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Профессору Владимиру Терентьевичу ДОЛГИХ — 75 лет

28 января 2023 г. исполнилось 75 лет Владимиру Терентьевичу Долