity of pneumonia, extent of lung damage, and moderate to severe ARDS were evaluated.

Significantly higher CRS measured on day 1 in patients with COVID-19 compared to those without COVID-19 is consistent with previous reports [18].

The evidence of greater pulmonary compliance during the first day of mechanical ventilation in patients with ARDS and COVID-19 compared to patients without COVID-19 is also in line with earlier findings [18].

High parameters of PEEP can cause excessive alveolar distention and increased physiological dead space, indirectly affecting VR and CRS. Thus, Yaroshetskiy A. I. et al. observed low potential of lung recruitment and response to PEEP increase in COVID-19 patients, and PEEP over 10 cm H_2O after 7 days resulted in lung overextension in most patients on mechanical ventilation [26].

Therefore, the identified patterns of respiratory mechanics to a greater extent reflect the differences in ventilator management than in pathophysiology of ARDS of various etiologies. In addition, the progression of any disease leading to tracheal intubation can neutralize the specific characteristics of respiratory biomechanics (including situations with practically identical initial PaO_2/FiO_2). The patients in the main group had more significant decrease of arterial blood oxygenation than those in the control group, which confirms the «discordance» between hypoxemia and lung compliance, and suggests that V_t reduction is mainly beneficial for patients with low CRS and good response to low PEEP.

Conclusion

We conclude that the management of patients with COVID-19-associated ARDS should be based on individual changes in disease severity, airway pressure, and lung compliance values.

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Structural and Functional Reorganization of the Sensorimotor Cortex During Ligation of the Common Carotid Arteries (Experimental Study)

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Summary

Aim of the study. To explore the structural and functional changes of neurons, glial cells, and synaptic terminals in layers I, III, and V of the sensorimotor cortex (SMC) of the rat brain after bilateral common carotid artery ligation (CCAL).

Material and methods. Incomplete cerebral ischemia was simulated by irreversible bilateral CCAL (2-vessel model of global ischemia without hypotension) on white rats (n=36). Comparative evaluation of the studied SMC structures was performed in the control group (intact rats, n=6) on days 1, 3, 7, 14, and 30 (n=30) after CCAL. Nissl, hematoxylin-eosin staining, and immunohistochemical reactions for NSE, MAP-2, p38, GFAP, and IBA1 were used. Numerical density of pyramidal neurons, astrocytes, oligodendrocytes, microglial cells, and relative area of p38-positive material (synaptic terminals) were determined. Statistical hypotheses were tested using nonparametric methods with Statistica 8.0 software.

Results. After CCAL, the number of degenerative neurons in rat brain SMCs increased. The peak of numerical density of unshrunken neurons was detected after day 1. Later, the numerical density of hyperchromic unshrunken neurons decreased, while that of shrunken neurons increased. These parameters did not reach the control values. The changes in SMC neurons were accompanied by an increase in the numerical density of microglial cells after day 1 and its subsequent decrease. Immunohistochemistry for IBA1 revealed signs of microglial cell activation such as change in shape and loss of processes. Maximum increase in the SMC density of oligodendrocytes was observed on day 7, and that of astrocytes on day 14 after CCAL. The maximum number of NSE-positive neurons occurred on day 1 after CCAL. There was a significant decrease in the number of NSE-positive neurons in SMC layer III on days 3, 7, and 14, and an increase in the number of NSE-positive neurons on day 30. The number of NSE-positive neurons in layer V of the SMC progressively decreased throughout the whole study period. The evolution of changes in the proportion of p38-positive material (synaptic terminal area) differed significantly between the layers of SMC. In the layers I and III, this parameter first decreased

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(days 1 and 3) and then increased (days 7, 14, and 30). In layer V of SMC, the activation of the protein expression was observed in the acute phase (days 1 and 3), then it decreased on days 7 and 14, and increased again on day 30. The changes found in the numerical density of neurons, glial cells and synaptic terminals were associated with dehydration and overhydration of SMC. We found strong to medium significant associations between the relative area of terminals and neuropil swelling and edema zones.

Conclusion. After CCAL, layers I, III, and V of the SMC of white rats revealed destructive and compensatory changes in neurons, glial cells, and inter-neuronal communication structures. Taken together, all these changes indicate a significant layer-by-layer variability of the neural tissue response to CCAL. Layer III (secondary projection complex) of the SMC was affected to a greater extent. Reorganization of neuronal-glial and interneuronal interrelations occurred along with a prominent neuropil overhydration.

Keywords: ischemia; swelling and edema; neurons; synapses; sensorimotor cortex; immunohistochemistry; morphometrics

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

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Introduction

The structural and functional organization of mammalian sensorimotor cortex (SMC) is well studied. Powerful bi- and polysynaptic connections between its layers and modules have been described in the literature [1–4].

The structure and functions of neurons, glial cells and inter-neuronal communication systems (dendrites, synapses) of SMC can be altered as a result of ischemia. These changes lead to reorganization of inter-neuronal and neuroglial interactions [5–7]. We have previously shown that irreversible bilateral ligation of common carotid arteries (LCCA) caused an increase in the numerical density of abnormal neuronal forms (hypochromic, hyperchromic shrunken/non-shrunken neurons, ghost cells) and appearance of neurons with pericellular edema in SMC starting from day 1 after LCCA. However, neuronal response and neuroglial interaction were not identical in different layers. Thus, in layer III of SMC, the numerical density of irreversibly altered neurons (hyperchromic shrunken) progressively increased and reached its maximum values 30 days after LCCA, while in layer V of SMC the number of irreversibly altered neurons decreased after 14 and 30 days compared to the previous time intervals [8, 9].

Ischemic damage of the brain neurons entails severe neurological consequences. Therefore, special attention has been focused on the studies of cerebrovascular diseases, which are the main cause of mortality worldwide [10–12]. Comprehensive morphological and morphometric studies of neurons, glial cells and inter-neuronal communication structures are required for a more detailed insight into the neural tissue response to ischemia and defense mechanisms ensuring neuronal survival in ischemia. Therefore, the aim of our study was to compare the histological and immunohistochemical data characteristic of structural and functional changes in neurons, glial cells and synaptic terminals in layers I, III and V of rat brain SMCs after bilateral LCCA. Special emphasis was placed on determining the role of overhydration of neuropil where the synapses, neuronal and astrocytic processes are localized.

Material and Methods

The study was carried out at Omsk State Medical University (approved by the University Ethics Committee, protocol 123, October 9, 2020). White Wistar rats weighing 250–300 g were used as experimental animals. Studies were conducted in accordance with the guidelines of the International Committee on laboratory animals supported by WHO, the European Parliament Directive 2010/63/EU of 22.09.2010 «On protection of animals used for scientific purposes».

The experiment was performed on sexually mature male Wistar rats (n=36). After premedication (atropine sulfate 0.1 mg/kg, subcutaneously), the animals were injected with Zoletil 100 (10 mg/kg, intramuscularly). Incomplete global cerebral ischemia was simulated by irreversible bilateral LCCA (2-vessel model of subtotal ischemia, without hypotension). Intact rats (n=6) served as a control. The animals were withdrawn from the experiment 1, 3, 7, 14, and 30 days after LCCA (n=30) under anesthesia (Zoletil 100). The cerebral vasculature was flushed by injecting 100–125 ml of 0.9% NaCl solution and Fragmin (5000 units) into the left ventricle of the heart and fixated by perfusion with 30 ml of 4% paraformaldehyde solution in phosphate buffer (pH 7.2–7.4) through the aorta at 90–100 mm Hg for 15 min. The brains were placed in 4% paraformaldehyde solution and stored in the refrigerator at + 4°C. One day later, the obtained material was embedded in homogenized paraffin (HISTOMIX®) using an STP 120 machine. Serial frontal sections (4 μm thick) were prepared using an HM 450 microtome (Thermo) at the SMC level, that is 1.2 to (–3.0) mm from bregma [13].

General qualitative evaluation of neural tissue and determination of the numerical density of neurons (only neurons with visible nuclei were counted) and glial cells were performed on preparations stained with thionine according to the Nissl method. Neuron identification was performed by the histochemical reaction for neuron specific enolase (NSE) using rabbit polyclonal antibodies at 1:100 dilution (PA5-27452), to identify glial fibrillary acidic protein (GFAP) of astrocytes for astrocyte identification and cytoskeleton studies (MA5-12023), the murine IgG1

monoclonal antibodies (clone ASTRO6) were used. The antibodies to IBA1 for identification of microglia by the calcium-binding protein specific for microglia (PA5-21274) were detected using tje rabbit polyclonal antibodies, 1: 100 dilution (all the above manufactured by ThermoFisher, USA). The neuronal cytoskeleton was studied using the immunohistochemical reaction for MAP2 (microtubule-associated protein 2, ab32454), rabbit polyclonal antibody, 1 μg/ml dilution (Abcam, USA). Synaptic terminals were studied using synaptophysin (p38) (PA0299) using the murine monoclonal antibody, clone 27G12, ready-to-use (Bond Ready-to-Use Primary Antibody; Leica Biosystems Newcastle Ltd, UK).

After reaction with primary antibodies, the sections were incubated with appropriate secondary antibodies, DAB (3,3'-diaminobenzidine) chromogen, stained with hematoxylin, and embedded in polystyrene. A NovolinkTM (DAB) Polymer Detection System (Leica Biosystems Newcastle Ltd, United Kingdom) multimeric kit was used for imaging. The preparations were made in accordance with the instructions of the reagent manufacturer.

Images were taken using a Leica DM 1000 microscope (GXCAM-DM800 Unique Wrap-Around 8MP AUTOFOCUS USB, pixel size 1.4×1.4 μm) and saved as tiff files (2592×1944 pixels) with subsequent upscaling using Photoshop CC (to 3780×2835 pixels/cm, 600 pixels/inch resolution).

In order to achieve maximum contrast and sharpness of the image, image adjustment was performed using a Camera Raw filter (contrast, white balance, and sharpness) in Photoshop CC. Morphometric examination was performed using ImageJ 1.53 software.

Enhance Contrast filter (https://imagej.nih.gov/ij/docs/menus/process) with subsequent image processing in Threshold (selection of synaptophysin labels and edema areas) was used to detect p38-positive terminals and edema and swelling zones in neuropil. Selection was performed for each ROI (20×20 μm) manually (Over/Under). Later, histograms of pixel distribution by brightness were plotted, and the obtained results (List) were transferred to Excel for further processing. Twenty ROIs were selected per time point using a random number generator.

Statistical hypotheses were tested using nonparametric criteria such as paired comparison (Mann–Whitney *U*-test, Wilcoxon test), analysis of variance (ANOVA Kruskal–Wallis, Friedman test),

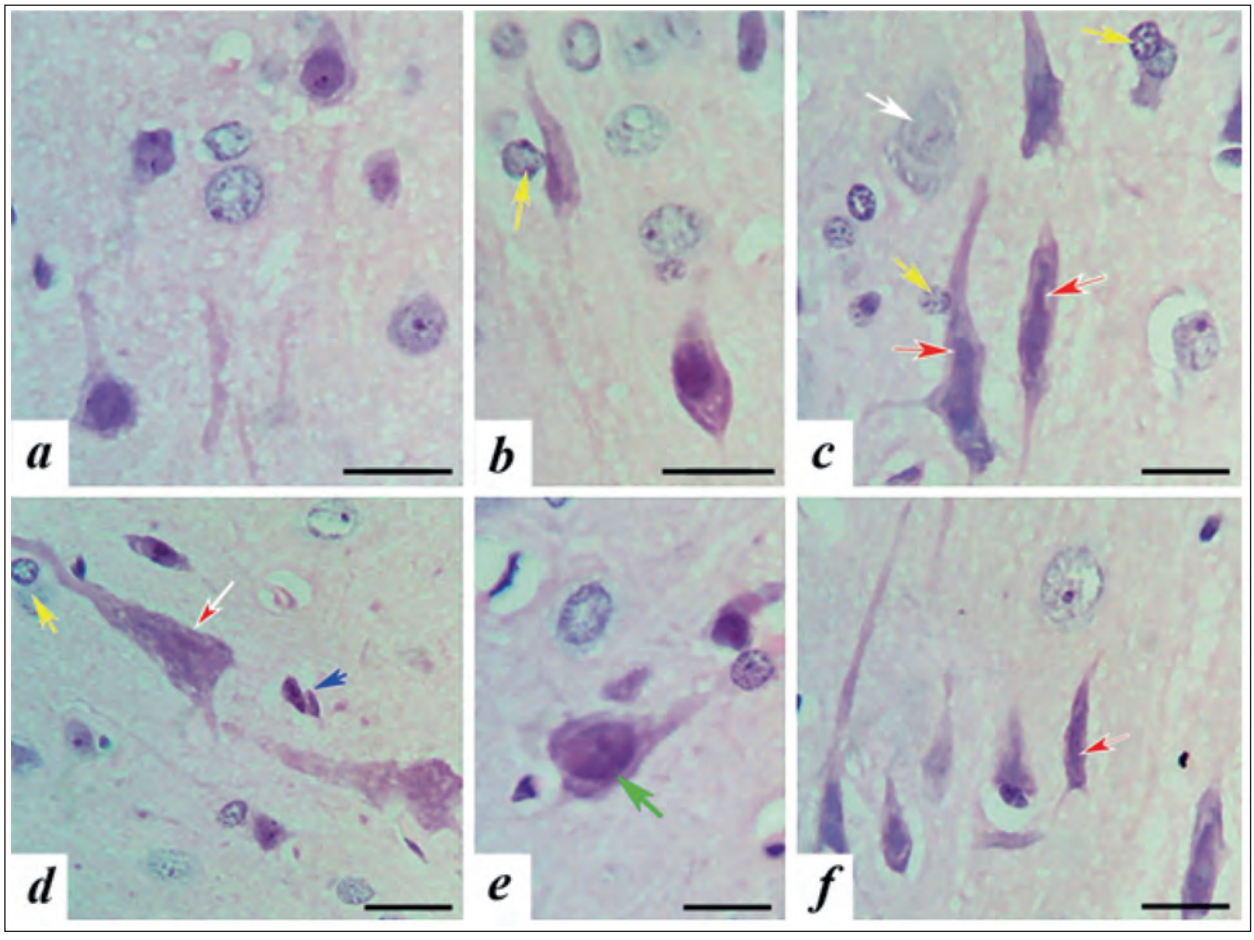

Fig. 1. Pyramidal neurons of layers III (*a, b*) and V (*c–f*) SMC at different stages of destruction after LCCA.
Note. Hyperchromic non-shrunken neurons (green arrows); shrunken neurons (red bars); ghost cells (white arrows); gliocytes (yellow arrows); microgliocytes (blue arrows). Hematoxylin-eosin staining, magnification ×100, scale 20 μm.

paired correlation analysis (Spearman method). Multiple regression analysis was used to assess the influence of the compared variables on each other. Independence of the observations was tested using the Durbin–Watson criterion. Statistica 8.0 software package (StatSoft, USA) was used. Quantitative data in the study were presented as medians (Me — 50% quartile, Q2), interquartile ranges (Q1–Q3 — 25–75% quartiles), (Min–Max), percentages (%) [14].

Results and Discussion

Previously, we found that normochromic neurons predominated in layers III and V of SMCs of control animals. There were no signs of hydropic degeneration (vacuolization of nuclei and cytoplasm, edema and swelling), necrosis (colliquative and coagulative) and reactive gliosis [8, 9].

After LCCA, layers III and V of SMC showed *in vivo* reversible and irreversible changes in neurons corresponding to different stages of degeneration. These changes were observed in the cytoplasm and nucleus of pyramidal neurons (vacuolation, homogenization of cytoplasm, changes in perikaryon and nuclear shape, hypo- and hyperchromia of nuclei and cytoplasm, karyolysis) and were accompanied by edema and swelling. Reversibly damaged neurons did not demonstrate any gross destruction of nucleus and cytoplasm, their nuclei were preserved, but had altered staining properties (hyperchromic non-shrunken neurons). Pyramidal neurons with reversible changes were found in layers III and V of the SMC during the entire study period (Fig. 1, *a–f*).

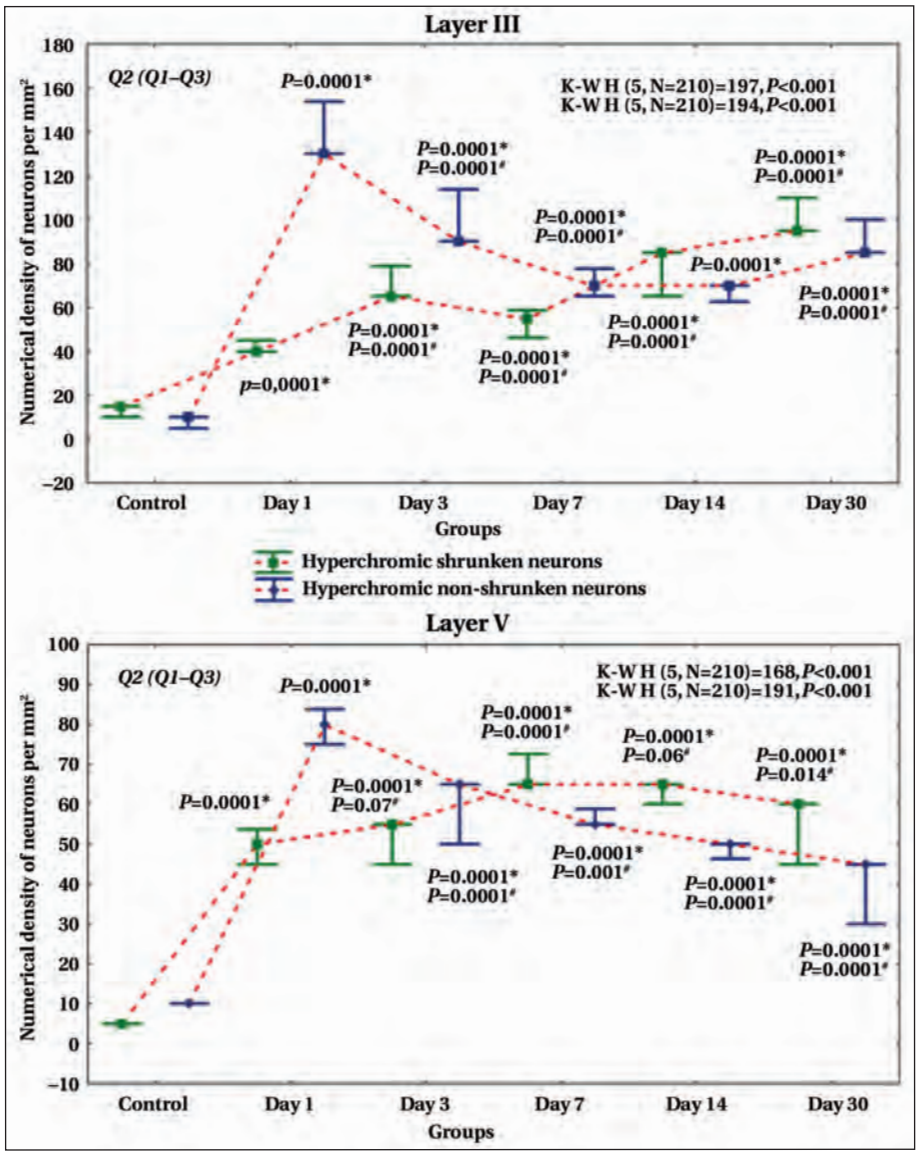

Fig. 2. Numerical density of hyperchromic non-shrunken and shrunken neurons in layers III and V SMC in the control, 1, 3, 7, 14 and 30 days after LCCA.

Note. * — vs the control; # — vs the previous time point (Mann–Whitney *U*-test). Differences were considered significant at $P<0.05$. Data presented as medians (Q2) and 25–75% quartiles (Q1–Q3). Differences between all time points after LCCA are significant based on the ANOVA Kruskal–Wallis test (K–W).

The numerical density of hyperchromic non-shrunken neurons in layer III SMC was not the same at different study periods, reaching its maximum values 1 day after LCCA, and a significant decrease in the numerical density of hyperchromic non-shrunken neurons in layer III SMC was noted on days 3–14, followed by a significant increase on day 30 vs the previous day (Fig. 2, *a*). In layer V of the SMC, the numerical density of hyperchromic non-shrunken neurons peaked 1 day after LCCA and significantly decreased by day 30 of the study, reaching the lowest values for the entire study period (Fig. 2, *b*).

Irreversible *in vivo* degeneration of neurons manifested as intense eosinophilia of the nucleus and cytoplasm, karyopyknosis, loss of nuclear boundaries, cytoplasm homogenization and reduction of the nucleus and perikaryon size (hyperchromic shrunken neurons and ghost cells) when stained with hematoxylin-

eosin (Fig. 1). The numerical density of hyperchromic shrunken neurons in layer III of the SMC was higher than the control values throughout the study period. In the acute period of ischemia (days 1 and 3), their significant increase in layer III of SMC was seen as compared to controls, on day 7, their density decreased (by 15.4% as compared with day 3), and on days 14 and 30, their density increased vs day 7, with a peak on day 30 after LCCA (Fig. 2, *a*). The maximum increase in the number of shrunken neurons in layer V of the SMC was observed on day 7 after LCCA. On days 14 and 30, there was a significant decrease in the number of shrunken neurons as compared to the previous day (Fig. 2, *b*).

After LCCA, the reorganization of glial cells was observed, manifesting as a change in their numerical density and neuroglial ratio. Thus, the maximum numerical density of microglial cells in layers III and V of SMC was observed after day 1, that of astrocytes after day 14, and that of oligodendrocytes after days 7 and 14 (layer III) and 7 (layer V) (Fig. 3).

After days 1 and 3, activation of microglial cells probably occurred, which manifested as a changing the shape of the cells to round or oval and loss of the processes. These changes were detected in IBA1-positive material (Fig. 4 *c, d*). Similar causal relationships have been noted in the literature. Thus, as a result of activation, a change in the shape of microglial cells to oval with the loss of processes was suggested to facilitate the movement of glial cells [15–17]. These changes are necessary for nerve tissue repair after ischemic damage. An increase in the numerical density of oligodendrocytes was observed. The maximum numerical density of these cells was detected 7 and 14 days after LCCA (Fig. 3).

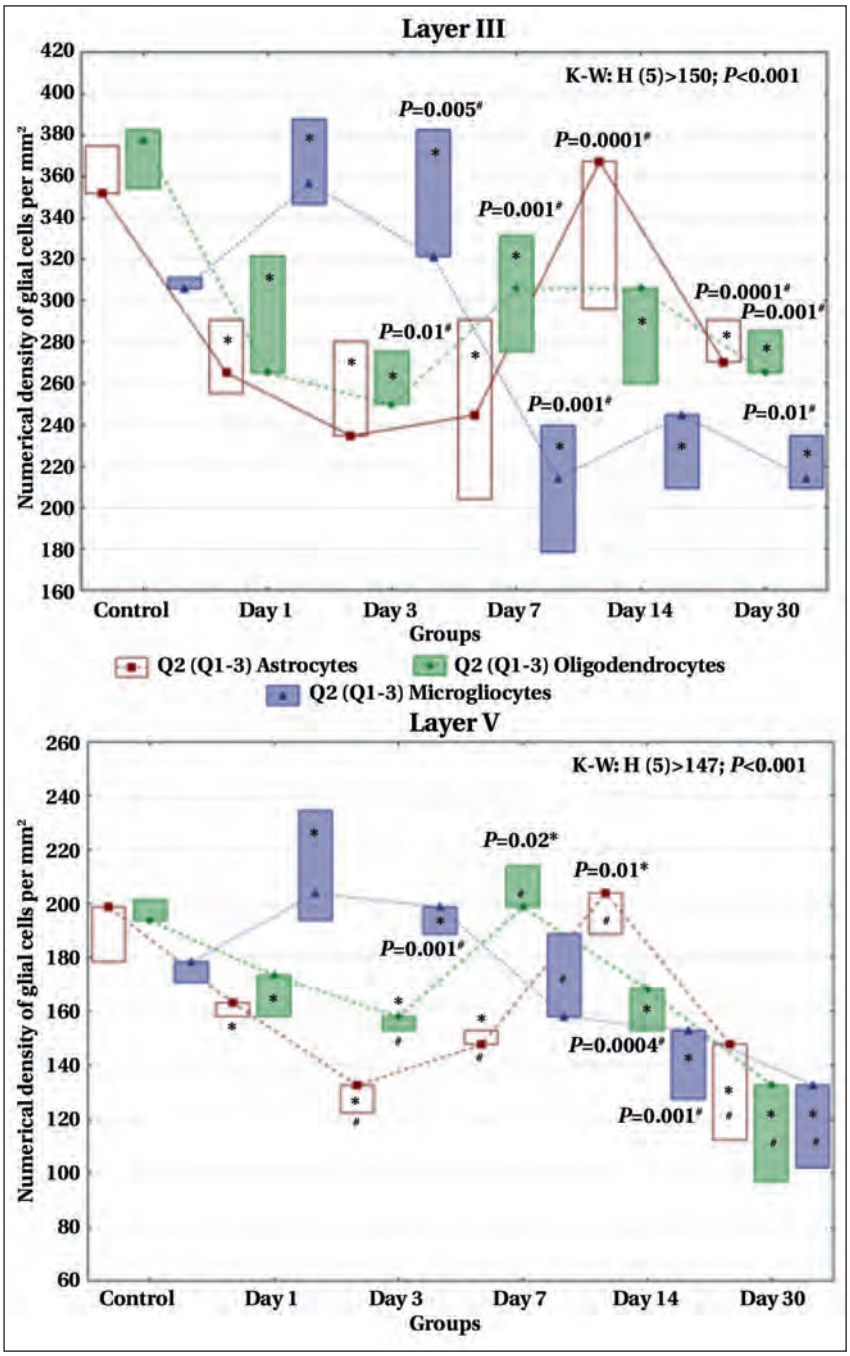

Fig. 3. Numerical density of astrocytes, oligodendrocytes and microgliocytes of layer III and V SMC in the control group and after irreversible bilateral LCCA on days 1, 3, 7, 14, and 30.

Note. * — pairwise comparison vs the controls; # — vs the previous time point (Mann–Whitney *U*-test). Separate asterisk and tick indicate *P*=0.0001. Data presented as medians (Q2) and 25–75% quartiles (Q1–3). Differences between all the time points after LCCA were significant based on the ANOVA Kruskal–Wallis (K–W) test. The differences were considered significant at *P*<0.05.

The peak of astrocyte numerical density was observed 14 days after LCCA in layers III and V of the SMC. Starting 1 day after LCCA, hypertrophy of astrocyte processes was observed (Fig. 4, *a, b*). Astrocytes are known to be involved in the regulation of extracellular levels of glutamate, gamma-aminobutyric acid, adenosine and synaptic plasticity [18, 19].

According to the literature, astrocyte hypertrophy results from their response to impaired ion homeostasis and energy balance after LCCA. In re-

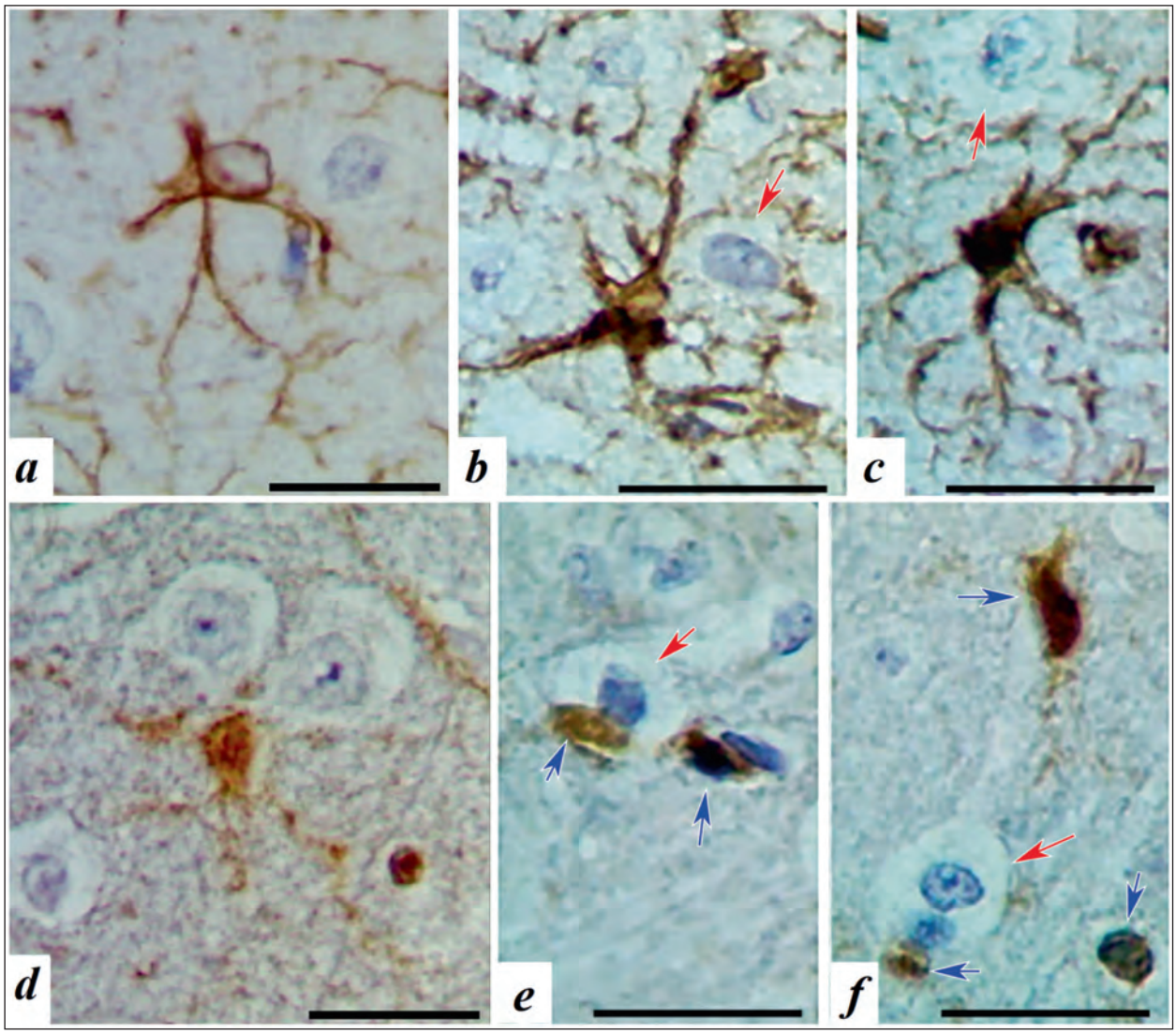

Fig. 4. Astrocytes (*a, b, c*) and microgliocytes (*d, e, f*) of layer III SMC in the control group (*a, d*) and on day 1 after LCCA (*b, c, e, f*).
Note. Astrocytes around pyramidal neurons (red arrow); process hypertrophy; elongated shape of microgliocyte bodies (blue arrow). Staining: GFAP reaction (*a, b*), IBA1 reaction (*c, d*). Magnification ×100; scale 20 μm.

sponse to ischemic damage, astrocytes try to stabilize the balance of substances and fluid in the intercellular space [20]. The activation of all glial cells as components of a single integrated cellular reparation system of the brain has been suggested. Probably, it is necessary for protection and repair of the nervous tissue after ischemic damage following irreversible bilateral LCCA and can promote activation of undamaged neurons and functional replacement of the dead neurons [21–23].

According to the morphometric study of NSE-positive material in layers III and V of the SMC, the maximum increase in the proportion of NSE-positive neurons was observed in the acute phase of ischemia (after day 1). A significant progressive decrease in the proportion of NSE-positive neurons was detected in layer III of the SMC on days 3–14 after LCCA as compared to day 1, and an increase was recorded after day 30 as compared to the previous day (Fig. 5).

These changes were associated with the significant increase in the numerical density of hyperchromic non-shrunken neurons (Fig. 2), which probably indicates an increase in NSE expression in neurons 30 days after LCCA [24, 25]. The proportion of NSE-positive neurons in layer V of the SMC throughout the study period (1, 3, 7, 14 and 30 days after LCCA) was significantly higher than in the controls (Fig. 5).

Immunohistochemical studies (p38) have shown that synaptic terminals in all SMC layers were distributed in the neuropil (axodendritic), perikaryons (axosomal), and large dendrites (axodendritic and axospinous synapses) of pyramidal neurons (Fig. 6, *a–c*). At the same time, different densities of this synaptic protein were visually observed in the layers of control animals and after LCCA. The differences in the layers were related to the specifics of their organization with the prevalence of neuropil and

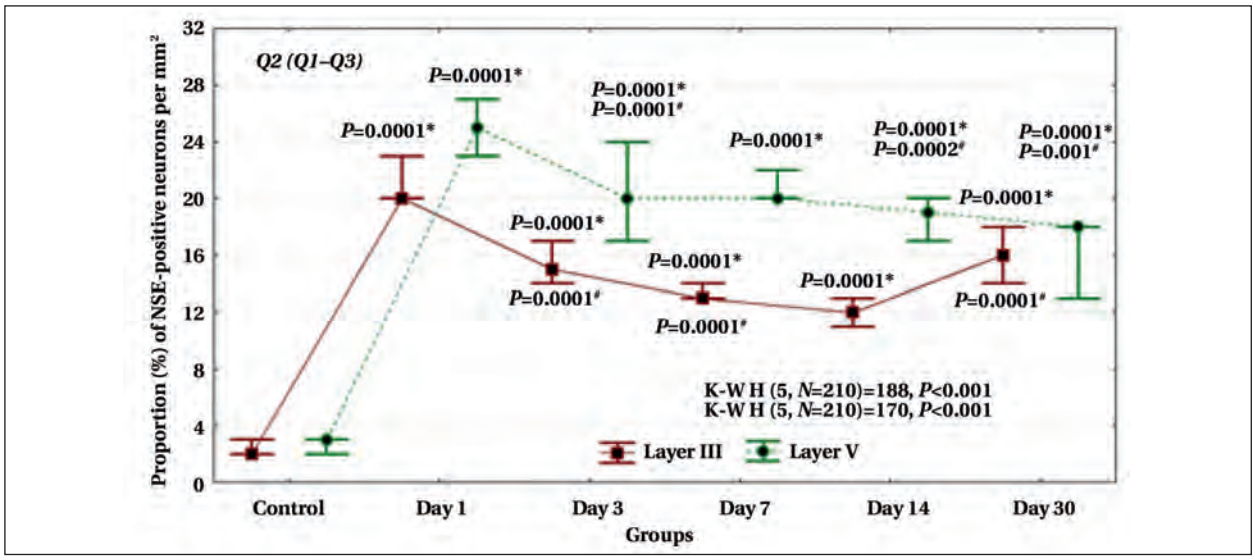

Fig. 5. Proportion (%) of NSE-positive neurons in layers III and V SMC in the control group and after LCCA.
Note. * — pairwise comparison with the control; # — vs the previous time point (Mann–Whitney *U*-test). Separate asterisk and tick indicate *P*=0.0001. Data presented as medians (Q2) and 25–75% quartiles (Q1–3). Differences between the time-points after LCCA were significant based on the ANOVA Kruskal–Wallis (K–W) test. The differences were considered significant at *P*<0.05.

apical dendrites of the underlying pyramidal neurons in the molecular layer. Small and large edema and swelling foci in the compared layers could also be visually identified. They appeared as areas of maximum image brightness (Fig. 7, *a–e*; Fig. 8, *a–e*).

Using the analysis of pixel distribution histograms of neuropil images (zones of interest of 400 μm²) we identified the relative area of terminals and edema and swelling zones. The main steps of this approach are shown in the Fig. 9.

Significant changes in the studied morphometric independent variables vs the control and over the follow-up period (days 1–30) were revealed (see Table). Peaks of increase in the relative area of terminals and edema and swelling zones were observed, as well as correlations between them.

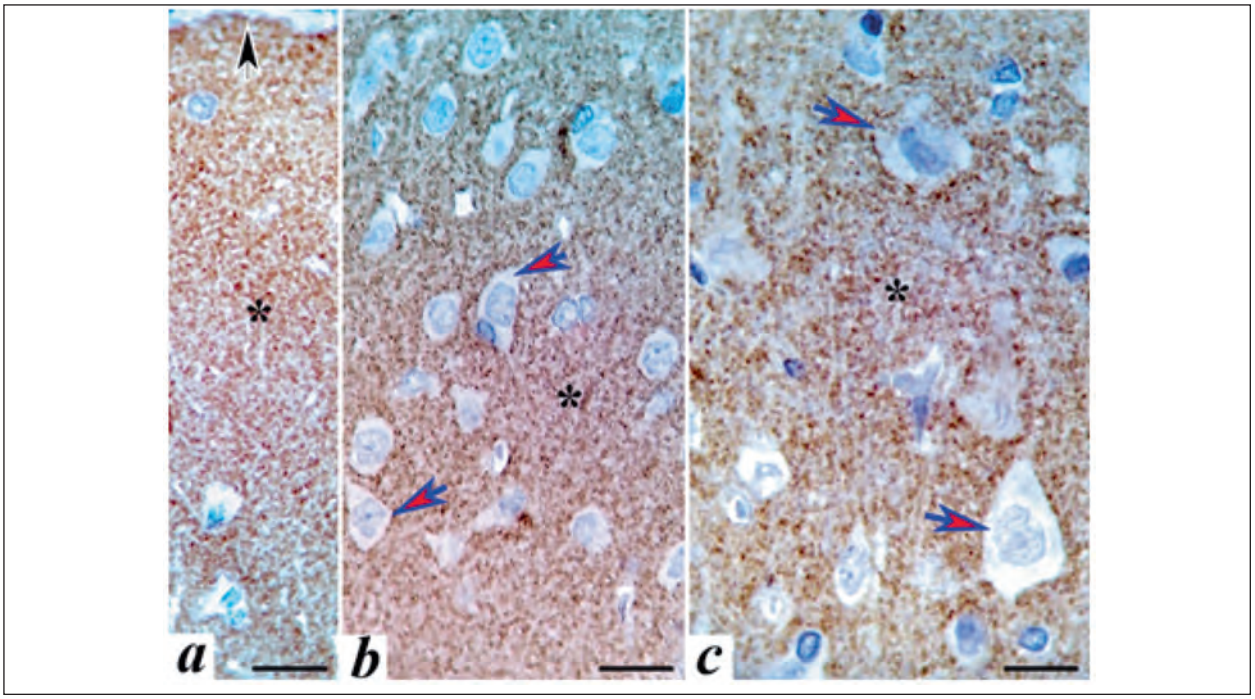

Fig. 6. Neuropil (*) and neurons (red arrows) of layers I (*a*), III (*b*) and V (*c*) SMC of rats after staining for a specific neuronal protein of synaptic terminals (synaptophysin, brown granules).
Note. *a, b* — control; *c* — day 1 after LCCA. Black arrow indicates the outer (pial) surface of layer I. Immunohistochemical staining for synaptophysin, hematoxylin counterstaining. Magnification ×100, scale 20 μm.

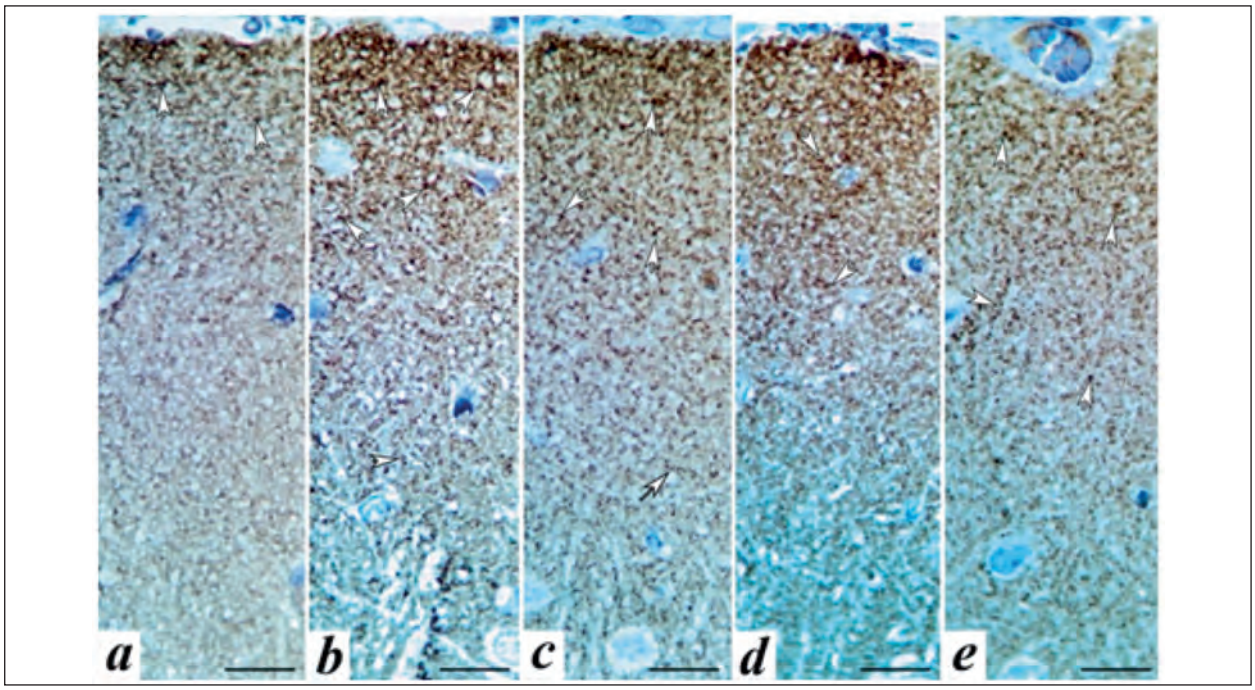

Fig. 7. Neuropil of layer III of SMC in rats on days 1 (*a*), 3 (*b*), 7 (*c*), 14 (*d*), and 30 (*e*) after LCCA.
Note. Different density of p38-positive terminals (arrows) and small vacuoles (light rounded). Immunohistochemical reaction for synaptophysin, hematoxylin counterstaining. Magnification ×100, scale 20 μm.

Using Friedman's ANOVA (multiple comparisons of the related variable), we found significant differences in the relative area of p38-positive material (synaptic terminal area) in the compared SMC layers (df=2) in all groups. The maximal differences were noted in the acute phase, when the highest values of the χ^2 criterion and the lowest p-values were observed. Thus, χ^2 was 6.9 (P=0.03) in the controls, 15.2 (P=0.001) on day 1, 5.2 (P=0.001) on day 3, 11.4 (P=0.003) on day 7, 12.8 (P=0.002) on day 14, and 10.9 (P=0.004) on day 30.

Analysis of the relative area of neuropil edema and swelling of the compared layers also showed greater differences in this variable in the acute

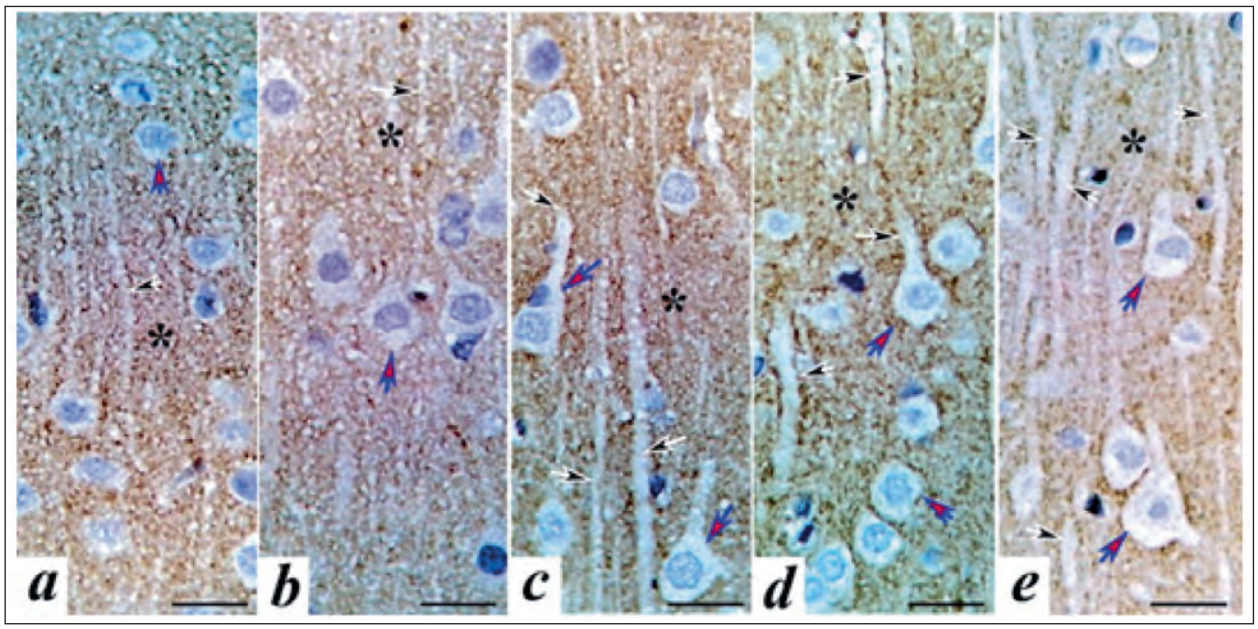

Fig. 8. Neurons (red arrows), dendrites (black arrows), and neuropil (*) of layer III of rat SMC on days 1 (*a*), 3 (*b*), 7 (*c*), 14 (*d*), and 30 (*e*) after LCCA.
Note. Different density of p38-positive terminals (brown particles) and small vacuoles (light rounded) is shown. Immunohistochemical staining for synaptophysin, hematoxylin counterstaining. Magnification ×100, scale 20 μm.

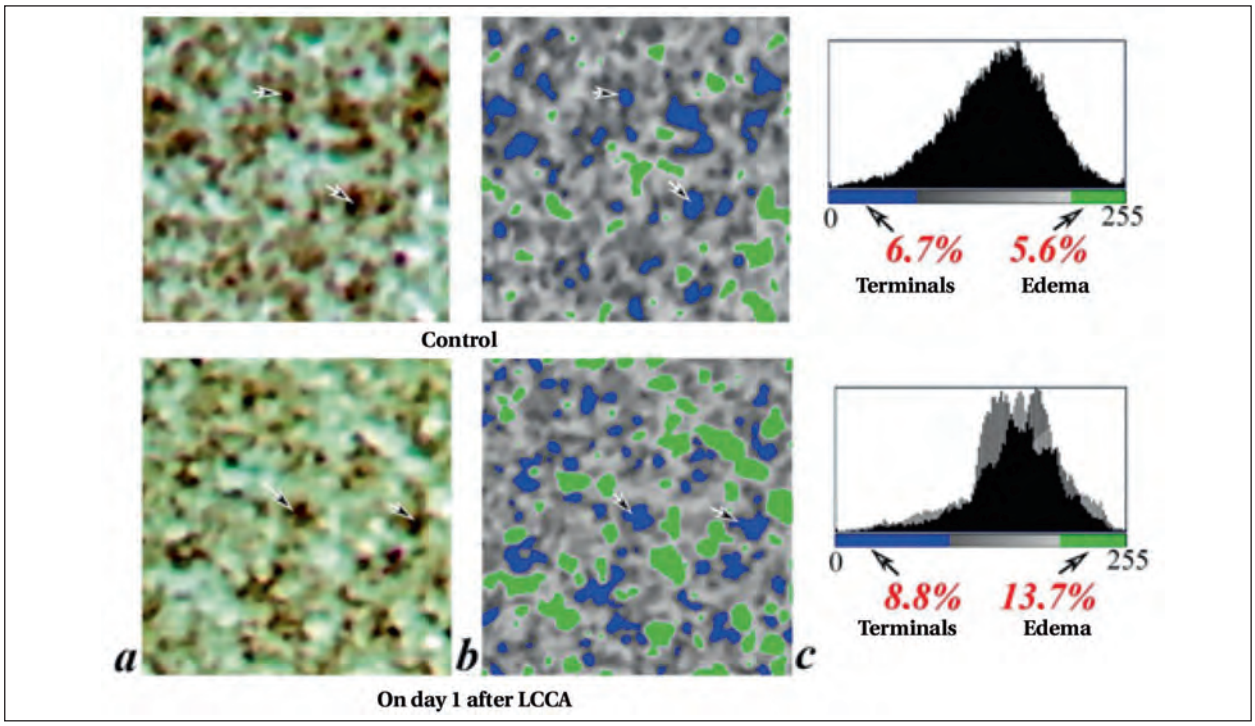

Fig. 9. Main stages of assessment of the relative area of terminals and small foci of edema (%) in the neuropil of layer I of rat SMC using the ImageJ 1.53 software.

Note. *a* — initial ROI (400 μm², RGB, Enhance Contrast filter); *b* — after image processing in Threshold (selection of synaptophysin labels and edema foci); c — distribution histogram of ROI image pixels with indication of their number and brightness. Arrows pointing at ROI indicate terminals at different stages of analysis. Terminals are stained blue, foci of edema, green. Immunohistochemical reaction for synaptophysin, hematoxylin counterstaining. Magnification ×100, scale on the ROI side 20.0 μm (area, 400 μm²).

phase of disease: χ^2 was 2.1 (P=0.4) in the control group, 20.0 (P=0.0001) on day 1, 18.2 (P=0.0001) on day 3, 13.4 (P=0.001) on day 7, 15.8 (P=0.0004) on day 14, 2.7 (P=0.26) on day 30. A paired comparison allowed us to reject the null hypothesis for these variables (Table 1, Wilcoxon test). In the neuropil of the studied layers 30 days after LCCA, there could be a partial restoration of water and ionic balance of SMC cells.

According to paired Spearman correlation analysis of the entire observation period (1–30 days), a strong and weak negative relationship (r=–0.52, P=0.0000 and r= –0.47, P=0.004, respectively) was found between the independent variables (relative area of terminals and neuropil edema and swelling areas) in layers I and III of SMC. A moderate positive relationship was seen in the layer V of SMC (r=0.54, P=0.0004). This could be due to the relation between the SMC layer and changes in terminal area and edema and swelling zones after LCCA. In the control values (for all layers), no significant relationships between these variables were found.

Importantly, a moderate positive correlation (r=0.58, P=0.02) on day 1 after LCCA and a negative correlation at other timepoints (r=–0.59, P=0.02 on day 3, r= –0.56, P=0.02 on day 7, r=–0.64, P=0.04 on day 14, and r=–0.50, P=0.04 on day 30) was found in layer I of SMC. For layer III of SMC, significant temporal correlations were found only after day 3 (r=–0.94, P=0.005), but their character was identical to that of layer I of SMC. This probably indicated a change in the causal relationships in these layers after day 3 or the new discriminative factors, such as compensatory increase in the new synaptic vesicles and terminals and hypertrophy of astrocyte processes. The layer V of SMC was characterized by a strong negative (r=–0.90, P=0.0003) correlation after day 3 and moderate negative correlation (r=–0.68, P=0.03) after day 7. Thus, we can assume that days 3 and 7 after LCCA were a certain breakpoint when the change in the domination of damage and recovery processes occurred. These changes followed a specific pattern depending on layer, which was confirmed by the character and strength of correlation during specific time periods.

The multiple regression analysis showed that on day 3 after LCCA (period of maximum strength relationship between the variables), a 1% change in the area of edema and swelling zones resulted in the following changes in terminal area: 0.57% in layer I of SMC, 0.31% in layer III of SMC, and 0.72% in layer V SMC. The coefficient of determination of regression models was 34% (P=0.02), 72% (P=0.03) and 80% (P=0.01), respectively. The Durbin-Watson criterion was 1.5–2.0 (acceptable range from 1 to 3), which indicated the reliability of the results.

Relative areas of p38-positive synaptic terminals and small foci of edema and swelling of the neuropil of various layers of rat SMC in normal animals and after LCCA, *Q2* (*Q1–Q3*).

Groups	The sensorimotor cortical levels and parameter values					
	Layer I		Layer III		Layer V	
	RAT	RAES	RAT	RAES	RAT	RAES
Control	12.8 (10.8–15.2)	9.6 (7.9–10.7)	7.95 (7.6–8.4) *P*=0.02$^{I–III}$	8.8 (7.1–9.7)	7.9 (7.4–8.2) *P*=0.01$^{I–V}$	7.2 (6.9–8.5) *P*=0.02$^{I–V}$
Day 1	11.4 (8.8–14.3)	17.3 (15.1–19.6) *P*=0.0001*	5.2 (4.7–7.2) *P*=0.001* *p*=0.001$^{I–III}$	29.7 (27.9–31.7) *P*=0.0000* *P*=0.005$^{I–III}$	12.0 (11.0–13.0) *P*=0.0003* *P*=0.005$^{III–V}$	14.5 (10.6–16.4) *P*=0.0004* *P*=0.005$^{I–V}$ *P*=0.005$^{III–V}$
Day 3	9.2 (7.0–11.7) *P*=0.04*	20.2 (14.5–21.3) *P*=0.0001*	4.0 (2.8–4.5) *P*=0.0001* *P*=0.01** *P*=0.001$^{I–III}$	23.7 (22.5–28.9) *P*=0.0001* *P*=0.019**	13.5 (11.8–14.6) *P*=0.0002* *P*=0.005$^{III–V}$	12.8 (11.5–15.2) *P*=0.0002* *P*=0.01$^{I–V}$ *P*=0.005$^{III–V}$
Day 7	15.1 (9.2–18.9) *P*=0.03**	12.8 (10.5–17.0) *P*=0.007* *P*=0.006**	6.7 (5.7–6.9) *P*=0.02* *P*=0.0004** *P*=0.002$^{I–III}$	16.9 (13.7–18.6) *P*=0.0001* *P*=0.001** *P*=0.02$^{I–III}$	9.8 (9.0–10.1) *P*=0.02* *P*=0.001** *P*=0.01$^{I–V}$ *P*=0.03$^{III–V}$	8.2 (7.7–8.9) *P*=0.03* *P*=0.001** *P*=0.005$^{III–V}$
Day 14	18.9 (13.4–23.4) *P*=0.01*	9.8 (8.4–10.6) *P*=0.01**	5.5 (4.4–9.8) *P*=0.001$^{I–III}$	21.0 (18.5–23.4) *P*=0.0001* *P*=0.005** *P*=0.005$^{I–III}$	9.8 (8.5–10.6) *P*=0.01* *P*=0.04$^{I–V}$ *P*=0.04$^{III–V}$	11.2 (7.8–12.1) *P*=0.001* *P*=0.005$^{III–V}$
Day 30	16.2 (12.5–24.0)	9.7 (8.1–14.1)	8.4 (7.2–10.6) *P*=0.049** *P*=0.007$^{I–III}$	15.0 (11.5–18.4) *P*=0.0001* *P*=0.01**	12.4 (12.3–12.8) *P*=0.0002* *P*=0.001** *P*=0.01$^{III–V}$	10.1 (8.9–11.2) *P*=0.001*
ANOVA K–W	H(4)=18.6 *P*=0.001$^{\#}$	H(4)=36.3 *P*=0.0000$^{\#}$	H(4)=27.4 *P*=0.0000$^{\#}$	H(4)=32.5 *P*=0.0000$^{\#}$	H(4)=15.9 *P*=0.003$^{\#}$	H(4)=13.3 *P*=0.01$^{\#}$

Note. * — significant differences vs the control at $P<0.05$; $^{\#}$ — significant differences vs the previous time point (Mann–Whitney *U*-test). $^{I–III}$, $^{I–V}$, $^{III–V}$ —comparison between the corresponding layers (Wilcoxon test) at $P\leqslant 0.02$. $^{\#}$ — differences between time points after LCCA were significant based on the one-way multiple analysis (ANOVA Kruskal–Wallis) test. RAT, relative area of the terminals, RAES, relative area of the edema and swelling zones. The data are presented as medians and interquartile ranges.

Thus, on day 3, only 34% of the relative area of neuropil edema and swelling zones could be explained by the lucid-type (edematous) type of terminal destruction in the layer I of SMC, while 66% were probably caused by hydropic degeneration of astrocyte and small dendritic processes. In the layers of pyramidal neurons (layers III and V of the SMC), significantly more terminals probably underwent the «lucid-type» destruction, with a determination coefficient of 72 and 80%, respectively. These differences in SMC layers could be due to the fact that the molecular layer contains significantly more fibrous astrocyte processes [26]. This probably allows efficient water reabsorption from edematous terminals, preventing their irreversible death through the lucid-type destruction mechanism. On the other hand, layer III of the SMC, which had maximal intensity neuropil edema and swelling and neuronal damage, showed the maximum decrease in the relative area of p38-positive material. Apparently, in this layer, the mechanisms of water reabsorption were disrupted which entailed the destruction of synaptic vesicles and terminals in general.

Our findings will help clarify the nature of reorganization of the components of different neuronal complexes of SMCs in relation to the possible de- and hyperhydration of neural tissue after LCCA.

Conclusion

After bilateral irreversible LCCA, destruction, compensation and restoration were observed in neurons, glial cells, and inter-neuronal communication structures in layers I, III, and V of the rat SMC. Reorganization of neuroglial and inter-neuronal interrelations occurred with the underlying severe neuropil hyperhydration, perikaryon dehydration and reactive gliosis. These SMC changes appeared at different time points. Thus, the numerical density of microgliocytes reached its maximum values on day 1, oligodendrocytes on days 7 and 14, and astrocytes on day 14. Maximum destruction of neurons and synaptic terminals was observed in layer III of

SMC. Overall, all these changes resulted in a significant heterogeneity of the neural tissue response to LCCA. The secondary projection complex of the SMC was affected to a greater extent. This should be taken into account when studying the pathophysiology of changes in SMC structure.

Authors' participation: the authors personally and equally participated in the implementation of the comphrehensive approach including the experimental, anatomical, histological, morphometric and mathematical methods, as well as methods of observation, description and analysis.

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Organoprotective Properties of Argon (Review)

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Органопротективные свойства аргона (обзор)

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Summary

The history of studying the organoprotective properties of argon (Ar) began in 1998 when a group of Russian researchers investigated the effect of hypoxic gas mixtures on mammalian organisms. Over several decades, evidence of the cardio-, neuro-, and nephroprotective effects of argon in various diseases and conditions in experimental models *in vivo* and *in vitro* have been accumulated. However, the lack of clinical studies to date has prompted us to carry out a systematic review analyzing the results of preclinical studies revealing organoprotective properties of argon, which could provide a rationale for its future clinical studies.

The aim of this review is to describe the mechanisms of organoprotective properties of argon determined in preclinical studies.

Material and methods. The search yielded 266 articles. The search algorithm was developed in accordance with the requirements and reporting guidelines for systematic reviews and meta-analysis (PRISMA) in the PubMed and Google Scholar databases. The methodology included using search queries, keywords (including MeSH), and logical operators. The keywords used for the search in the PubMed and Google Scholar databases were «argon», «ar», «protection», and «mechanism». The review included *in vivo* and *in vitro* studies.

Results. The following mechanisms of argon action were identified: activation of N-terminal c-Jun kinase (JNK), p38(ERK1/2), and ERK1/2 in models of airway epithelial cells, neuronal and astroglial cell cultures, as well as in models of retinal ischemia and reperfusion injury in rats and a rabbit model of ischemia-reperfusion myocardium. Significant neuroprotective effects of argon and its influence on apoptosis were shown using small rodent models.

Conclusion. The results of preclinical studies of argon have proved both its safety and organoprotective properties in *in vitro* and *in vivo* models. Analysis of the data provides a rationale for the initiation of clinical studies of argon, which could significantly improve outcomes in patients after cerebrovascular accidents, particularly post ischemic stroke.

Keywords: argon; organoprotective properties; neuroprotection; TBI; stroke; CPR

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

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Introduction

The history of studying the organoprotective properties of argon (Ar) dates back to 1998, when a group of Russian authors studied the effects of hypoxic gas mixtures based on argon on mammals [1]. Three experiments were performed in this study which showed that the addition of argon to hypoxic mixtures containing 4–5% oxygen increased the survival rate of animals compared to similar nitrogen-based mixtures.

Since then, a large number of papers have been published on this subject. Over several decades data on the cardio-, neuro-, and nephroprotective properties of argon in various diseases and conditions have been discovered in experimental models *in vivo* and *in vitro* [2–36]. New knowledge on the molecular mechanisms of argon action has been obtained, and the protective effects of argon and other noble gases, in particular xenon, have been compared [37–39].

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However, the lack of clinical studies on this subject has prompted us to conduct a systematic review with the analysis of preclinical studies demonstrating the organoprotective properties of argon, which would provide a rationale for initiation of its clinical investigation [40–42].

The aim of this review is to study the mechanisms of organoprotective properties of argon in preclinical settings.

Material and Methods

The paper is based on selection of relevant studies through searching published papers. The information search algorithm was developed in accordance with the requirements and reporting guidelines for systematic reviews and meta-analysis (PRISMA) [43] in PubMed and Google Scholar databases. It involved searching for studies using search queries, keywords (including MeSH), and logical operators. According to the search objective, abstracts, conference proceedings, and books were excluded. The search was limited by English-language sources. Keywords for the PubMed database and Google Scholar search included «argon», «ar», «protection», and «mechanism». *In vivo* and *in vitro* studies were included in the review. Papers containing «ar laser» and «ar coagulation» were excluded. The selection process of records for the study is shown in Fig. 1.

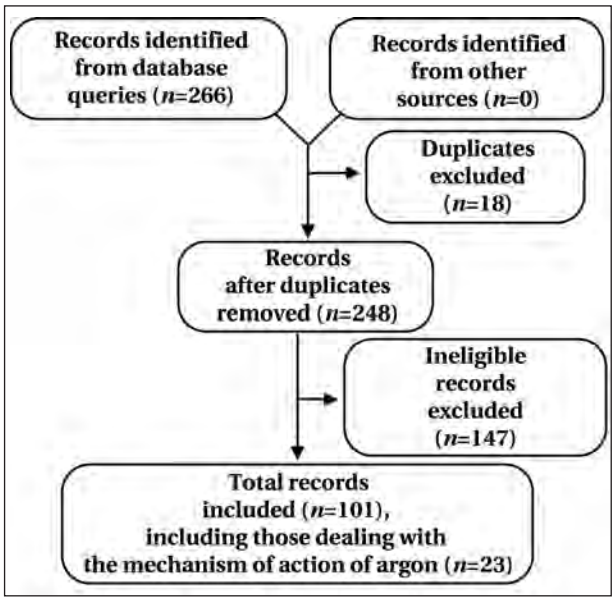

Fig. 1. Flowchart of source inclusion in the review.

Organoprotective properties

The results of recent studies on the organoprotective properties of argon using different models are presented in literature [44–48]. In these studies, either positive or neutral results of argon exposure were usually obtained, which most likely depended on gas concentration, duration of exposure, and experiment model [49, 50].

Table shows the main studies of the mechanism of action of argon in *in vitro* and *in vivo* experiments.

Figure 2 shows the main mechanisms of action of argon.

Neuroprotective properties

A model of traumatic brain injury. The neuroprotective effects of argon were examined in the *in vitro* and *in vivo* animal studies. The model of traumatic brain injury described by Grüßer L. et al. [26] was used for this purpose. In this study, the effects of 50-percent argon, 6-percent desflurane, alone and in combination, were investigated in an *in vitro* model of TBI with incubation time similar to the time intervals between drug administration in daily clinical practice. Injury severity was assessed by fluorescence imaging. The results showed that neither argon 50%, nor desflurane 6% nor their combination could significantly reduce the severity of injury compared to standard ambient. However, compared to desflurane, argon had a rather strong neuroprotective effect during the first 2 hours after focal mechanical injury (P=0.015).

The neuroprotective effects of argon after traumatic brain injury were also confirmed in a study [27, 51] comparing the effects of 24-hour inhalation of argon 70%/O_2 30% and N_2 70%/O_2 30% mixtures initiated within the first 10 min after a traumatic brain injury in a murine model of TBI. This study revealed a neuroprotective effect of argon in mice, manifested as a reduction in neurological deficits during the first week after injury (SNAP, P<0.001 and NeuroScore, P<0.01; beam walk, P<0.05) compared with the control group. On day 3 after the traumatic injury, the argon inhalation group showed a decrease in brain lesion on MRI examination compared with the control group (6.3±0.4 and 9.6±0.5 mm^3; P<0.001), as well as faster memory recovery to 6 weeks (mean latency: 14±2 and 32±6 s, respectively; P<0.05).

In another large study conducted by Creed J. et al. [28], in a model of closed traumatic brain injury, argon inhalation for 24 hours with argon 70%/O_2 30% and argon 79%/O_2 21% mixtures had no advantages over N_2 70%/O_2 30% and N_2 79%/O_2 21% inhalation.

Ischemic injury model. Zhuang L. Yang et al. [16] in a study comparing the neuroprotective effects of inert gases showed that argon provides neuroprotection in both moderate and severe ischemic brain damage, probably due to stimulation of production of proteins preventing apoptosis. The study used argon 70%, helium, xenon, or nitrogen with oxygen in the hypoxia-ischemia brain injury model. Interestingly, argon improved cell survival, whereas

xenon and helium did not. Quantitative analysis showed that treatment with argon, helium, and xenon significantly increased the number of healthy cells in the right CA region of the hippocampus from 37±8 in the control group to 54±6, 48±5, and 47±5, respectively (F=25; P<0.001). Xenon and argon reduced brain infarct volume by 42% (F=4.4, P<0.05) and 38% (P<0.05) compared with controls. In addi-

Main studies of the argon mechanism of action.

Authors	Model	Argon	
		Protective effects	Mechanism of action
Hafner C., Qi H., Soto-Gonzalez L. et al. [2]	A549 (airway epithelial cells)	Increase of cellular viability, 5–47% (P<0.0001)	Activation of c-Jun N-terminal kinase (JNK), p38 (ERK1/2), ERK1/2, but not the Akt pathway.
Brücken A., Kurnaz P. et al. [3]	Cardiac arrest in rats	Reduced neuronal damage index in the neocortex CA, 3/4 hippocampal region	No effect on ATP-dependent potassium channels.
Lemoine S., Blanchart K. et al. [4]	Male Wistar rats and guinea pigs, human atrial appendages	Recovery of contractile force in human atrial appendages after hypoxia/reoxygenation in the argon group from from 51±2% in the unconditioned group to 83±7% in the argon-treated group (P<0.001)	Inhibition of the mitochondrial permeability transition pore opening.
Mayer B., Soppert J., Kraemer S. et al. [5]	*in vitro,* model of primary isolated cardiac myocytes	Increased viability 24 h after preconditioning (second window of preconditioning) (P=0.015)	Induction of the HSP27 gene transcripts. Increased expression of the heat shock protein (HSP) mRNA B1 (HSP27) (P=0.048), superoxide dismutase 2 (SOD2) (P=0.001), vascular endothelial growth factor (VEGF) (P<0.001) and inducible nitric oxide synthase (iNOS) (P=0.001).
Ulbrich F., Kaufmann K., Roesslein M. et al. [6]	Neuroblastoma cells (SH-SY5Y cell line; ATCC CRL-2266)	Antiapoptotic and neuroprotective effect through inhibition of TLR2, TLR4	Inhibition of AV-positive and PI-negative cells and caspase-3 activity. Reduction of TLR2 and TLR4 receptor density on the cell surface. Decreased IRAK phosphorylation, but not the MyD88 protein expression. Increased phosphorylation of ERK-1/2.
Ulbrich F., Lerach T., Biermann J. et al. [7]	Neuroblastoma cells (SH-SY5Y, ATCC CRL-2266)	Neuroprotective effect (reduced severity of retinal ischemia)	Inhibition of NF-κB and STAT3 transcription factors activation. Reduced expression of interleukin-8 *in vitro* and *in vivo.*
Spaggiari S., Kepp O., Rello Varona S. et al. [8]	Human osteosarcoma cell culture U2OS stably expressing the histone 2B red fluorescent protein (RFP-H2B) chimera (which labels chromatin)	Antiapoptotic effect	Inhibition of several STS-induced apoptosis manifestations, including dissipation of membrane potential and caspase-3 activation.
Fahlenkamp A. V., Rossaint R. et al. [9, 10]	Primary cultures of neurons and astroglia cells, BV-2 microglia cell line	Increased ERK1/2 activity in the microglia	Effect on the extracellular signal-regulated kinase (ERK1/2). Addition of the MEK inhibitor U0126 abolished the induced phosphorylation of ERK1/2.
Zhao H., Mitchell S. et al. [11]	Rat cortical neuronal cultures	Reduced brain infarction size	Activation of the PI-3K/Akt pathway, activation of HO-1 and inhibition of GSK-3β. Suppression of NF-κB activation. Activation of caspase-3 and nuclear factor-κB in the cortex and hippocampus.
Zhao H., Mitchell S. et al. [12]	Cortical cell cultures of seven-day-old rats *in vitro* and *in vivo*	Decreased activation and proliferation of hippocampal astrocytes	Activation of transcription factor NF-E2 related to the factor 2 (Nrf2) Increase in p-mTOR and nuclear factor (erythroid factor 2)

Main studies of the argon mechanism of action.

Authors	Model	Argon	
		Protective effects	Mechanism of action
Harris K., Armstrong S. P. et al. [13]	An *in vitro* model using organotypic sections of mouse brain hippocampus, injury	Reduction of secondary damage	No effect on TREK-1 currents, indicating that the potassium channel is not involved in argon neuroprotection.
David H. N., Haelewyn B. et al. [14]	Ischemic stroke, *in vivo*	Elevated thrombolytic and enzymatic activity	Discussion of the mechanism of interaction between argon and tPA.
Höllig A., Weinandy A. et al. [15]	Rats, subarachnoid hemorrhage	Reduction in the risk of premature death (death before scheduled euthanasia) to 20.6% compared to the control group (95% CI, 4.39–96.7)	Hypoxia-induced expression of heme oxygenase 1α, induced by the 1α factor, leading to improved neuronal survival, may contribute to the favorable effect of argon administration after subarachnoid hemorrhage.
Zhuang L., Yang T. et al. [16]	Model of asphyxia in rats	Reduction of hypoxic-ischemic damage	Increased Bcl-2 expression.
Fahlenkamp A. V., Coburn M. et al. [17]	Rats, two-hour transient occlusion of the middle cerebral artery	Neuroprotective properties	Increased expression of TGF-β, expression of IL-1β, IL-6, iNOS, TGF-β, and NGF.
Ulbrich F., Schallner N. et al. [18]	Retinal ischemia and reperfusion injury in rats	Decrease in the number of damaged retinal ganglion cells	Argon-mediated inhibition of NF-κB. Bcl-2, Bax, and caspase-3 expression, NF-κB.
Ulbrich F., Kaufmann K. B. et al. [19]	Retinal ischemia and reperfusion injury in rats	Reduction of ischemic and reperfusion damage to retinal cells	Increased phosphorylation of p38 and ERK-1/2, but not JNK MAP kinase. HSP expression. Alteration of HO-1.
Abraini J. H., Kriem B., Balon N. et al. [20]	Rats	Increase in the argon threshold pressure for the onset of loss-of-righting-reflex (P<0.005)	Action on GABA-receptors.
Faure A., Bruzzese L., Steinberg J. G., et al. [21]	Heterotopic kidney autotransplantation in pigs	Improved recovery of function as measured by creatinine clearance, excreted sodium	Increased expression of Hsp27. Expression of TNF-alpha, IL-1-beta, and IL-6.
Liu J., Nolte K., Brook G. et al. [22]	Rats, transient occlusion of the middle cerebral artery	Reduction of neurological deficit during the first week and preservation of neurons in the border zone of ischemia 7 days after the stroke	Shift in microglia/macrophage polarization toward the M2 phenotype after ischemic stroke. Change in the number of NeuN-positive cells in ROIs.
Quentin de Roux Q., Lidouren F. et al. [23]	Rabbits, ischemic injury	Increased cardiac output, decreased norepinephrine demand, decreased severity of metabolic acidosis, decreased kidney and liver damage	Initial decrease in HMGB1.
Qi H., Soto-Gonzalez L. et al. [24]	Myocardial ischemia/reperfusion model, rabbits	Reduction of ischemic myocardial damage	Activation of JNK, ERK1/2 and Akt pathways. Changes in LDH and mtDNA, interleukin 1β.
David H. N., Dhilly M. et al. [25]	Rats, drug administration	Block of motor sensitization and context-dependent motor activity induced by repeated administration of amphetamine over a long period of time	Inhibition of the mu-opioid receptor and vesicular monoamine-2 transporter. Reduction of dopamine release induced by KCl.

tion, the study showed increased expression of Bcl-2, which inhibits apoptosis. The Bcl XL expression was increased in the helium and xenon group compared to the control group (F=5.9; P=0.0025).

Koziakova M. et al. [29] used hypoxia-ischemia model *in vitro* to evaluate the neuroprotective properties of several noble gases, such as helium, neon, argon, krypton and xenon. Organotypic murine hippocampal brain sections were subjected to oxygen-glucose deprivation, and damage was assessed using propidium iodide fluorescence. Both xenon and argon were equally effective neuroprotectors, with 0.5 atm of xenon or argon reducing the severity of brain tissue damage by 96% (P<0.0001), whereas helium, neon, and krypton lacked any protective effect.

The study of Ulbrich F. et al. [7] *in vitro* and *in vivo* confirmed the protective effect of argon and reported the details of the molecular mechanism of its action (Fig. 2). Argon exhibited a neuroprotective effect by inhibiting the activation of NF-κB and STAT3 transcription factors. While STAT5 and CREB remained intact, inhibition of TLR2 and TLR4 prevented the action of argon on NF-κB and STAT3.

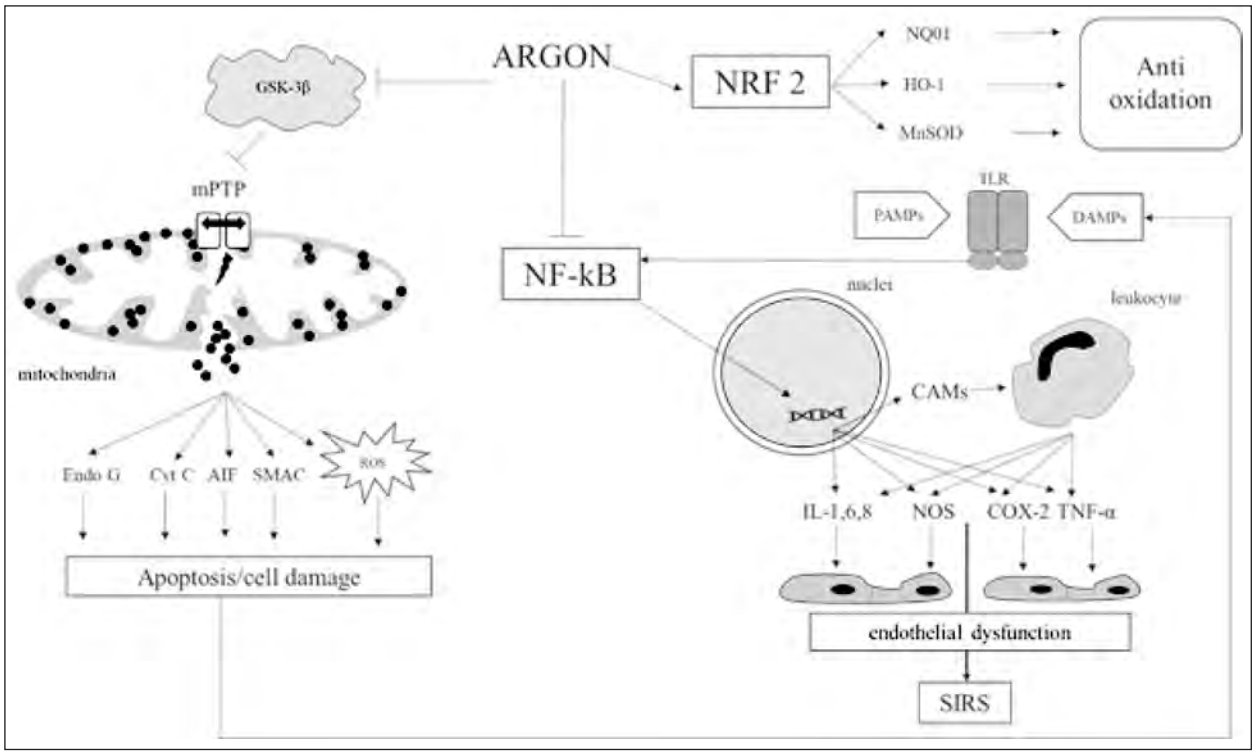

Fig. 2. Molecular mechanisms of the organoprotective properties of argon.
Note. GSK-3β — glycogen synthase kinase 3β; AIF — apoptosis-inducing factor; ROS — reactive oxygen species; Cyt C — cytochrome C; Endo G — endonuclease G; SMAC — apoptotic protein; CAM — cell adhesion molecules; COX — cyclooxygenase; I/R — ischemia/reperfusion; TLR — toll-like receptor; TNF-α — tumor necrosis factor-alpha; mPTP — nonspecific mitochondrial permeability transition pore; NOS — NO synthase; HO-1 — heme oxygenase; MnSOD — mitochondrial Mn-superoxide dismutase; NF-κB — nuclear factor κB; NRF — nuclear respiratory factor (redox sensitive transcription factor); NQ01 — quinone 1.

Inhibition of either NF-κB or STAT3 reversed the beneficial effects of argon. In addition, argon was found to have specific anti-inflammatory properties: IL-8 protein and mRNA expression was altered upon argon exposure. Argon exposure significantly decreased IL-8 protein expression (rotenone, 1.28±0.20 versus rotenone+argon, 0.90±0.13, P<0.001). Argon treatment also reduced IL-8 mRNA expression (untreated cells versus rotenone, 2.93±0.49, P<0.001; rotenone, 2.93±0.49 versus rotenone+argon, 1.54±0.25, P<0.01).

Large studies conducted by Ulbrich F. et al. [6, 7, 19] demonstrated the dose- and time-dependent effect of argon on neuronal protection which can be mediated through ERK1/2 and NF-kB-dependent pathway *in vivo*. Argon was found to be soluble in the cell culture medium, while the distribution equilibrium was reached in less than 2 hours. In addition, argon has a significant dose-dependent anti-apoptotic effect on human neurons (human neuroblastoma cell line model), with its concentration of 75 vol.% demonstrating the most dramatic effect. Argon inhibited rotenone-induced apoptosis, as evidenced by inhibition of AV-positive and propidium iodide (PI)-negative cells and caspase-3 activity. The proportion (%) of AV-positive and PI-negative cells was significantly higher in the FR180204+rotenone+argon 75 vol.% group [2 h] at 21.2±1.9%, P<0.001. The study revealed that argon mediates antiapoptotic signaling by reducing the density of TLR2 and TLR4 receptors on the cell surface.

Fahlenkamp A. et al. [9, 10] exposed primary cultures of neurons and astroglia cells as well as microglia cell line BV-2 to argon 50 vol.%. Further possible effects were studied after stimulation of microglia with LPS at a concentration of 50 ng/ml. Increased phosphorylation of ERK 1/2 after argon exposure was also found in astrocytes and neurons, but its change was not significant. Argon had no substantial effect on LPS-induced activation of ERK1/2 and induction of inflammatory cytokines in microglia. Addition of the MEK inhibitor U0126 eliminated induced phosphorylation of ERK 1/2. Cellular phosphatase activity and inactivation of phosphorylated ERK 1/2 were not altered by argon. Argon enhanced ERK 1/2 activity in microglia by «upstream» MEK kinase, probably through a direct activation pathway. Hence, this *in vitro* study determined the effect of argon on the ERK1/2 kinase regulated by extracellular signaling. This is a ubiquitous enzyme with numerous roles in cell proliferation and survival.

Zhao H. et al. [11] exposed neuronal cell cultures of rat cerebral cortex to oxygen and glucose *in vitro* for 90 min with 70% Ar or N2 with 5% CO_2 balanced with O_2 at 33°C for 2 h. Protein kinase-B (PI-3K/Akt pathway) activation, heme oxygenase (HO-1) activation, and GSK-3β inhibition have been demonstrated to be possible molecular mechanisms underlying the beneficial effects of argon both *in vivo* and *in vitro* [52, 53]. Furthermore, inhibition of HO-1 and PI-3K/Akt pathway activation significantly attenuated argon and hypothermia-induced neuroprotection in OGD-induced injury *in vitro* or *in vivo*. These data suggest that argon in combination with hypothermia could provide robust neuroprotection in a rat stroke model.

In the study, the authors suggested that argon during hypothermia increases HO-1 expression mainly in neurons, providing their cytoprotection, although it is likely that multiple molecular pathways may also be involved in protective mechanisms during ischemia. In addition, suppression of NF-κB activation has been shown to reduce neuronal damage in a model of global cerebral ischemia. NF-κB activation was suppressed by a combination of argon and hypothermia.

Zhao H. et al. [11] carried out the oxygen-glucose deprivation (OGD) of rat cortical neuronal cell culture *in vitro* for 90 min followed by exposure to 70% argon or nitrogen with 5% CO_2 and equilibrated with oxygen for 2 h. *In vivo*, seven-day-old rats underwent unilateral common carotid artery ligation followed by hypoxia-induced ischemia (8% oxygen balanced with nitrogen) for 90 minutes. Then they were exposed to 70% argon or nitrogen balanced with oxygen for 2 hours. *In vitro* exposure of cortical neuronal cultures to argon resulted in a significant increase in p-mTOR and nuclear factor (erythroid 2-like derivative, Nrf2) (P<0.05) and protection against OGD. Inhibition of mTOR by rapamycin or Nrf2 by siRNA abolished argon-mediated neuroprotection. *In vivo*, argon exposure significantly enhanced Nrf2 and its downstream effector NAD(P)H dehydrogenase, as well as quinone 1 (NQO1), and superoxide dismutase 1 (SOD1) (P<0.05). Argon potentially acts through the PI-3K cell signaling cascade as well as ERK, and, in addition, it may also work through cross pathways between P13K and ERK. This was also confirmed when using the PI-3K inhibitor wortmannin and the ERK1/2 inhibitor U0126. Thus, the neuroprotective mechanisms of argon have been shown to include activation of the transcription factor NF-E2 related to the Nrf2, which is considered to be a key mediator of organoprotection upregulating many antioxidants [54, 55].

The pathophysiology of secondary brain damage is complex and includes many cascades with the glutamate considered as a key player [56]. Harris K. et al. [13] showed that the neuroprotective properties of argon were not abolished by glycine, indicating that the neuroprotective effect of argon is not mediated by the glycine site of NMDA-receptor. This is confirmed by the electrophysiological data showing that argon has no effect on NMDA receptors at high or low concentrations of glycine. The lack of effect of argon on TREK-1 currents indicates that this potassium channel is also not involved in neuroprotection.

Jawad N. et al. [57] investigated the neuroprotective properties of krypton, argon, neon and helium in an in vitro model of neuronal damage. Pure cultures of neurons obtained from the brain cortex of embryonic BALB/c mice were subjected to oxygen-glucose deprivation. Cultures were exposed to either nitrogen hypoxia or hypoxia due to noble gas ventilation in a balanced salt solution without glucose for 90 minutes. Cultures were allowed to recover in normal culture medium for an additional 24 hours, in nitrogen or noble gas. Oxygen-glucose deprivation caused a reduction in cell recovery down to 0.56±0.04 in contrast to noble gas (P<0.001). Like xenon (0.92±0.10; P<0.001), argon provided neuroprotection (0.71±0.05; P<0.01). Argon showed improvement in recovery capacity to 1.15±0.11 (P<0.05). The study demonstrated that the inexpensive and widely available noble gas argon possesses potential neuroprotective properties.

The study by Höllig A. et al. [15] analyzed the effect of argon in subarachnoid hemorrhage. One hour after subarachnoid hemorrhage induction by endovascular perforation, a breathing gas mixture containing 50 vol.% argon/50 vol.% oxygen (argon group) or 50 vol.% nitrogen/50 vol.% oxygen (control group) was given for 1 hour. Argon postconditioning resulted in a 20.6% lower risk of premature death (death before scheduled euthanasia) compared to the control group (95% CI, 4.39–96.7). Expression of hypoxia-inducible factor 1α and heme oxygenase 1 in the hippocampus was increased in the argon group. Thus, hypoxia-induced factor 1α induces the expression of heme oxygenase 1, leading to improved neuronal survival, which may contribute to the positive effect of argon after subarachnoid hemorrhage.

The study of Fahlenkamp A. et al. [17] aimed to determine the protective mechanisms of argon treatment in a model of transient middle cerebral artery occlusion (tMCAO) in rats. The study identified several genes whose transcription was elevated 24 h after the intervention and whose expression levels differed significantly between the groups. In animals of the placebo group, the number of astrocytes, microglia, and neurons did not differ significantly between the study groups. After argon treatment, several inflammatory markers showed significantly higher expression levels 24 hours after the inter-

vention. The expression of interleukins IL-1β and IL-6 was significantly increased in the tMCAO+argon group compared to the tMCAO+placebo group (IL-1β: 1.7-fold increase, $P<0.05$; IL-6: 1.7-fold increase, $P<0.05$). The same was found for iNOS expression, which was significantly induced in the tMCAO+argon group (3.5-fold increase vs tMCAO+placebo, $P<0.001$). The study found that TGF-β expression was elevated after 24 h in the tMCAO+argon group, while it did not change in the tMCAO+placebo group.

The neuroprotective properties of argon were investigated by Ma S. et al. [58]. Prolonged inhalation of 70% argon for 24 hours after an *in vivo* stroke provides neuroprotection and improves neurological outcome and overall recovery after 7 days. Rats underwent middle cerebral artery occlusion followed by inhalation of 70% argon or nitrogen and 30% oxygen for 24 hours. On day 7 postoperatively, neurological status was assessed based on 48-point scale and the histological size of the lesion. After argon inhalation for 24 hours immediately after induction of «severe permanent ischemia», neurological outcome (Neuroscore, $P=0.034$), overall recovery (body weight, $P=0.02$), and cerebral infarct volume (total infarct volume, $P=0.0001$; cortical infarct volume, $P=0.0003$; subcortical infarct volume, $P=0.0001$) were significantly better compared with controls. At the same time, neurological outcome and overall recovery also improved significantly, even when argon treatment was delayed by 2 hours or until the end of reperfusion.

Kremer B. et al. [59] evaluated the neuroprotective and immunomodulatory properties of argon after experimental subarachnoid hemorrhage (SAH), studying different hippocampal and cortical regions with regard to neuronal damage and microglia activation 6, 24 and 72 hours after SAH. One hour after SAH (rat model with endovascular perforation), a gas mixture containing 50% argon (argon group) or 50% nitrogen (nitrogen group) was administered. Six hours after SAH, the reduction in neuronal damage of the hippocampal areas was found in the argon group vs the control one ($P<0.034$). The basal cortical areas did not show a different lesion pattern, but microglia activation was significantly reduced in the argon group 72 hours after SAH ($P=0.034$ vs the control group). Argon treatment only improved early hippocampal neuronal damage after SAH.

Liu J. et al. [22] were the first to show that argon promoted switching of microglia/macrophages polarization towards M2 phenotype after ischemic stroke.

The model of circulatory arrest. Brücken A. et al. [3] conducted a study to assess the effect of 70% argon when administered one hour after cardiac arrest in rats. According to the protocol, the animals were randomized into the argon group ventilated with either 70% or 40% vol.% argon 1 h after successful cardiopulmonary resuscitation, and into the control group without argon exposure. During seven days after the experiment, the neurological deficit severity was assessed prior to the animal withdrawal. The neurological deficit was more severe in the animals ventilated with 40% argon vs the 70% argon group ($P<0.05$). Concurrently, there was a significant decrease in the neuronal damage index in the neocortex and CA 3/4 hippocampus area (4.2 in the control group, 2.9 in the argon-ventilated group, $P<0.05$). Administration of the KATP channel antagonist 5-hydroxydecanoate (5-HD) did not abolish the positive effect on either the functional recovery or the histopathological changes observed in the argon exposure group.

Brücken A. et al. conducted another study to evaluate the neuroprotective effect of argon [60]. During the experiment, 7-minute cardiac arrest and 3-minute CPR were simulated in rats. Animals on argon showed significant improvement on the neurological disorders scale during all postoperative days even when argon administration was delayed by 3 hours ($P<0.05$). In addition, there was a significant decrease in the neuronal damage index in the neocortex and hippocampal CA 3/4 area in animals that received argon, regardless of the timing of its administration ($P<0.05$).

Zuercher P. et al. [61] tested the hypothesis that administration of 50% helium or 50% argon within 24 h after resuscitation improves clinical and histological results in the model of 8-minute cardiac arrest in rats. Cardiac arrest was induced in forty animals by administration of potassium and esmolol, after which they were randomized to be ventilated with either helium/oxygen, argon/oxygen, or air/oxygen for 24 h. The primary outcome was neuronal damage assessment in the CA1 hippocampal area in those animals that survived on day 5. The secondary outcome was behavioral assessment. Compared with rats in the air/oxygen group, where 80% [61–93] cell death of the hippocampal area (CA1) was observed, animals ventilated with the noble gas tended to have less damage (helium 53% [24–76], argon 59% [44–86], $P=0.09$). Thus, the results showed that replacing air with helium or argon in a 50:50 air/oxygen mixture for 24 h improved histological or clinical parameters in rats after an 8-minute cardiac arrest, but the differences in this experiment were not significant.

Fumagalli F. et al. [62] studied the neuroprotective effects of argon in a severe preclinically significant model of cardiac arrest in pigs. Animals were randomized to 4-hour post-resuscitation ventilation using 70% nitrogen + 30% oxygen (control), 50% argon, 20% nitrogen, 30% oxygen (Ar 50%)

and 70% argon, 30% oxygen (Ar 70%) groups. Hemodynamic parameters, myocardial function, and serial blood samples were monitored. The pigs were monitored for up to 96 hours to determine survival and neurological recovery. The Ar 50% and Ar 70% groups achieved good neurological recovery, unlike the control group (P<0.0001). Histologically, there was less neuronal degeneration in the cortex (P<0.05) (but not in the hippocampus) and less activation of reactive microglia in the hippocampus (P=0.007) after argon ventilation. Animals receiving argon showed a smaller increase in circulating biomarkers of brain damage (neuron-specific enolase, glial fibrillary acidic protein, ubiquitin c-terminal hydrolase) and markers of kynurenine pathway activation (P<0.05) vs the control group. A complete recovery of left ventricular function, lower infarct volume, and cardiac troponin release were observed in 70% of pigs on argon (P<0.01). Thus, lung ventilation with argon in the post-resuscitation period was shown to significantly improve neurological recovery and alleviate brain damage after cardiac arrest with prolonged interruption of blood flow. The effectiveness of 70% argon was higher than that of 50% argon.

Fumagalli F. et al. [63] also studied the effect of post-resuscitation argon treatment on neurological recovery in a model of cardiac arrest in pigs with acute myocardial infarction. Twelve pigs underwent occlusion of the left anterior descending coronary artery with subsequent cardiac arrest. After 8 minutes, cardiopulmonary resuscitation was performed for 5 minutes before defibrillation. After resuscitation, animals were subjected to 4-hour ventilation with 70% argon and 30% oxygen or 70% nitrogen and 30% oxygen. Myocardial function was evaluated by echocardiography and serum neuron-specific enolase was measured. Animals were observed for up to 72 h to assess survival and neurological recovery. Argon ventilation had no detrimental effect on hemodynamics and gas exchange. All six animals treated with argon showed rapid and complete 72-hour neurological recovery, in contrast to only two of the six control animals (P<0.05). The seventy-two-hour neurological alertness score and neurological deficit score were 100 and 0, respectively, in the argon group and 79 and 29 in the control group (P<0.01 and P<0.05). Significantly smaller increase in serum neuron-specific enolase levels (12% versus 234%) and minimal brain damage (neuronal degeneration was histologically 0 versus 1) were also observed in animals ventilated with argon.

Other models. Hafner C. et al. [2] studied airway epithelial cells exposed to a cytotoxic concentration of H_2O_2 after exposure to standard air, either 30 or 50% argon, 21% O_2, 5% CO_2 with an appropriate concentration of nitrogen in each mixture for 30, 45, or 180 minutes. Protective signaling pathways were identified by Western blotting. The study found that preconditioning with 50% argon for 30, 45, and 180 min and 30% argon for 180 min protected A549 cells from apoptosis, increasing cell viability by 5–47% (P<0.0001). Argon exposure resulted in early activation of the c-Jun N-terminal kinase (JNK) and p38 with a peak 10–30 min after the onset of preconditioning and delayed activation of the extracellular signal-regulated kinase 1/2 (ERK1/2) pathway.

Abraini J. et al. [20] administered drugs selective to GABA or GABA receptors to rats. Anesthesia was given using nitrogen, argon, or medical-grade nitrous oxide in a dose sufficient to induce complete loss of the righting reflex. Nitrogen and argon were delivered to the high-pressure chamber at a compression rate of 0.1 MPa/min, whereas nitrous oxide was delivered at a compression rate of 0.016 MPa/min. Hyperbaric helium induced increased excitability, which could affect both sensory and motor aspects of the reflex. The results confirmed the pharmacological rather than physiological antagonistic effect of gabazine and flumazenil in anesthesia induced by argon and nitrogen at elevated pressures. These results may be consistent with either a direct or indirect action of argon on GABA receptors.

Spaggiari S. et al. [8] in their study showed that argon is able to limit internal mitochondria-mediated apoptosis stimulated by the broad-spectrum kinase inhibitor staurosporine (STS), a DNA-damaging agent mitoxantrone (MTX) and several mitochondrial toxins. Argon inhibited several manifestations of STS-induced apoptosis, including $\triangle\psi$ mitochondrial inner membrane potential dissipation and caspase-3 activation.

Loetscher P. et al. [64] found neuroprotective properties of argon on organotypic sections of hippocampus in mice after treatment with argon at different concentrations (25, 50 and 74%). The 74% concentration of argon was the most effective (0.52±0.05), but concentrations of 25% (0.60±0.05) or 50% (0.56±0.03) also showed a significant reduction in the severity of brain damage ($P \leqslant 0.001$).

The effect of argon on production of NF-κB transcription factor was studied by Ulbrich F. et al. [18]. Postconditioning with argon inhibited the expression of Bax and Bcl-2 mRNA as well as the expression and cleavage of caspase-3 mRNA. A possible molecular mechanism of argon-mediated protection may involve suppression of the NF-κB transcription factor production. Interestingly, postconditioning with argon attenuated IRI-mediated leukocyte growth in peripheral blood. These results support the hypothesis that argon post-conditioning exerts neuroprotection by inhibiting apoptosis and thus provides cytoprotective effects after neuronal damage. In this study, NF-rB mRNA expression

was suppressed and phosphorylation of the p65-NF-κB subunit was attenuated by argon (75 vol%) in a time-dependent manner (up to three hours). Argon-mediated inhibition of NF-κB may be at least a possible molecular mechanism of apoptotic protein suppression.

Quentin de Roux Q. et al. [23] showed that argon reduces the level of HMGB1 in blood and also has a direct antiischemic effect, which decreases the passive release of nuclear HMGB1.

Alderliesten T. et al. studied the neuroprotective properties of argon on piglets. Several groups were formed in the experiment (the group on increasing concentrations of argon; the group exposed to hypoxia; the group of animals which underwent hypothermia after hypoxia). Inhalation of 80% argon had no effect on blood pressure, heart rate, cerebral saturation, and electrocortical activity of the brain in normoxic animals and in 50% of hypoxic animals, as well as in animals post hypoxia followed by therapeutic hypothermia [65].

Broad K. et al. [66] performed 45–50% argon inhalation in a model of newborn piglets after hypoxia-ischemia, which resulted in enhanced neuroprotective effect of hypothermia. Recovery of the baseline EEG was faster (P<0.01). Inhalation of 45–40% argon for 2–26 hours enhanced the protection against hypothermia 48 hours after hypoxia-ischemia.

Nephroprotective properties

The protective effects of argon during preconditioning, recovery and post-conditioning from renal ischemia-reperfusion in small rodents are quite well studied [67]. In this context, the hypothesis that postconditioning with argon inhalation will improve graft function in a pig kidney autotransplantation model was tested [49, 68]. The pigs underwent resection of the left kidney after 60 minutes of warm ischemia (renal artery and vein clamping). The removed kidney was autotransplanted in a separate procedure after 18 hours of cold storage, immediately after right-sided nephrectomy. After reperfusion, pigs were randomized to inhale control gas (70% nitrogen and 30% oxygen), argon (70% and 30% oxygen), or xenon (70% and 30% oxygen) for 2 hours. The primary outcome parameter was peak plasma creatinine concentration, while the secondary outcome parameters included additional markers of graft function (creatinine level, urine output), graft damage assessment (aspartate aminotransferase level, histology). Also, apoptosis and autophagy were examined, inflammatory mediators and markers of cell survival/growth (mRNA and tissue protein quantification) as well as animal survival were determined. The researchers concluded that argon postconditioning did not improve kidney graft function in this experimental model. The peak plasma creatinine concentration was similar in the control and argon groups. The intervention did not affect any other secondary outcome parameters, including animal survival.

Irani Y. et al. [69] showed that cold storage solution saturated with noble gas (xenon or argon) limits ischemia-reperfusion damage after cold ischemia. Creatinine clearance was significantly higher and urinary albumin level was significantly lower in the argon and xenon groups than in the other groups on days 7 and 14 (P<0.05). These effects were significantly more pronounced for argon than for xenon. In addition, argon-treated kidneys and, to a lesser extent, xenon-treated kidneys exhibited intact architecture as well as higher CD10 expression and lower caspase-3 activity compared with the other groups (P<0.05).

Cardioprotective properties

In addition to the neuroprotective properties of argon, much attention is paid to the study of its cardioprotective effects [70].

Previous studies demonstrated that preconditioning with argon provided a remarkable decrease in inflammation and apoptosis and increased myocardial contractility in acute ischemia-reperfusion (IR). Rats were anesthetized, ventilated, and divided into the control and argon groups, the latter receiving 3 sessions of argon (50% argon, 21% oxygen, and 29% nitrogen). Cold ischemia (4°C) for 60 minutes was induced by histidine-tryptophan-ketoglutarate cardioplegia followed by 40-minute reperfusion. The functional parameters of the heart were evaluated. The expression of extracellularly regulated kinase (ERK1/2), AKT serine/threonine kinase (Akt), jun N-terminal kinase (JNK), endothelial nitric oxide synthase (eNOS), and HMGB1 protein was studied in left ventricular tissue samples. At the end of reperfusion, argon preconditioned rats showed better recovery of cardiac output (101±6% versus 87±11%; P<0.01), stroke volume (94±4% versus 80±11%; P=0.001), and coronary blood flow (90±13% versus 125±21%; P<0.01) compared with controls. In addition, argon preconditioning significantly reduced JNK activation (0.11±0.01 versus 0.25±0.03; P=0.005) and HMGB1 protein expression (0.52±0.04 versus 1.5±0.10; P<0.001) after reperfusion. These results suggest a potentially new cardioprotective approach in cardiac surgery.

Lemoine S. et al. [4] investigated the role of MPTP induction (pore of nonspecific mitochondrial permeability, PNMP) in the mechanism of argon action (Fig. 2). This nonselective channel of the inner mitochondrial membrane opens during ischemia-reperfusion following the calcium overload of cardiac cells [71–78]. In rats, ischemia-reperfusion was induced *in vivo* using temporary coronary artery ligation, and cardiac function was assessed

by magnetic resonance imaging. Hypoxia-reoxygenation (HR)-induced arrhythmias were assessed *in vitro* using intracellular microelectrodes on both an isolated rat ventricle and a guinea pig ventricular borderline model. Loss of contractility during hypoxia-reoxygenation was evaluated in human atrial auricles. In these models, post-conditioning was induced by a 5-minute administration of argon during reperfusion. In the *in vivo* model, ischemia-reperfusion (IR) led to a decrease in left ventricular ejection fraction (24%) and an increase in wall motion index (36%), which was prevented by argon during post-conditioning. Post-conditioning with argon *in vitro* eliminated the IR-induced rhythm disturbances, such as early post-depolarizations, conduction blocks, and re-entry arrhythmias. Recovery of contractility in human atrial auricles after HR was better in the argon group, increasing from 51±2% in the unconditioned group to 83%±7% in the group using argon (P<0.001). In the experiment on the atrial auricle model, the use of PNMP activator prevented the cardioprotective effect of argon. This may indicate that argon acts directly or indirectly by inhibiting PNMP opening, thereby protecting the mitochondria. However, PNMP is also known to be controlled by the RISK pathway, the activation of which prevents PNMP opening [79–81]. Researchers have shown that inhibition of PI3K-Akt and MEK/ERK1/2 signaling kinases of the RISK pathway suppresses the cardioprotective effect of argon, which may suggest that the RISK pathway is involved in the inhibitory effect of argon on PNMP opening. In addition, inert gases including argon have been hypothesized to act by disrupting the structure and dynamics of lipid membranes and thereby indirectly altering protein function as an alternative or additional way of modulating the activity of ion channels.

Mayer B. et al. [5] observed the induction of HSP27 gene transcription during argon exposure in an *in vitro* model study [82–84]. The argon-mediated increase in HSP27 mRNA was hypothesized to contribute to delayed cardioprotection by enhancing protein folding, abnormal protein degradation, apoptosis inhibition, and cytoskeleton stabilization. In this study, isolated cardiomyocytes from rats were exposed to 50% argon for 1 h and then subjected to sublethal hypoxia (<1% O_2) for 5 h during either the first (0–3 h) or second window (24–48 h) of preconditioning. Subsequently, cell viability and proliferation were measured. Argon preconditioning significantly increased mRNA expression of heat shock protein (HSP) B1 (HSP27) (P=0.048), superoxide dismutase 2 (SOD_2) (P=0.001), vascular endothelial growth factor (VEGF) (P<0.001) and inducible nitric oxide synthase (iNOS) (P=0.001). These results provide the first evidence for the effect of argon on cardiomyocyte survival during the second preconditioning window, which may be mediated by the induction of HSP27, SOD_2, VEGF, and iNOS.

Qi H. et al. [24] confirmed in their study the action of argon through ERK1/2, JNK, and Akt pathways. The study showed that myocardial protection against oxidative stress-related damage by preconditioning with argon is at least partially mediated by phosphoactivation of MAPK and Akt pathways. Argon rapidly activates JNK phosphorylation within 15 minutes and then dephosphorylates the protein again to below baseline. Interestingly, the JNK inhibitor SP600125 reduces the protective effect of argon on cardiomyocytes, although to a lesser extent than the MEK1 inhibitor U0126. Downstream effectors of MAPkinase activation were also identified. The c-Jun, a member of the activator protein-1 (AP-1) family of transcription factors, is activated by the ERK1/2 and JNK pathways and is involved in cell cycle proliferation and progression with its activity being highly enhanced upon argon exposure [85–87]. Akt activation occurred through Ser473 phosphorylation, and the Akt inhibitor MK2206 could completely abolish the protective effect of argon.

Possible additional protective properties of argon have been studied in several studies. For example, in a study by David H. et al. [14] argon was suggested to affect the thrombolytic efficacy of tPA (tissue plasminogen activator). Previous data clearly demonstrated the inhibitory effect of xenon on enzymatic and thrombolytic efficiency of tPA and the critical importance of the time of xenon administration (during or after ischemia in order to prevent thrombolysis inhibition for better neuroprotective effect). The study showed that argon has a concentration-dependent dual effect on the enzymatic and thrombolytic efficacy of tPA. Low and high concentrations of argon (25 and 75 vol%) block and enhance respectively enzymatic and thrombolytic efficacy of tPA. The possible use of argon at low and high concentrations in the treatment of acute ischemic stroke during or after tPA-induced reperfusion with respect to its neuroprotective effects and its inhibitory and facilitation effects has been considered.

The same authors have recently obtained other important results [25]. Argon blocked the expression of motor sensitization to amphetamine by inhibiting the mu-opioid receptor and the vesicular transporter monoamine-2, which plays a critical role in drug addiction.

Ulbrich F. et al. [19] studied the effect of argon on retinal ischemia and reperfusion. Retinal ischemia and reperfusion are known to cause significant damage and apoptosis of the retina, measured by the decrease in the number of vital retinal ganglion cells and caspase cleavage [88]. Argon inhalation

suppressed endogenous cell defense mechanisms, such as the expression of HSP-70, HSP-90, and HO-1 [89,90]. At the same time, argon inhalation differentially induced stress kinases, as evidenced by increased phosphorylation of p38 and ERK-1/2, but not JNK MAP kinase. Inhibition of ERK-1/2 regulated argon-mediated HSP expression in this lesion model because inhibition of ERK-1/2 partially counteracted argon-mediated suppression of HO-1. Argon exposure resulted in a distinct suppression of various heat shock proteins after retinal ischemia reperfusion injury, leading to additional cytoprotective effects. Thus, the study confirmed the hypothesis that argon exerts neuroprotection through the ERK-1/2-dependent pathway.

Faure A. et al. [21] observed an increased Hsp27 expression after air/argon exposure in a pig liver transplant model. However, two days after reperfusion, the expression continued to rise only when argon was used during storage. These data suggest that argon exerts its protective effect, at least in part, by increasing the expression of Hsp27 [91]. These results are consistent with previous reports, which showed that Hsp27 expression provides a significant survival advantage under conditions of redox stress and inflammation, in particular by stimulating the antioxidant defense of the cell.

Clinical applications. Argon has been already used in various areas of science and medicine [92–100] where its safety has been demonstrated, including the study of hemodynamic parameters (cardiac output) and lung volume using the assessment of inert soluble gas absorption from lungs as well as the operation of respiratory mass spectrometer [101–103]. In contrast to argon, another noble gas, xenon, was already approved for clinical use as a general anesthetic and demonstrated neuroprotective properties in numerous *in vitro* and *in vivo* studies [108–112].

However, its use in routine clinical practice is still challenging due to its high cost and narcotic effect, which complicates the neurological assessment of patients.

Conclusion

Discussed studies show the neuroprotective effectiveness of argon. Argon is inexpensive to produce and does not require a closed breathing circuit. It has no sedative properties and, therefore, does not affect the neurological status. The simplicity of administration (via a face mask), absence of toxicity and influence on the cerebral blood flow enable argon administration starting from the moment of hospital admission. The results of preclinical studies of argon showed safety and organoprotective properties of the gas in *in vitro* and *in vivo* models using different animal species. All of the above provides a rationale for initiating clinical studies of argon, which could significantly improve the outcomes of patients after cerebral accidents, in particular, ischemic strokes.

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Inotropes and Vasopressors Use in Critical Care and Perioperative Medicine: Evidence-Based Approach (Review)

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Применение инотропных препаратов и вазопрессоров в реаниматологии и периоперационной медицине: доказательный подход (обзор)

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Summary

Inotropes and vasopressors are frequently required in critically ill patients and in patients undergoing major surgery. Several molecules are currently available, including catecholamines, phosphodiesterase-3 inhibitors, vasopressin and its analogues, and calcium sensitizers.

We will review current evidence on inotropes use in perioperative and critically ill patients, with focus on most recent randomized controlled trials (RCTs).

Despite being widely used in anesthesia and intensive care, evidences on safety and efficacy of inotropes are scarce. Data from observational studies suggest that inotropes administration may increase mortality in cardiac surgery, acute heart failure, and cardiogenic shock patients. However, randomized controlled trials did not confirm these findings in acute care settings.

Epinephrine has been associated with increased mortality especially in cardiogenic shock, but randomized trials failed to show evidence of increased mortality associated with epinephrine use. Norepinephrine has been traditionally considered contraindicated in patients with ventricular dysfunction, but recent trials suggested hemodynamic effects similar to epinephrine in patients with cardiogenic shock. Dopamine has no additional advantages over norepinephrine and increases the risk of tachyarrhythmias and may increase mortality in cardiogenic shock. Phosphodiesterase-3 (PDE-3) inhibitors are equivalent to catecholamines in terms of major outcomes. Levosimendan is the most investigated inotrope of the last 30 years, but despite promising early studies, high-quality multicenter RCTs repeatedly failed to show any superiority over available agents. There is no high-quality RCT clearly demonstrating superiority of one agent over another. In summary, current evidence suggest that the choice of inotrope is unlikely to affect outcome, as long as the target hemodynamic goals are achieved.

Finally, in recent years, mechanical circulatory support (MCS) has become increasingly popular. Thanks to improvement in technology, the safety and biocompatibility of devices are constantly growing.

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MCS devices have theoretical advantages over inotropes, but their use is limited by costs, availability, and invasiveness.

Conclusion. Future studies should investigate safety, efficacy, and cost-effectiveness of primary MCS versus primary inotropes in patients with acute cardiovascular failure.

Keywords: hemodynamic management; inotropes; vasopressors; catecholamines; shock; intensive care; mortality

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Introduction

It is well recognized that low cardiac output (CO) state is associated with an increased risk of organ dysfunction, hospital stay, and mortality, both in critical illness and post-operative settings [1–5]. More in general, the inability of the circulatory system to match oxygen demand is considered the main pathophysiological cause underlying the development of multi-organ failure and death [6].

Cardiac output is a key determinant of oxygen delivery. When heart function is incapable of providing enough CO to support tissues metabolic demands, inotropes can be administered with the goal of improving cardiac contractility and, therefore, restore and maintain an adequate oxygen delivery [7, 8].

As a consequence, inotropes are well-known medications to every physician caring for patients with any kind of cardiovascular dysfunction. These typically includes patients with acute and chronic heart failure, patients undergoing cardiac surgery, but also patients with septic shock, major trauma, or undergoing high-risk non-cardiac surgery. In general, every critically ill patient may require some degree of inotropic support.

Inotropic drugs have been administered for decades to patients with heart failure, and, as many other intervention (e. g. blood products transfusion, intra-aortic balloon pump), entered in routine clinical practice well before development of the «Evidence-Based Medicine» concept, and their safety and efficacy have never been formally tested.

Aim of this review is to summarize current evidence regarding use of inotropes and vasopressors in critically ill patients.

Hemodynamic and Side Effects of Inotropic Agents

Every available inotropic agent increases cardiac contractility and CO to a variable degree. Effect on vascular tone is variable, with some agents being also vasoconstrictors («inoconstrictors» or «inopressors») and other vasodilators («inodilators»). As a result, the net effect on mean arterial pressure (MAP) is variable, and, as it depends also on volume status of the patient, may not be easy to predict. Pure vasoconstrictors generally increase mean arterial pressure, while the effect on CO is variable and dependent from baseline cardiac function and indirect effects on heart rate, although they do generally reduce CO while increasing MAP [9, 10]. A list of the most frequently used agents and their hemodynamic effects is presented in Table 1 [8, 11–16].

Despite the proven positive hemodynamic effects, inotropes are not free from side effects. The most frequently described are tachycardia, ventricular and supraventricular arrhythmias, and (with the possible exception of levosimendan [17,18]) increase in myocardial oxygen consumption [7, 19, 20]. In addition, inodilator agents may also cause severe hypotension [18, 19], while inoconstrictors may cause limb and mesenteric ischemia [21].

Catecholamines, the most frequently used inotropic agents, also have a wide range of effects on respiratory, gastrointestinal, endocrine, immunological and coagulation system that could result detrimental when adrenergic stimulation becomes excessive [22–25]. Increase in cardiomyocytes apoptosis may be particularly important in patients with a limited cardiovascular reserve [26–28] and cardiac side effects have been described in almost half of patients receiving catecholamine therapy [20].

Current Evidence by Clinical Settings

Between the end of the 80s and the early 90s, several large randomized trials demonstrated an increase in mortality in patients with chronic, stable heart failure treated with daily administration of inotropes, regardless of molecule tested [29–31] and with the exception of oral digoxin, which showed a neutral effect on mortality [32]. Since then, it is generally accepted that, in patients in a stable clinical condition, side effects of inotropes outweigh the positive hemodynamic effect of these drugs.

More recently, several authors have raised concerns regarding safety of inotropes also in «acute» clinical settings.

Several observational trials and data from registries have found an association between inotropes administration and mortality in patients presenting with acute heart failure [33–39]. In addition, some meta-analyses also highlighted a trend towards increased mortality when catecholamines are administered in patients with heart failure [40, 41]. In more recent years, observational studies have suggested reduced survival associated with inotropes administration also in the settings of cardiac surgery [42–44] and septic shock [45]. Of note, other observational trials did not found a similar association [46].

Despite evidences from observational trials, there is currently no randomized clinical trial demonstrating that inotropes administration increase mor-

Table 1. Summary of hemodynamic effects of commonly used inotropes/vasopressors.
Modified from Jentzer et al.

Drug	Pharmacology	Main teoretical hemodynamical effects				
		CO/CI	SVR	PCWP	MAP	HR
Dopamine (>4 мкг/кг/мин)	β_1-agonist ≈α-agonist > β_2-agonist	↑	↑	↑	↑	↑↑
Dobutamine	β_1-agonist > β2-agonist >> α-agonist	↑↑	↔↓	↔↓	↑↔↓	↑
Norepinephrine	α-agonist > β_1-agonist > > β_2-agonist	↑↓	↑↑	↑	↑↑	↑↔
Epinephrine	β_1-agonist ⩾ α-agonist ⩾ β_2-agonist	↑↑	↑	↑	↑↑	↑↑
Milrinone/ Enoximone	PDE-3 inhibitor	↑↑	↓↓	↓↓	↓↔	↑↔
Levosimendan	Calcium-sensitizer + PDE-3 inhibitor	↑↑	↓↓	↓↓	↓↔	↑↔
Digoxin	Na^+/Ca^+ ATPase inhibitor	↔↑	↔	↔↓	↔↑	↓
Vasopressin	$V_1 + V_2$ vasopressin receptor agonist	↓	↑↑	↑	↑↑	↔↓
Terlipressin	Selective, long-acting V_1-vasopressin receptor agonist	↓	↑↑	↑	↑↑	↔↓
Angiotensin II	Angiotensin receptor agonist	↓	↑↑	↑	↑↑	↔↓

Note. CI — cardiac index; CO — cardiac output; HR — heart rate; MAP — mean arterial pressure; PCWP — pulmonary capillary wedge pressure; PDE-3 — phosphodiesterase-3; SVR — systemic vascular resistances.

tality in settings other than chronic stable heart failure [47]. On the contrary, inotropes may actually improve survival in certain clinical settings [47].

Cardiac Surgery

In cardiac surgery, patients frequently receive inotropes. In several series, more than 50% of patients required some degree of inotropic support [48], although use of inotropes remains highly variable [46, 49, 50]. Difficult weaning from cardiopulmonary bypass and post-operative low cardiac output syndrome (LCOS) are the most frequent indication for inotropes administration [4, 51, 52]. Cardiac function frequently declines in the first hours following cardiac surgery [53, 54], and it's a common experience for the cardiac anesthesiologist or intensivist to treat patients with inotropes for few hours to restore adequate organ function. Rapid clinical deterioration is also frequently seen following inappropriate inotrope discontinuation. Several trials comparing inotropes against each other and against non-inotropic drugs have been published. Unfortunately, studies are small and not powered enough to adequately assess clinically relevant endpoint [11, 47], with the notable exception of levosimendan, the only agent investigated in several multicenter RCTs [55–58]. Definitive evidence strong enough for high-grade recommendations is lacking, even though it is almost thirty years that experts advocate the need for high-quality studies [11, 51, 59–62], and meta-analyses showed controversial results depending on the molecule investigated [47, 63–65].

Septic Shock

In septic shock, vasoactive medications are generally administered to increase MAP, rather than to improve CO [66]. Indeed, several large RCTs compared different vasoconstrictors in the setting of septic shock, showing no clear superiority of one agent over another [67–72]. Although the classical view of septic cardiovascular dysfunction is that of distributive shock with loss of peripheral vascular resistance and normal or increased CO [73], the role of septic myocardial dysfunction is being increasingly recognized [74, 75]. Several trials comparing vasoactive agents against each other are available [76–78]. We are aware of only one small RCT comparing an inoconstrictor with no vasoactive therapy [79], while only few trials compare inodilators against each other or against placebo [78]. However none of them has been designed to address a difference in survival. Levosimendan is the only inotropic agent that has been investigated a multicenter RCT, with organ function as primary outcome and short-term survival as secondary outcome (details on the Levosimendan for the Prevention of Acute Organ Dysfunction in Sepsis [LeoPARDS] trial are provided below) [80, 81]. Nevertheless, mRCTs comparing higher versus lower MAP targets (and hence greater versus lower exposure to exogenous vasopressors) for septic shock patients showed no difference in mortality, although trends towards lower mortality but higher rate of AKI were generally observed in the low-MAP groups [82, 83]. As of today, experts recommend the use of norepinephrine as first line vasopressor in septic shock, while dobutamine or epinephrine are recommended in case of concomitant myocardial dysfunction with low CO or evidence of hypoperfusion despite intravascular volume and MAP optimization, although they acknowledge the low grade of evidence for this recommendation [66].

Acute Heart Failure

Acute heart failure in non-cardiac surgical settings is currently carrying the highest controversies regarding inotropes use. Most of the observational trials which found association between inotropes administration and increased mortality were performed in acute heart failure setting [33–39]. Nevertheless, almost 20% of patients hospitalized for heart

failure still receive treatment with inotropes [84]. Surprisingly, even in this controversial setting, only few, large, multicenter RCTs have been performed. As for cardiac surgery, the largest number of trials investigate levosimendan [85–89], with the notable exception of the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study, which investigate milrinone [90]. Interestingly, none of these studies showed that inotropes use is associated with increased mortality, nor demonstrated a benefit of non-adrenergic agents over dobutamine. Of note, the OPTIME-CHF study, which compared milrinone versus placebo and showed an increase in hypotensive episodes and arrhythmias in the milrinone-treated group, and a non-significant trend towards increased 60-day mortality, enrolled patients judged to not require inotropic treatment. While for mild cases of acute heart failure inotrope use remains controversial, an observational study suggests that, in patients with cardiogenic shock (the most severe form of acute heart failure), adding an inodilator to treatment might actually improve survival [91].

Non-Cardiac Surgery

There are only few studies investigating in isolation the use of inotropes in non-cardiac surgery [47], as a large number of RCTs rather investigated the effect of goal-directed hemodynamic therapy (GDT) [92–94]. GDT consists of a bundle of provisions, including administration of variable combinations of fluids, inotropes/vasopressors and blood products, according to a specific protocol aimed at specific hemodynamic or tissue perfusion indexes targets, performed during the first hours following a surgical procedure. In this context, there is general agreement that GDT may improve survival or at least reduce complications in patients undergoing high-risk surgery [94–98]. Interestingly, GDT seems to reduce also cardiac complications, which, at least in theory, may increase when catecholamines are administered [99]. Importantly, no evidence of harm from treatment with inotropes or vasopressors when used in context of perioperative GDT emerged so far. Nevertheless, the question of whether inotropes in addition to fluids provide increasing benefit remains open according to some authors [100].

Specific Molecules

In this section, we will review the latest evidence on specific inotropes/vasopressors used in clinical practice in intensive care medicine, with focus on most recent or largest RCTs and meta-analyses. A detailed review of pharmacology of inotropes and vasopressors is beyond the scope of this article, and readers are referred to other specific reviews on the topic [7, 8, 12–16]. Readers are referred to other reviews also for vasopressors use during cardiopulmonary resuscitation [101].

Major findings are summarized in Table 2.

Catecholamines

Catecholamines are usually the first-line vasoactive drugs administered to critically ill, hemodynamically unstable patients, as recommended by several professional experts and guidelines for different clinical contexts [51, 66, 102–106]. Among catecholamines, the most commonly used agents are norepinephrine, dopamine, dobutamine and epinephrine [14].

Norepinephrine is the first-line vasopressor recommended by the most important guidelines to restore MAP in all clinical contexts [66, 102, 103]. An interesting observational study performed in United States assessed patients outcome during a period of norepinephrine shortage, and showed that unavailability of norepinephrine was associated with increased mortality despite use of alternative agents [107]. Norepinephrine has been studied in several multicenter RCTs against dopamine, epinephrine, and vasopressin [67–69, 71, 108, 109]. Collectively, these studies showed no differences in survival between norepinephrine and other agents. In the Sepsis Occurrence in Acutely Ill Patients II (SOAP-II) trial, 1679 patients requiring vasopressors were randomized to receive norepinephrine or dopamine [67]. The Authors found no difference in 28-days or 1-year survival in the overall study population. However, norepinephrine use was associated with lower incidence of arrhythmias, and a higher survival rates in the subgroup of patients with cardiogenic shock. Improvement in survival associated with norepinephrine use as compared with dopamine has been confirmed in meta-analyses of RCTs mostly including septic shock trials [110, 111].

Epinephrine is commonly used in critically ill patients as second-line or alternative vasopressor, especially in low-income settings [66]. Traditionally, epinephrine is considered more an inotrope than a vasoconstrictor, while the opposite is true for norepinephrine. Accordingly, epinephrine has been generally considered to be preferrable in the setting of myocardial dysfunction, while norepinephrine is generally considered contraindicated due to concerns of potential decrease in cardiac output due to afterload increase. However, recent evidence from observational studies suggested that epinephrine use may be associated with increased mortality in patients with cardiogenic shock [112, 113]. Nevertheless, a recent meta-analysis of RCTs did not find evidence of increased mortality associated with epinephrine use [114]. The systematic review, however, also underlined the very limited number of RCTs performed in the setting of cardiogenic shock.

Table 2. Summary of current evidence from multicenter randomized controlled trials on the effect of commonly used inotropes/vasopressors on outcomes of critically ill patients.
Modified from Belletti et al.

Drug	Setting	Effect on survival	Additional findings
Norepinephrine	Shock of any etiology	No improvement	Lower incidence of arrhythmias as compared with dopamine. Lower lactate levels as compared with epinephrine.
	Sepsis/vasodilatory shock	No improvement as compared with vasopressin/terlipressin/epinephrine	
	Cardiogenic shock	Possible higher survival as compared with dopamine. No improvement and trend towards increased survival as compared with epinephrine (study not powered to detect mortality difference).	Lower lactate levels as compared with epinephrine. Lower CI (with similar stroke volume but lower heart rate) as compared with epinephrine.
Epinephrine	Shock of any etiology	No improvement	Higher lactate level as compared with norepinephrine (± dobutamine).
	Sepsis	No improvement	Higher lactate level as compared with norepinephrine (± dobutamine).
	Cardiogenic shock	No improvement. Trend towards increased mortality (study not powered to detect mortality difference).	Possible trend towards higher rate of refractory shock. Higher lactate levels as compared with norepinephrine. Higher CI (with similar stroke volume but higher heart rate) as compared with norepinephrine.
Dopamine	Shock of any etiology	No overall improvement. Possible lower survival as compared with norepinephrine in cardiogenic shock.	Higher rate of arrhytmias as compared with norepinephrine.
Vasopressin	Sepsis	No improvement	Possible reduction in need for RRT. Possible reduction in norepinephrine requirements.
Angiotensin II	Vasodilatory shock	No overall improvement (study not powered to detect mortality difference). Possible improvement in survival in patients receiving RRT.	Improvement in MAP. Possible increase in thrombotic adverse events.
Levosimendan	Acutely decompensated heart failure	No improvement	Reduction in BNP and improvement in symptoms.
	Cardiac surgery	No improvement	Reduction in need for catecholamines and incidence of perioperative LCOS. Possible improvement in survival in patients with very low LVEF (⩽25%) undergoing CABG.
	Sepsis	No improvement	Improvement in cardiovascular SOFA score. Increased risk of arrhythmias and hypotension.
Milrinone	Acutely decompensated heart failure	No improvement Possible increase in mortality in patients with ischemic heart failure	Increased risk of arrhythmias and hypotension.
	Cardiac surgery	No improvement (study not powered to detect mortality difference)	Lower CI (with similar stroke volume but lower heart rate), lower PCWP, lower MAP, and lower incidence of AF as compared with dobutamine.
Terlipressin	Sepsis	No improvement	Increase in serious adverse events

Note. AF — atrial fibrillation; BNP — b-type natriuretic pepetide; CABG — coronary artery bypass graft; CI — cardiac index; LCOS — low cardiac output syndrome; LVEF — left ventricular ejection fraction; MAP — mean arterial pressure; PCWP — pulmonary capillary wedge pressure; RRT — renal-replacement therapy; SOFA — sequential organ failure assessment.

In a recent, interesting study by Levy et al., epinephrine was directly compared against norepinephrine in 57 patients with cardiogenic shock due to acute myocardial infarction [109].

The trial was interrupted early due to safety concerns because of a higher incidence of refractory shock and a trend towards increased mortality in the epinephrine group. Furthermore, hemodynamic data collected in the trial showed that while epinephrine actually increases cardiac index more than norepinephrine, this is driven by an increase in heart rate, while measured stroke volume remains similar. This might be relevant in the context of myocardial ischemia, as heart rate is a major determinant of myocardial oxygen consumption. However, it should be noted that very high dose of catecholamines (0.6-0.7 μg/kg/min) were used in this trial. One may argue that with this dose, subtle pharmacological differences between the drugs may become irrelevant. The trial has some limitations, such as including

lactate as a component of a safety outcome of «refractory shock» despite the well-known effect of epinephrine on lactate and higher lactate levels at baseline in the epinephrine group. These results challenge the notion that norepinephrine is detrimental in AMI-related cardiogenic shock, and provide a background for its use in this clinical setting, and for further studies of norepinephrine in patients with myocardial dysfunction [115].

Vasopressin and Terlipressin

Vasopressin is a pure vasoconstrictor that has become increasingly used in recent years as an alternative to norepinephrine.

A first, large RCT comparing vasopressin versus norepinephrine in septic shock was the Vasopressin and Septic Shock Trial (VASST) published in 2008 [68]. In this study, 778 patients with septic shock requiring 5 μg/min of norepinephrine were randomized to vasopressin or norepinephrine on top of open-label vasopressor.

The study showed that vasopressin improve MAP and reduce requirements of concomitant vasopressors, but with no effect on mortality. However, subgroup and post-hoc analyses suggested that vasopressin, especially in combination with steroids, may reduce mortality and acute kidney injury in patients with less severe shock [116, 117]. Accordingly, a 2×2 factorial trial investigating the effect of vasopressin and hydrocortisone in early septic shock (Vasopressin vs Norepinephrine as Initial Therapy in Septic Shock, VANISH) trial was designed [118].

This subsequent RCT enrolling 409 patients with early septic shock [71] showed no difference in mortality, a lower rate of need for renal-replacement therapy (RRT) in the vasopressin group (but driven by reduction in RRT only in non-survivors), and a higher rate of digital and myocardial ischemia in the vasopressin group. Taken together, these data suggest that vasopressin does effectively increase blood pressure and reduce norepinephrine requirements, but with no significant effects on major outcomes and with the potential to increase adverse events. The only potential benefit may be on renal function, as also suggested by a recent single-center RCT performed in the setting of post-cardiotomy vasoplegic shock [119].

Similarly, terlipressin (a long-acting analogue of vasopressin), despite some promising early results [120–123], failed to show improvement in outcomes in a recent mRCT of 617 patients [70]. On the contrary, terlipressin use increased rate of adverse events.

Phosphodiesterase 3-inhibitors

Phosphodiesterase-3 inhibitors are inodilators frequently used as inotropic agents in patients with LCOS, especially in patients receiving chronic beta-blocker therapy [103, 124–127]. They are generally considered as an alternative to catecholamines, or as agents with synergistic action in patients requiring high-dose inotropic support.

In the previously mentioned OPTIME-CHF study, patients with acutely decompensated heart failure but without shock were randomized to receive milrinone or placebo [90, 128]. Patients in the milrinone group had a higher rate of hypotension and arrhythmias, without differences in major outcomes. An interesting post-hoc analysis suggested that milrinone may worsen outcome in patients with ischemic heart failure, while it may be beneficial in patients with other causes of heart failure [28].

Another multicenter RCT performed in the setting of cardiac surgery compared milrinone versus dobutamine in patients with LCOS after cardiac surgery [129]. The study focused on hemodynamic rather than clinical endpoints, and showed that dobutamine was associated with higher cardiac index (driven by a greater increase in heart rate), higher MAP, and higher incidence of atrial fibrillation, while milrinone was associated with greater decrease in pulmonary capillary wedge pressure.

More recently, a single-center study randomized 192 patients with cardiogenic shock (Society of Cardiovascular Angiography and Interventions [SCAI]-stage B or higher [130]) to receive milrinone or dobutamine as primary inotropic agent (Dobutamine Compared to Milrinone [DOREMI] study) [131]. The Authors found no difference in terms of mortality, adverse events, hemodynamic parameters or need for vasopressors. Collectively, these studies confirm the hemodynamic efficacy of milrinone, but demonstrate neutral effects on clinical outcomes, as compared with catecholamines.

Interestingly, a recent experimental, physiologic study showed that milrinone has no direct inotropic effect when tested in conditions independent from pre- and afterload. Accordingly, the authors hypothesized that the increase in cardiac output observed with PDE-3 inhibitors may be related to their pre- and afterload modulation properties, rather than a direct inotropic effect [132]. This might also explain the greater effect on PCWP observed as compared with dobutamine.

Levosimendan

Levosimendan is a calcium-sensitizer and PDE-3 inhibitor that has been extensively investigated as inotropic agent in recent years. Indeed, it is the most investigated inotrope of the last 30 years, with more than 100 RCTs including almost 10000 patients [47].

Several RCTs and meta-analyses suggested a mortality benefit with levosimendan administration in a wide variety of clinical settings [133].

In the past years, several mRCTs has been conducted in the settings of acute heart failure, cardiac

surgery and sepsis [56-58, 80, 81, 87, 88, 134–136]. Collectively, all of these studies failed to show a beneficial effect of levosimendan on mortality or other major clinical outcomes. These studies showed that levosimendan administration is associated with a reduction in need for other concomitant inotropes and higher rate of hypotension (results that are consistent with its inodilator effect) and arrhythmias. The only potential beneficial effect has been suggested for the limited group of patients with very low left ventricular ejection fraction undergoing CABG, when administered prophylactically [137], and for patients on chronic beta-blocker therapy [138].

Interestingly, while traditionally considered a calcium-sensitizer, some experimental studies challenged this view and suggested that the inotropic effects of levosimendan are almost exclusively related to its PDE-3 inhibitor effect [139], and potentially to its effect on vascular K^+-ATP channels [16].

Angiotensin II

Angiotensin II is a potent pure vasoconstrictor that has been increasingly studied in recent years and suggested as a potential catecholamine-sparing agent for patients with vasodilatory shock.

In the largest and most recent mRCT performed, 344 patients with vasodilatory shock requiring high-dose norepinephrine and with normal cardiac index were randomized to receive angiotensin II or placebo on top of open-label norepinephrine [140]. The study showed that angiotensin II effectively increases MAP and reduces norepinephrine requirements. Although the study was underpowered to detect outcome differences, no hints for benefit or harms were reported. A subgroup analysis focusing on patients with need for RRT suggested that angiotensin II may be particularly beneficial in this subgroup of patients in terms of mortality and renal recovery [141]. However, these findings require further investigations. Of note, a potential increase in adverse events such as decreased cardiac output, thrombotic events, delirium and fungal infections has been associated with angiotensin II use [9, 10, 142].

Discussion

Despite concerns raised regarding their safety, inotropes are still widely used in critically ill patients. There are currently controversies in evidences since the increase in mortality associated with inotropes use reported in observational trials have not yet found confirm in RCTs. This attitude of physician may derive from the fact that, despite evidences from observational studied, RCTs have not yet shown an increase in mortality associated with inotropes use. Limits of observational trials are well known. Even with the best statistical methods, unreported clinical data may render correct matching of cases and controls impossible also when baseline characteristics are apparently similar. For example, several recently published meta-analyses showed that the association between a liberal transfusion strategy and mortality in cardiac surgery suggested by a large number of observational trials was not find confirm in RCTs [143, 144]. Patients requiring inotropic support are usually the most severely ill, with increasing doses of inotropes usually indicating increase disease severity [145]. In such a context, it may be very easy to find an association between inotropes use and increased mortality, yet determining the exact cause-effect relationship might be very difficult. Multicenter RCTs and meta-analyses of RCTs are currently considered by clinical scientists to provide the highest level of evidence regarding the effectiveness of a given treatment [146, 147]. Unfortunately, mRCT in critical care setting often provide neutral or contradicting results, with only few trials associated with a clear indication towards benefit or harm of a specific intervention [148–153]. These discouraging results may derive from true lack of effect, but also from organizational problems, patients heterogeneity, limited statistical power, or by difficulties in applying standardized protocols in the highly dynamic and variable setting of intensive care medicine [152, 154].

An important limitations of trials on inotropes use is that, unless they directly compare an inotrope against another, they generally exclude the most severely ill patients. This is because, in the history of critical illness, there is often a «turning point» at which the feeling of clinicians that treatment with inotropes is keeping the patients alive becomes so strong, that withholding such treatment would be unethical. In such a context, designing and conducting a trial comparing an intervention with no intervention would be really challenging from an ethical point of view [155]. Indeed, despite all concerns raised regarding safety of inotropes treatment, there is no trial randomizing patients judged to require treatment with inotropes to inotropes administration or no inotropes at all [47]. Indirect evidence may derive from studies investigating «liberal» (or higher) versus «restrictive» (or lower) hemodynamic targets (e. g. high vs low MAP, high vs low CO). Collectively, these studies suggested that higher targets (and hence greater use of interventions including fluids, vasopressors, and inotropes) are generally not necessary and sometimes may be harmful [82, 83, 156–158]. Indeed, future studies should probably focus on defining optimal hemodynamic targets, rather than comparing one molecule against another.

In the future, increasing clinical experience and technological advances in mechanical circulatory support (MCS) devices might change this situation and allow comparison between a pharmacological and a mechanical treatment; however it doesn't seem that this will happen in the short period, as use of

MCS still require a huge amount of expertise and resources, and MCS devices are still associated with several complications that requires careful weighting of benefit and risks in each single case [159–161]. Nevertheless, some pilot studies are now being performed and showed promising results in favor of MCS [162]. In addition, the recently developed concept of «mechanical unloading» as a new paradigm to improve outcome in heart failure and cardiogenic shock is gaining increasing popularity [163–165]. In general, mechanical circulatory support should be considered early in case of dependency on high-dose inotropes/vasopressor (especially with vasoactive-inotropic score [VIS] [145] >20).

Notably, even in patients with chronic heart failure, when disease reach an advanced phase available studies did not show a clear increase in mortality associated with inotropes use [166]. On the contrary, the definition of «inotrope-dependent» heart failure is widely used, particularly for patients waiting for therapy with either long-term ventricular assist devices (VAD) or heart transplantation [167, 168]. As correctly underlined by Guglin and Kaufman, if a patient cannot be weaned off inotropes because of inacceptable worsening organ function than we have to accept that inotropes prolong life [166]. In cardiac surgery, patients will often experience a potential life-threatening post-operative depression of cardiac function which is however likely to improve in few hours [169]. However, the LCOS associated with post-operative myocardial stunning or afterload mismatch might lead to multiorgan failure and death before spontaneous recovery occur, and temporary support with inotropes could allow patients to survive this critical phase [170, 171].

Therefore, according to current evidence, it seems that the question should not be whether inotropes increase mortality or not; we should instead focus our research in determining which patients and at which disease time-point will benefit from treatment with inotropes, and when, on the contrary, our treatment is harmful or futile [172, 173]. For example, Kastrup and colleagues observed that, while prolonged treatment with epinephrine and norepinephrine above a certain threshold is associated with poor survival rates, short-term use of high doses of these drugs was not linked to increased mortality [174]. In another interesting study, Prys-Pricard et al found that only 9% of critically ill patients receiving three or more vasoactive drugs survived to hospital discharge [175]. All of these surviving patients have received inotropic therapy, but, above all, all of these received an intervention aimed at correcting the underlying cause of cardiovascular dysfunction (e.g. surgery for control of infection source, myocardial revascularization, or heart transplantation). Early myocardial revascularization is, indeed, one of the very few treatment demonstrated in a RCT to improve survival in patients with cardiogenic shock following acute myocardial infarction [176–178]. All these studies suggest us that, regardless of the intensity of pharmacological inotropic support, unless the primary cause of hemodynamic instability could be treated, outcome will be poor. Patients whose ultimate cause for hemodynamic compromise can not be treated, will likely require prolonged treatment with increasing-dose of vasoactive drugs, thereby influencing results of observational trials on inotropes use.

To add further complexity, hemodynamic management of critically ill patients is not as easy as a simple decision to use or not inotropes. There is a complex interaction between fluids requirement and administration, pre-existing and new-onset cardiovascular and renal disease, and treatment with vasoactive drugs which often need to be carefully evaluated for each single patient, and continuously reviewed as treatment progresses [179–181]. After all, the strongest evidences in favor of inotropes use are in the setting of perioperative goal-directed hemodynamic optimization, which requires a combination of fluids, inotropes and appropriate hemodynamic monitoring aimed at reaching specific target parameters while avoiding unnecessary, excessive drug administration. Cardiopulmonary interaction and hemodynamic effects of mechanical ventilation should also be considered, especially in patients with both cardiovascular and respiratory failure [182, 184].

A greater attention has been given in recent years towards so-called metabolic resuscitation for patients with cardiovascular failure. Metabolic resuscitation includes a combination of steroids and vitamins (Vitamin C and vitamin B1) and a large number of RCTs has been performed to test these agents or combination of agents [185, 186]. Collectively, current evidence suggest that metabolic resuscitation does not provide survival benefit, with the potential exception of high-dose vitamin C [186]. Nevertheless, steroids administration in patients with septic shock reduces duration of vasopressor therapy and length of stay in ICU without increasing adverse events [186]. Additional areas of investigation include various alternative «metabolic» strategies of myocardial protection including amino acids and insulin-potassium-glucose [187–190], which are currently under investigation.

While hemodynamic management traditionally focused on macrocirculation and gross hemodynamic parameters (such as MAP), the role of microcirculatory dysfunction during critical illness is being increasingly recognized as a determinant of outcome [191]. As a result, the effect of the different agents is being investigated, and there are some evidences that inodilators may improve microcirculatory function and ultimately effective tissue perfusion, as compared

Table 3. Summary of current major evidence and concepts on inotropes/vasopressor use in critically ill patients.

Catecholamines (norepinephrine) remain first-line agents in almost every setting
Achievement of adequate hemodynamic goals is probably more important than molecules
Supraphysiological hemodynamic targets are harmful, restrictive targets (e.g. permissive hypotension) may be acceptable in several cases
Norepinephrine shortage is detrimental
Dopamine (high-dose) is detrimental
Vasopressin and angiotensin II reduce norepinephrine requirements, increase MAP but do not improve outcomes
PDE-3 inhibitors and levosimendan are not superior to catecholamines
Steroids reduce vasopressor requirements in septic shock and may improve survival
Interaction with preload/afterload/fluids/mechanical ventilation is important and under-investigated
Chose a simple inotropic-vasoconstrictor combination for your department and be ready to change it quickly if the patient is a non-responder or develops side effects
Consider early mechanical circulatory support (especially with VIS>20)

Note. MAP — mean arterial pressure; PDE-3 — phosphodiesterase-3; VIS — vasoactive-inotropic score.

with vasoconstrictors or inoconstrictors [78, 91, 192–194]. Future research should focus on the different effect of vasoactive medications on microcirculation and tissue perfusion independently of traditional hemodynamic parameters.

Finally, a new concept of «broad-spectrum vasopressors» has been recently described [195]. As for broad-spectrum antibiotic therapy, some experts suggest combination use of different vasopressors with different mechanism of action (e. g. norepinephrine, vasopressin and angiotensin II) to reduce the dose of each drug and limit side effects. Whether this concept translated into greater clinical benefit remains to be determined. Table 3 provides a final take-home message on inotropes and vasopressors use in critical care.

Conclusions

Inotropes are powerful drugs with relevant side effects that need to be known and acknowledged, and incorrect prescription of inotropes administration can increase morbidity and mortality Determination of when, to whom and how administer inotropes is of utmost importance to correctly manage critically ill patients.

The choice of molecule or combination of molecules does not seem to influence outcome as long as comparable hemodynamic parameters are obtained. Clinicians should chose the drug or combination of drugs they are most familiar with.

Future studies should focus on interaction with vasoactive drugs, fluids, pre-load and afterload, optimal timing of vasoactive initiations, and the role of MCS.

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Polytrauma: Definition of the Problem and Management Strategy (Review)

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Политравма: определение термина и тактики ведения больных (обзор)

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Summary

Polytrauma is a highly relevant problem from both scientific and clinical perspectives due to its high mortality rate (>20% in young and middle-aged individuals and >45% in the elderly). The lack of consensus in the definition of polytrauma complicates data collection and comparison of available datasets. In addition, selection of the most appropriate management strategy determining the quality of medical care and magnitude of invested resources can be challenging.

Aim of the review. To revisit the current definition of polytrauma and define the perspective directions for the diagnosis and management of patients with polytrauma.

Material and methods. Based on the data of 93 selected publications, we studied the mortality trends in the trauma and main causes of lethal outcomes, analyzed the polytrauma severity scales and determined their potential flaws, examined the guidelines for choosing the orthosurgical strategy according to the severity of the patient's condition.

Results. The pattern of mortality trends in trauma directly depends on the adequacy of severity assessment and the quality of medical care. The Berlin definition of polytrauma in combination with a mCGS/PTGS scale most accurately classifies polytrauma into four severity groups. For the «stable» patients, the use of primary definitive osteosynthesis with internal fixation (early total care, or ETC) is the gold standard of treatment. For the «borderline» and «unstable» groups, no definitive unified strategy has been adopted. Meanwhile, in «critical» patients, priority is given to general stabilization followed by delayed major surgery (damage control orthopaedics, or DCO), which increases survival.

Conclusion. The use of artificial intelligence and machine learning, which have been employed for more specific goals (predicting mortality and several common complications), seems reasonable for planning the management strategy in the «controversial» groups. The use of a clinical decision support system based on a unified patient registry could improve the quality of care for polytrauma, even by less experienced physicians.

Keywords: polytrauma, Berlin definition of polytrauma; orthosurgical strategy; trauma registry; machine learning

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

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Introduction

Despite all the measures taken to reduce trauma incidence over the past 30 years, the mortality rate has decreased only modestly by 1.8% [1, 2]. In the tertiary trauma care centers, about 20–25% of patients under 60 years of age die [3–5], and with

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increasing age the mortality rate increases to 45–60% [6, 7]. Urbanization and industrialization have a direct impact on the incidence of trauma owing to an increased number of personal vehicles in the population and more frequent road traffic accidents (RTAs), as well as industrial emergencies, fires, domestic traumas, and military conflicts. In cities and large settlements, the majority of patients with polytrauma arrive at the emergency room in the evening, during off-hours and weekends [8]. Brinck et al. link this fact with the recreational use of alcohol and other drugs [9], which are the dominant causes of road and domestic accidents [10]. According to the World Health Organization (WHO) report on «Global Road Safety», about 1.35 million people are killed each year in traffic accidents, and up to 50 million suffer nonfatal injuries. Road traffic injuries are the eighth leading cause of death in all age groups, and the first in the 5 to 29 age group. Over 90% of all deaths occur in low- and middle-income countries (27.5 and 14.4 cases per 100,000 population, respectively), while high-income countries have much lower death rates (9.3 cases per 100,000 population) [11]. In 50–80% of cases, the injured patient is a man of young/middle age [10, 12, 13]. More than half of polytrauma survivors subsequently have a significant reduction in quality of life or disability [14, 15]. According to the WHO forecast, by 2030 trauma will become one of the five leading causes of death. For example, in the People's Republic of China, where over 400,000 people die annually (23% of them due to road traffic injuries), polytrauma mortality is already in fifth place [10].

According to the Federal State Statistics Service of the Russian Federation, in 2020, out of 2.1 million deaths in the Russian Federation, more than 60,000 deaths were directly related to injuries, of which 17,000 were transport accidents [16]. In the Republic of Kazakhstan, the situation is summarized in the report of the Bureau of National Statistics of the Agency for Strategic Planning and Reforms. It presents summary data on mortality «from accidents, poisonings and injuries», based on which road traffic injuries rank 7th among all causes of death in Kazakhstan (14.7 cases [the 10-year average is 16.9] per 100,000 population per year) [17].

The aim of the review: to update the definition of «polytrauma» term and outline promising directions in diagnosis and management of patients with polytrauma.

Material and Methods

The literature review was based on available publications that included data on patients with severe polytrauma. Sources were retrieved from the PubMed/Medline database and limited to English language. No depth of search limitations were used. For the epidemiology section of the review, the following MeSH terms in various combinations were used: «multiple trauma», «polytrauma», «epidemiology», «mortality», «complications», and «causes of death». For the section on clinical course and severity of polytrauma, keywords such as «trauma assessment», «triage», «injury assessment scale», «trauma process», and «death tirade» were used. Also, for the Discussion section on the use of neural networks, artificial intelligence, and machine learning in emergency medicine and trauma, we searched for «clinical decision support systems», «artificial intelligence», «neural networks», «decision tree», and «machine learning» MeSH terms in combination with «multiple trauma» / «polytrauma» terms. Some of the material missed in the initial search was taken from citations in the retrieved publications and used for further detailed analysis. When selecting the publications for the review, we used the following criteria:

- Original full-text publications focusing on the main subject of the review.
- Papers published in international peer-reviewed journals with a study design of at least C level of evidence.
- Sources dealing with physiological and pathophysiological aspects were not time-limited

The publications that did not contain information on predicting patient condition based on physiological parameters were excluded, except for their sections covering artificial intelligence.

A total of 216 publications were reviewed, of which 93, containing relevant information, were selected. Using the selected sources, we studied the mortality patterns in trauma and its main causes, analyzed polytrauma severity scales and identified their potential flaws, examined guidelines for selecting orthosurgical strategies based on the severity of disease.

Definition of Polytrauma

In the second half of the 20th century, after the adoption of the term «polytrauma» and many refinements of its definition, Oestern et al. proposed the most comprehensive one, which is «polytrauma is a traumatic injury to two body regions, of which one or combination of all the existing injuries is life-threatening» [18]. This term is widely used in the Eurasian continent, especially in post-Soviet countries. In U.S. literature, the terms «multiple trauma» or «major trauma», with the added distinction of its life-threatening character, are more common [19].

An in-depth examination of the trauma pathophysiology produced an understanding of the need to assess not only anatomical lesions [20], but also physiological factors and parameters. In order to identify such parameters, which are associated with

mortality exceeding 10% in patients with polytrauma, in 2012 the International Working Group on Polytrauma was established, including organizations most actively involved in studying trauma care (American Association for the Surgery of Trauma (AAST), European Society for Trauma and Emergency Surgery (ESTES), German Trauma Society (DGU), British Trauma Society (BTS), New Zealand Association for the Surgery of Trauma (ANZAST)) [21]. They coined the «Berlin definition» (BD), according to which polytrauma is an injury to two or more body regions with an AIS score ⩾3 and one or more of the following values: systolic blood pressure (SBP) ⩽90 mmHg; Glasgow coma scale (GCS) score ⩽8; base excess (BE) ⩽6.0 mmol/l; international normalized ratio (INR) ⩾1.4 or activated partial thromboplastin time ⩾40 seconds; age ⩾70 years [21].

In 2017, Rau C. et al. conducted a retrospective study (n=1629) aimed at testing the validity of these criteria. Two groups of patients similar in medical and anatomical condition were defined, one of which had the physiological criteria from the BD. Mortality in the polytrauma group was significantly higher (OR 17.5; 95%; CI 4.21–72.76; P<0.001). Also these patients were more likely to be admitted to the intensive care unit (ICU) (84.1% vs 74.1; P=0.013) with a longer stay (10.3 days vs 7.5 days; P=0.003). In addition, the treatment of polytrauma was generally more costly for the hospital (by 31.5%) with increased spending on tests (by 33.1%), surgical interventions (by 40.6%), and medication treatment (by 53.9%) [22]. In the Driessen et al. study, the BD was applied to the Dutch national trauma registry (300,649 cases included in the study). The authors concluded that adding physiological parameters to the anatomical scale improved the sensitivity in estimating the likelihood of an adverse outcome. Thus, in patients classified as «polytrauma» according to the BD (n=4,264), the mortality was 27.2%, and the need for admission to an ICU was 71.2% [23].

Patterns of Mortality Distribution

Assessment of polytrauma severity and further management strategy are directly related to the risk of adverse outcomes. In 1980, Baker et al. conducted one of the key studies [24] in the epidemiology of mortality among polytrauma patients. A tri-modal mortality distribution was revealed [25], which later was studied in more detail [13, 26–29]. Three mortality peaks were identified: within the first hour after the injury, during the first 24 hours of hospital stay, and «late death» (within several days or weeks). However, in high-income countries with advanced emergency medical services, this tri-modality is not always evident [1, 2, 12]. Here, the patient after receiving the minimal efficient care in the prehospital period, including fracture stabilization, can be transported from the scene to a tertiary trauma center within the first 30 minutes after the trauma team activation [30, 31]. This approach is associated with a unimodal or bimodal distribution of fatalities, due to the superposition of the first peak on the second [8].

Regardless of the modality of fatality distribution, the main causes of death remain the same [28]. Looking at the tri-modality, which is more characteristic of middle- and low-income countries, the researchers found that about half of all fatal cases occurred during the first peak due to severe fatal injuries. Of these, craniocerebral trauma (skull base fracture, intracranial hemorrhages, cerebral edema, cerebral necrosis) accounts for up to 70% of cases. From 25 to 80% of deaths are associated with the consequences of bleeding and/or coagulation disorders. In addition, mortality is high in acute multiple organ failure (MOF) or systemic inflammatory response (SIR). During the second peak, the causes are similar, but their clinical progression is not so dramatic, and usually no fatal outcome during the first hour of injury occurs. During the third peak, death is due to septic complications, slowly progressing MOF, and comorbidities (coronary heart disease, chronic heart failure, and chronic pulmonary conditions) [1, 13]. Often, delayed mortality is due to a longer stay in the ICU with the underlying brain damage and associated respiratory complications (damage of brain respiratory center, ventilator-associated pneumonia, acute respiratory distress syndrome) [32].

Assessment of Polytrauma Severity and Orthosurgical Approach

One of the best approaches to medical care for trauma patients involves a trauma team in the emergency department, operating according to a standard algorithm [33, 34]. The scope of their activities should include correct assessment of the disease severity, performing cardiopulmonary resuscitation (CPR), and determining the necessary surgical strategy [35, 36]. An early involvement of such team can significantly reduce the incidence of complications and adverse outcomes [10], but in practice, this occurs in only half of all cases [37]. This is due to the lack of training of emergency department staff in the algorithms and criteria for involvement [38]. In addition, non-specialized hospitals often lack a trauma team, and all care is provided by general anesthesiologists, intensive care specialists and trauma surgeons [39]. The quality of care remains a matter of medical experience and competence, the low level of which inevitably leads to inaccurate assessment of risks and likely outcomes in every particular case of polytrauma [40]. The assessment of patient severity is an obligatory skill for every physician, but the variability of polytrauma injuries complicates such assessment and requires

special training and licensing [41]. Internationally, a trained intensivist, anesthesiologist, or orthosurgeon is responsible for assessing the status of a polytrauma patient [34, 42].

All scales used can be divided into three groups: anatomical, physiological, and combined. Internationally, the basic anatomical scale describing traumatic injuries is the Abbreviated Injury Scale (AIS), which characterizes three aspects of injury such as body region, type of anatomical structure, and severity of injury [41]. This scale characterizes each injury separately and does not allow evaluating patients with multiple fractures as a whole. The Injury Severity Score (ISS) was developed to describe polytrauma, based on the AIS injury assessment. The scale principle is based on calculating the sum of the squares of the three maximally injured body regions. At the end of the last century, clinicians used to define an injury as «severe» if mortality exceeded 20%, corresponding to an ISS score ⩾16 [23]. However, with the development of the trauma care service, mortality began to decrease, which led to disagreement concerning the minimum ISS threshold, which now varies from 15 to 26 points [19].

The ISS scale was modified in respect to the final score calculation for improving sensitivity [43]. Thus, in the New ISS modification (NISS), the final score consists of the sum of squares of the three maximum AIS scores with the possibility of repeated inclusion of body regions [44]. This modification increased sensitivity concerning the necessity of tracheal intubation and mechanical lung ventilation. Unfortunately, evaluation of trauma with true anatomic scales is not flawless. The most frequent problems are discrepancies between anatomical and physiological severity and inherent inconsistency, where cases of the same injury severity score in different regions have dramatically different outcomes [37, 45]. In addition, the complexity of correct coding and mathematical calculation is the reason for the low inter-researcher reproducibility of the polytrauma definition compared to the BD (Cohen's kappa coefficient for ISS ⩾ 16 = 0.521; ISS ⩾ 16 = 0.521; BOP = 0.781) [46].

Physiological scales are mostly used in the ICU setting, where assessment of severity correlates closely with mortality. The most common scales that can be used in polytrauma are the Sequential Organ Failure Assessment (SOFA) [47–49] and the Acute Physiology and Chronic Health Evaluation II (APACHE-II) [50–52]. Both scales are based on the assessment of vital and biochemical parameters and aimed at predicting the risk of septic complications and MOF which are the most common causes of death in ICU [53, 54]. The SOFA scale assesses functional changes in respiratory, cardiovascular, coagulation and nervous systems, as well as indirectly evaluates liver and renal function. In turn, the APACHE-II is aimed at assessing both the current and preclinical physiological state of the patient. A limitation of the use of intensive care scales is the need for rapid laboratory testing, as well as the intricate scoring principles. If the scales are simplified by excluding laboratory parameters, most surrogate points, such as mortality and the need for intubation [55], are still available, but with a significant sacrifice in specificity.

Among trauma physiological scales, the Revised Trauma Score (RTS) is widely used, which assesses neurological status using GCS, respiratory rate and systolic BP, multiplying them by special coefficients and then adding the products [56]. In the emergency room setting, the RTS is sufficient to assess adverse outcomes, but not the injury severity [45]. The RTS, like other scales based on fixed coefficients, has been criticized over time and requires adjustment of coefficients [57–59].

Among combined scales, Trauma Injury Severity Score (TRISS) [60] and its simplified modification, A Severity Characterization of Trauma (ASCOT), remain the most used. The scale is based on ISS, RTS and age of the patient multiplied by coefficients whose exact values are also debated [61, 62] due to medical progress and increasing experience with polytrauma patients [45]. Given the modality and causes of death, there is a need to assess the patient's severity in terms of nervous system injuries and coagulation disorders. In pediatric practice, the BIG scale is used for this purpose, and has also shown satisfactory results in adults [59]. BIG is an abbreviation of BE, INR (both indicating hemorrhagic shock severity) and GCS . The lack of assessment of skeletal injuries makes it narrowly focused and not applicable when no traumatic brain injury is present.

All of the above physiological scales are aimed more at determining the risk of death relative to the baseline condition, rather than at actually categorizing patients. In addition, some researchers, due to unclear reasons, fabricate novel scales from those already available by adding several nominally new clinical variables [10, 48, 68, 50, 55, 59, 63–67].

As of the time of writing this paper, the authors had not found any generally accepted criteria for differentiating patients with polytrauma in relation to the severity of their condition. However, the problem of categorizing patients was addressed by German researchers, led by Pape H. C. [69]. After a series of studies the authors came to the conclusion that in addition to the classical «deadly triad» (BE<–6 mmol/l, pH <7.2, t<35°C) [70–72], the extent of soft tissue injuries directly influences the trauma outcome. Based on this finding, the Clinical Grading System (CGS), an anatomical and physiological scale for assessing the severity of polytrauma with classification of patients into «stable», «borderline», «unstable» and «critical» groups was proposed. The

original version contained several flaws such as the presence of little-known anatomical scales, expensive laboratory tests, and poor internal consistency of the criteria. For the latter reason, the groups of borderline and unstable patients are the most controversial with respect to the selection of surgical treatment strategy. Later, the authors revisited the data to expand the patient sample and developed Polytrauma Grading Score (PTGS) based on CGS (Table 1) [63]. This version did not contain the doubtful variables while maintaining the ability to differentiate between patients.

In parallel with Pape H. C., Nahm et al. modified the original CGS by simplifying and adapting it to real clinical setting and proposed the the mCGS (Table 2) [39].

Recently, Halvachizadeh et al. [74] conducted a large comparative analysis (*n*=3368) of CGS [69], mCGS [39], PTGS [63] and Early Appropriate Care (EAC) protocol [75] for sensitivity in determining the risk of early (death in the first 72 hours from traumatic brain injury and/or blood loss) and late (MOF, acute respiratory distress syndrome (ARDS), pneumonia, sepsis and death after 72 hours) complications in patients with polytrauma. According to mCGS, the change in transfusion volume estimation during the first 24 hours significantly affected the accuracy of determining the «stability» of the patient's clinical condition. The «borderline» patients had a higher mortality rate (50%) when categorized using the PTGS scale than similar groups based on CGS (35.9%) or mCGS (37.8%). Overall, the study showed that the proposed scales are effective in categorizing patients by severity of condition into groups and can be improved in terms of the criteria used.

The adequacy of severity assessment using physiological scales is closely related to the pathophysiology of trauma [69]. Any tissue damage is known to result in changes in immune status. Initially, hyperinflammation develops, followed by counter-regulatory anti-inflammatory response.

Table 1. The Polytrauma Grading Score (PTGS).

Parameter	Value	Points
Systolic blood pressure, mm Hg	76–90	1
	⩽75	2
BE, mmol/l	–(8–10)	2
	<–10	4
INR	1.4–2,0	1
	>2.0	3
NISS assessment	35–49	3
	50–75	4
The volume of hemotransfusion, units	3–14	2
	⩾15	5
Platelet count, $\times 10^9$/l	<150	2

Note. BE — base excess; INR — international normalized ratio; NISS — New Injury Severity Score. Interpretation. Less than 6 points, stable (mortality up to 5%); 6–11 points, borderline (mortality up to 15%); more than 11 баллов, unstable (mortality up to 40%).

In the literature, this stage is called the «first hit», and its severity is directly related to the extent of injury. Thus, in monotrauma, the above-described immune response changes are not crucial for the patient, while in polytrauma, surgical intervention together with complications (coagulation disorder, bleeding and hypothermia) enhance the body's response to tissue damage and can lead to the «second hit», which involves systemic hyperimmune response [42]. Depending on the predisposing factors, the «second hit» in blunt extensive soft tissue trauma causes subacute complications such as ARDS, SIRS or MOF [76].

Based on the pathophysiology of trauma and the decision making regarding the risks in the patient, one of two orthosurgical approaches is commonly used in developed countries: primary definitive osteosynthesis with internal fixation (Early Total Care, ETC) and temporary external fixation followed by secondary definitive osteosynthesis with internal fixation (Damage Control Orthopedics, DCO). ETC is the «gold standard» [69] in terms of orthosurgery, as it allows early patient mobilization and has a lower incidence of late complications,

Table 2. The Modified Clinical Grading System (mCGS).

Factor	Parameter	Stable (grade I)	Borderline (grade II)	Unstable (grade III)	In extremis (grade IV)
Shock	SBP, mm Hg	⩾100	⩾80 – <100	⩾60–<80	<60
	BE, mmol/l	⩾–2.3	<–2.3–⩾–4.5	<–4.5–⩾–6.0	<–6.0
	Lactate, mmol/l	0,5–⩽2.2	>2.2–⩽2.5	>2.5–⩽4.0	>4.0
	PRBC transfusion (on day of injury), units	⩽2	3–8	9–15	⩾16
Coagulation	Platelets, $\times 10^3$/μl	>110	>90–⩽110	>70–⩽90	⩽70
Temperature	°C	>34	>33–⩽34	>30–⩽33	⩽30
Soft tissue injury	Chest injury AIS	⩽2	3	4	⩾5
	Moore OIS [73]	⩽2	3	4	⩾5
	Pelvic injury (AO/OTA)	нет	A	B	C or crush
	Extremities AIS	⩽2	3	4	5 or crush

Note. SBP — systolic blood pressure; BE — base excess; AIS — Abbreviated Injury Scale; PRBC — packs of red blood cells; OIS — organ injury severity; AO/OTA — AO Foundation and Orthopaedic Trauma Association. A patient can be classified into a specific group if three of the four factor criteria are met.

but often leads to the development of «second hit». Early final fixation in unstable and critical patients can cause fat embolism, which enhances lung damage associated with their contusion or rib fractures [36]. In turn, DCO allows resuscitation and stabilization of injuries of the long tubular bones and pelvis, thus stopping massive bleeding, followed by transferring the patient to ICU for further correction of vital signs. This approach increases the total length of stay in the ICU and the hospital, is not cost-effective and associates with a significantly higher incidence of late thrombotic and septic complications due to delayed major surgery [35]. In a systematic review conducted by P. Lichte et al. [42], numerous evidence has been found that DCO dramatically reduces blood loss in patients in comparison with ETC (up to four times) and the duration of surgical intervention (over three times). The sparing and protective approach of DCO has a positive effect on the patient's immune status, which was confirmed in a high-quality study by Pape H. C. et al. [77]. Meanwhile, the review presents contradictory results on the relationship between the categorization of patients («stable», «borderline», «unstable», «critical») and the use of DCO for stable and borderline patients. This could be due to the lack of universal tools and criteria for accurate triage, which can improve survival rate [10, 36]. Despite attempts to classify patients into severity groups to determine orthosurgical strategies aimed at minimizing complications, there are many nuances in each individual patient's body that affect approach and outcome (e. g., need for general anesthesia, presence of initial hemorrhagic shock, changes in blood buffer capacity and anatomical regions of injury) [78–82]. The available studies comparing DCO and ETC are mostly retrospective and based on a small sample of patients with polytrauma, but their results provide background for the development of additional criteria to define borderline patients [83].

Clinical Decision Support Systems

Clinical decision support systems (CDSS) based on artificial intelligence (AI) are being widely implemented to improve approaches to the diagnosis and treatment of various diseases. The main objective of such a system is to analyze the information collected by a physician and produce a certain result. Algorithms that perform this kind of activity are commonly referred to as «models». Linear and logistic regression, neural networks, decision trees, and the Rotation Forest method serve as examples of such models [84]. Unlike statistical packages, an AI-based model is in most cases capable of continuous self-learning, thus improving its performance.

The issue of using a computer in the management of severe trauma patients emerged at the end of the twentieth century. At that time, medicine was already using simple CDSSs based on rigid «If — Then» conditions. The «algorithm» for assessment, in fact, being a set of conditions, was based on the treatment protocols of that time and compared the patient's condition with already described variants of trauma manifestations [85]. With the development of information technology, the science of machine learning, and big data analysis, simple systems began to evolve into more powerful tools. Recently, a niche in the field of trauma patient management has been actively filled by various AI solutions. For example, in order to describe injuries more accurately on different types of images, models have already been developed that show superiority over physicians [86]. In addition, there are two models that allow to suspect with high accuracy the development of acute traumatic coagulopathy [87]. Other studies have attempted to use AI to predict the incidence of trauma admissions relative to weather conditions, day of the week, and time [88].

Ehrlich et al. noted that AI-based systems are necessary in the emergency room setting to quickly provide quality triage of patients and determine further treatment strategies [89]. Almost all used scales of patient assessment try to assign the severity of the condition to a number, which should give the physician a clear understanding of the clinical situation and determine what decision will be taken. With a large quality database, it is possible to create a computer model that performs these procedures automatically with high reliability [90, 91]. However, any assessment scale consists of two parts which are a set of variables and a rule defining the principle of calculating the final score for interpretation. Despite all the computational power, a computer is not capable of presenting every physiological aspect of a patient as a set of variables. This necessitates the analytical determination of a minimum set of input parameters that more accurately reflect the clinical condition and course of trauma. Wide variability and multiple inputs often require different modeling approaches. For these reasons, the currently available solutions are narrowly focused. The use of AI in the field of medicine is one of the priority areas and requires additional research [89].

Limitations

The selection of material for the review was difficult because of the heterogeneity of the literature and the lack of a unified definition of polytrauma. This was due to the heterogeneity of publications in levels of evidence (I–II) and grades of recommendation (A–C), as well as the lack of a unified definition of polytrauma. After analyzing the original material, the authors achieved most of their aims by drawing additional conclusions.

The largest percentage of people die from craniocerebral trauma, which is mostly incompatible

with life, as well as from the sequelae of massive bleeding. In emergency care, timely control of bleeding improves the survival rate of patients during the «golden hour», as well as is directly related to the development of late complications [92, 93]. Improvement of the medical care and management organization could help significantly reduce mortality and avoid its trigger-modal distribution [1].

The authors agree with the international opinion about the best accuracy and adequacy of the Berlin definition of polytrauma, which has shown high interobserver reproducibility.

The authors failed to identify generally accepted criteria or scales for classifying patients into groups with respect to the severity. The most used scales, such as AIS, ISS, TRISS, SOFA, have various limitations and are not helpful in patient classification [37, 45, 49, 62]. The large choice of scales obliges a clinician to spend time studying their characteristics and choosing the best one. For this reason, there is a need to develop international criteria for categorizing patients with polytrauma in respect to the severity of their initial condition.

German researchers focusing on polytrauma have developed several scales (CGS, mCGS, PTGS) categorizing patients according to the severity of diseases based on a large database of clinical cases [39, 63, 69]. Obviously, there is a need for additional exploration of the experience of German colleagues in local populations with adaptation of the scales to the existing medical capacities.

The issue of optimal timing of definitive osteosynthesis with internal fixation also remains controversial [10, 36]. The algorithm-guided patient management is known to increase the likelihood of a favorable outcome [34, 35]. Currently, several guidelines indicate the need for ETC in «stable» patients and DCO in «critical» patients. However, for the «borderline» and «unstable» patients, there are no clear recommendations for a specific orthosurgical approach due to inconsistent research results [36, 42, 80]. Analyzing the physiological status of an individual patient and predicting the risks of complications in an emergency setting is a great challenge for the physician. Information technologies can be successfully implemented in the polytrauma management practice, as well as in other areas of medicine [89]. With a well-trained computer model, even physicians with minimal experience with polytrauma are able to perform high-quality assessment and categorization of patients [87]. In addition, clinical decision support systems can predict risks and determine the best tactics for a specific patient.

There is an obvious need for a registry of polytrauma patients accessible to all clinics providing orthosurgical care. Participation in such a registry facilitates access to information and enables researchers to conduct clinical studies with the development of treatment and diagnostic protocols, especially in regions with limited exposure to these data [90]. Unification of the database record format allows to construct big databases and improves the quality of statistical analysis. An excellent example of such registers is the Trauma Register of the German Trauma Society (TraumaRegister DGU®), which requires mandatory participation of all clinics in Germany and also provides the possibility of free participation to clinics from other countries. Since its introduction in 1993 and with more than 700 clinics, it has been able to collect a database of over 450,000 patients in 28 years.

Conclusion

A possible solution to the issue of defining an optimal management strategy for «vulnerable» groups of patients is the use of artificial intelligence and machine learning, which are already applicable to more specific problems (predicting mortality and the development of some common complications based on initial patient assessment). The use of a clinical decision support system based on a unified patient registry will improve the quality of polytrauma care, even by less experienced specialists.

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Neurotoxicity of Anaesthetics and Sedatives and Their Influence on Post-Operative Maladaptive Behavioural Disorders in Paediatric Anaesthesia (The Letter)

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Нейротоксичность анестетиков и седативных средств и их влияние на послеоперационные дезадаптивные расстройства поведения в педиатрической анестезиологии (Письмо в редакцию)

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Summary

Neurotoxicity of anaesthetics have become one of the most discussed problems in paediatric anaesthesiology. The experimental studies on animal models have shown that the anaesthetics used in general anaesthesia should have an influence on neurodegenerative processes, neuroapoptosis and the irregulated death of the neuronal cells. Because of this fact, scientists are trying to discover the possibilities of how to minimize the adverse effects of anaesthesia and revise the other alternatives of prevention of anaesthesia-induced maladaptive behavioural disorders.

Key words: neurotoxicity of anaesthetics; maladaptive behavioural disorders; mechanism of neurotoxicity; post-anaesthesia behavioural changes in children; future of paediatric anaesthesiology

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

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Introduction

The results of recent studies indicate a neurotoxic effect of commonly used inhaled and intravenous anaesthetics on the developing brain of mammals, which has been long overlooked.

In retrospective and observational studies, data appear to indicate behavioural and neurocognitive abnormalities in children who have undergone general anaesthesia. These disorders occur in up to 50% of children operated on at the youngest age and are resolved within 1 month after the operation. This phenomenon is observed more often the lower is the age of the child, the more painful is the operation and the more restless is the introduction to anaesthesia.

In critically ill new-born children, especially those with low birth weight, a decrease in IQ, a higher incidence of cerebral palsy and visual and hearing impairments have been reported at a later age. Espe-

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cially at this age, it is very difficult to separate the consequences of stress, homeostasis disorders, surgery and several days of critical condition from the effect of anaesthetics.

Influence of Anaesthetics and Sedatives on Ontogenesis

The development and growth of the mammalian brain is a complex process starting with neurogenesis, continuing with the differentiation of neurons into different subpopulations, migration of nerve cells to their definitive localisation in the central nervous system (CNS), synaptogenesis, synapse formation and myelination of neuron-axon connections. These processes differ significantly depending on the gestational age and species of the mammal in direct relation to the expected life expectancy of the mammal.

Synaptogenesis begins in humans in the third trimester of pregnancy. Brain growth ends at the age of 2–3 years. During physiological development, CNS neurons are produced in considerable abundance. Their subsequent elimination is crucial for achieving normal brain size as well as its morphology. During ontogenesis, excess neurons are eliminated 50–70% by apoptosis [1].

Laboratory work on in vitro cultures demonstrates the dependence of the extent of neurodegenerative changes on the age of the individual, the dose of anaesthetic and the duration of its exposure. Differences in regional distribution and cell-specific deleterious effects of anaesthetics on the developing brain as well as their persistence into adolescence in the dentate gyrus and bulbus nervus olfactorius areas were found. A similar effect is described after long-term administration of drugs (especially benzodiazepines) during treatment in intensive care units.

While the sensitivity of neurons to anaesthesia-indicated toxicity corresponds to a maximum in the development of synaptogenesis, the greatest susceptibility of oligodendrocytes during exposure to anaesthesia occurs at the time of myelination. Thus, both CNS components are highly sensitive to apoptotic neurodegeneration [2].

Recent research points to a developmentally determined protective role of microglia during brain development and maturation because, under physiological conditions, the microglia alter the synaptic transmission and plasticity of the brain. Under certain conditions — hypoxia, infection, traumatic brain injury, autoimmune neurodegenerative processes — microglia function is enhanced and can modify synaptic connections and plasticity of memory and learning [3].

Many current research findings point to the neurotoxic effect of commonly used anaesthetics and sedatives on animal models after exposure to doses of anaesthetics used in paediatric anaesthesiology [4].

The neurotoxicity of anaesthetics in animals, which persists into adulthood, depends on the dose and number of anaesthetics used, the maturity of the developing brain at the time of exposure to the anaesthetic and the presence of other factors, especially inflammatory processes in the body. The combination of all influences increases the sensitivity of the brain to the effect of the anaesthetic [3]. «Pharmaceuticals commonly used in intensive care units and operating theatres, such as isoflurane, benzodiazepines, barbiturates, etomidate, propofol and ketamine, are involved in the development of neurotoxicity in animals» [3].

Although these effects on the human body have not yet been clearly demonstrated, a link between anaesthetic exposure and acquired neurological development disorder in children is evident.

In particular, exposure of children to anaesthetics at an early age causes transient suppression of neurogenesis, ultrastructural abnormalities of synapses and alterations in the development of the signalling and neuroinflammatory neural network, loss of neurons, production of free radicals and alterations of mitochondrial integrity. These side effects on the basis of developing neuronal connections can result in acute neuronal damage as well as long-lasting neurocognitive dysfunctions [3–5]. Cognitive deficits are mainly related to the hippocampal region, where the extent of damage to their neurons is much greater compared to other brain regions.

This provides a possible explanation for the neuroapoptosis following anaesthesia described in this area by most studies, while long-term neurocognitive dysfunctions are described in only a few of them. An increase in the incidence of cell death after anaesthetic exposure does not necessarily lead to a significant reduction in neuronal density in old age. During development, 50–70% of all CNS cells undergo natural cell death, thus maintaining the physiological structure of the CNS. It remains unclear whether anaesthesia accelerates the apoptosis of neurons that are primarily destined for death in physiological degeneration, or damages healthy neurons that are not primarily destined for death. Thus, the fact that cognitive deficit is caused by cell death with consequent loss of neurons, i. e. not only by cell death itself, remains an important finding. At the same time, it remains unclear whether neuroapoptosis is the only cause of cognitive dysfunction [5].

In children, associations have been found between long-term exposure to anaesthetics and sedatives, especially GABAergic, and subsequently lower levels of neurological development until the age of 12–48 months.

A special group among these patients are children with congenital heart and vascular diseases, whose survival has increased by up to 90% compared to the past due to neonatal surgery. In 30–50% of these children, intelligence disorders, major or minor motor dysfunctions, and receptive and expressive speech disorders occur after undergoing cardiac surgery. Memory disorders, speech disorders, counting disorders and visual-motor coordination are observed at the age of school entry and integration of these children.

The Mechanism of Anaesthesia-Induced Neurotoxicity

The effect of most anaesthetics results from their action as NMDA receptor antagonists and/or GABA A agonists. Anaesthesia-induced neurotoxicity is mediated through the mitochondrial apoptotic cascade (the internal part of the anaesthetic-induced apoptotic cascade), which activates the neurotropic cascade and subsequently the cascade leading to the destruction of these receptors. Thus, commonly used anaesthetics cause extensive apoptotic neurodegeneration in various parts of the brain during its development.

The main role of every mitochondrion in the cell is the production of energy through oxidative phosphorylation. However, mitochondria also have many regulatory functions that are important for further survival as well as cell death, as exemplified by the intrinsic apoptotic cascade, which leads to organised and controlled cell death. Activation of this cascade is caused by the release of cytochrome c from the mitochondria into the cytosol. Cytochrome c forms apoptosomes followed by activation of apoptotic protease factor (APAF-1) to form deoxyadenosine triphosphate (dATP) and adenosine triphosphate (ATP). Binding of the apoptosome complex activates procaspase-9. Activated caspase-9 activates caspase-3, resulting in deoxyribonucleic acid (DNA) fragmentation and cell death.

The physiological function of cytochrome c is the transfer of electrons between complex III and IV of the respiratory chain during oxidative phosphorylation. However, in binding to cardiolipin, it can also have peroxidase effects, by inducing the oxidation of hydroperoxycardiolipin thereby contributing to the development of pro-apoptotic stimuli. Oxidative stress contributes significantly to its production.

Andropoulos D. B. et al. showed the internal and external pathway of the apoptotic cascade, as well as the antiapoptotic effects of dexmedetomidine and erythropoietin [2].

Many inhaled (isoflurane, sevoflurane) and intravenous (propofol) anaesthetics increase free radical production in the developing brain. Exposure to anaesthetics, even under conditions of normoxemia, increases the production of free oxygen and nitrogen radicals in developing neurons, hippocampus, subiculum, and thalamus. Oxidative stress caused by anaesthetics leads to peroxidation of membrane lipids, damage to mitochondria and their impaired integrity.

Binding of apoptosis-induced ligands to cell death receptors activates the external part of the anaesthetic-induced apoptotic cascade. The main pro-apoptotic ligands are: tumour necrosis factor alpha (TNF), Fas and TNF-related apoptosis-including ligands (TRAILs). Activation of cellular death receptors by the adoption of the intracellular Fas-associated death domain (FADD) leads to the internalisation of procaspase-8, which results not only in its activation but also in the activation of caspase-3. Exposure of isoflurane together with nitric oxide and simultaneously midazolam upregulated Fas receptors and activated caspase-8 in the parietal and occipital cortex in an experiment in 7-day-old laboratory rats. While the internal pathway of the apoptotic part of the cascade was activated as early as 2 hours after exposure to this combination of anaesthetics. The time difference was due to the dependence on Fas protein expression and upregulation.

NMDA antagonists and GABA receptor agonists cause neuronal cell death by activating the mitochondrial portion of apoptosis.

Neurotrophins belong to growth factors that determine the survival and differentiation of neurons and the plasticity of synapses. Already in 7-day-old laboratory rats exposed to a 6-hour mixture of isoflurane, nitric oxide and midazolam, a decrease in the activity of their main representative BDNF (brain-derived neurotrophic factor) in the developing thalamus was demonstrated.

There are suspicions that opioids may induce apoptosis of developing neurons. For example, infusion of continuous fentanyl results in an increase in caspase-3 levels in specific brain sections of 5-day-old pigs compared to unexposed individuals. Other studies describe the determining effect of morphine on the developing cortex and amygdala. The area of the hippocampus remains surprisingly spared from these influences. The neurotoxic effects of propofol have also been extensively studied and its induced neuronal apoptosis has been described in both rodents and primates [2].

The immature brain is very susceptible to anaesthesia-induced neuronal apoptosis. The fact remains that despite the fact that some neurons undergo cell death after exposure to anaesthetics, while other neurons survive intact [6] demonstrated that the neurotoxicity of anaesthetics depends more on the age of the neuron than on the age of the organism. They pointed out that postnatal gyrus cells undergoing isoflurane-induced neurodegeneration

are young and relatively immature. They reach the maximum anaesthetic-induced vulnerability at the age of 2 weeks after birth. They have also focused their research on olfactorius bulbus cells, which undergo neurogenesis into adulthood, where they have also demonstrated their susceptibility to anaesthesia-induced apoptosis.

The heterogeneity of susceptibility to neurotoxic effects may vary with age. This fact increases the possibility of confirming the assumption that anaesthesia-induced neurotoxicity depends on the age of the organism at the time of its exposure to the adverse effect. Furthermore, the time of manifestation of the neurotoxic effect may exceed the time of early childhood. Young rhesus macaque which were repeatedly exposed to Sevorane developed anxiety behaviour up to 6 months after exposure compared to the unexposed sample. Thus, the study only confirms the effect of general anaesthesia on the development of behavioural disorders with a longer time interval from exposure to anaesthetics in primates [4]. Neurodegenerative and neuroprotective effects of anesthetics have been described in the study by Andropoulos D. B. et al. [2].

Consequences of Neurotoxicity

The success of current intensive care therapy contributes significantly to the increased survival rate of critically ill patients. However, after overcoming this critical and life-threatening period, a significant proportion of paediatric patients have motor, cognitive, and psychological consequences. «Cognitive deficit after overcoming a critical illness leads to a decrease in IQ, poorer school performance and attention and memory disorders. Risk factors for cognitive impairment in patients after hospitalisation in intensive care units include: artificial lung ventilation, extracorporeal vital signs, traumatic impairment, oncological and neurological diseases, and the use of medication for sedation as well as opiates» [3].

Postnatal neurogenesis is a critical period for the development of learning and memory, which are located mainly in the hippocampus. Exposure to the anaesthetic during peak synaptogenesis significantly reduces synaptic transmission and synapse density, thereby causing inhibition of synaptic transmission.

The development of neurons also depends on the integrity of the CNS and the proper function of the astroglia, so there is a reasonable suspicion that the adverse effects of anaesthesia may also occur through its pathways. The adverse effect of reducing the levels of the excitatory neurotransmitters aspartate and glutamate in the cortex and hippocampus on the modulation of learning and memory is also expected [5].

The focus of current laboratory studies is developing therapeutic and preventive strategies to fight neurotoxicity. Of these, the beneficial effects of dexmedetomidine, the mechanism of upregulation of anti-apoptotic proteins, are evident [2]. Erythropoietin also crosses the blood-brain barrier, stimulates neurogenesis, induces neuronal differentiation, activates neurotropic signalling, and also has anti-apoptotic, antioxidant, and anti-inflammatory properties. Due to the anaesthetic-induced production of inflammatory mediators and the development of oxidative stress described after the use of inhaled anaesthetics (isoflurane), the effects of vitamins (vitamin B3, vitamin D3) and other nutrients are also studied [2].

Conclusion

Anaesthesia-induced neuronal damage should have far-reaching consequences in the future of paediatric patients. Therefore, research into the neurotoxicity of drugs used in patients in paediatric intensive care medicine and anaesthesiology should be aimed at elucidating the absolute and dose-effect of anaesthetic drugs on the developing brain. Understanding the mechanism of toxicity of anaesthetics to the developing nervous system, in particular the mechanism by which anaesthesia impairs brain function for up to one month, would significantly contribute to the prevention and development of therapeutic strategies [5]. Further research will be needed to clarify the stage of hippocampal neurogenesis with which anaesthetics interfere, thereby inducing impaired synapse development and their remodelling as a potential cause of cognitive dysfunction. Research will also focus on neurotoxicity therapy options, preventive methods and protection of the developing brain from neurotoxic effects. Some ongoing preclinical animal studies have already shown positive results. If the neurodegenerative effects of anaesthetics are explicitly demonstrated in the future, it will be important to apply therapy and procedures to maintain safety with minimal risk to the paediatric patient. It is also important to focus on the possibilities of adaptation of paediatric anaesthesiologists and paediatric intensivists to prevention and the possibilities of limiting the potential negative impact of anaesthesia on the neurological development of children.

Given the repeated observations of daily practice, other relevant and informative scoring systems will need to be developed in the near future, with not only value for identifying behavioural changes but also for the speed and quality of recovery from original cognitive function as well as recovery time from potential adverse effects of anaesthesia.

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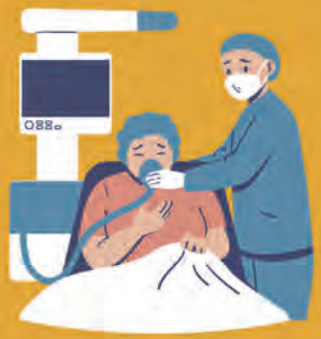

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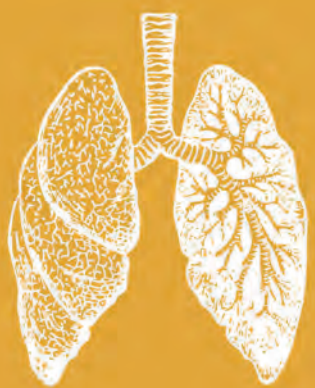
Пропофол

VS

Севофлуран

Дизайн исследования

Многоцентровое рандомизированное активно-контролируемое двойное слепое исследование



Продолжение на последней странице обложки

310 пациентов

Рассчитанный объем выборки для получения статистически достоверного результата относительно первичной конечной точки.

72 часа

Максимальное время от появления первых респираторных симптомов до момента рандомизации. Мы предполагаем, что в таком случае будет зафиксирован максимальный эффект от методов седации.

28 дней

Максимальное время соблюдения стратегии седации, которая была определена для пациента по результатам рандомизации.

1 год

Максимальная длительность наблюдения за пациентами от момента рандомизации. В рамках исследования состояние пациентов определяется в 3-х временных точках: 28 дней, 6 месяцев и 1 год после рандомизации.

4 центра

Количество центров, которые принимают участие в исследовании INVERSE. Наша главная задача - увеличить количество центров, чтобы создать большое многоцентровое РКИ.

3 вида анализа

В рамках исследования будет проведено 3 вида анализа: Intention-to-treat, Per-protocol и As-treated. Данные виды анализа позволят проанализировать и наиболее полно определить влияние метода седации на исходы лечения пациентов.

2 стратегии

В исследовании изучаются 2 стратегии. Экспериментальная стратегия - седация севофлураном. Контрольная седация пропофолом. Обе стратегии в настоящее время разрешены к использованию в палатах реанимации и интенсивной терапии.

1 результат

По итогам исследования будет получен однозначный ответ на вопрос: является ли стратегия седации севофлураном лучше, чем стратегия седации пропофолом для пациентов с острым респираторным дистресс-синдромом средней степени тяжести.

Будем рады сотрудничеству!

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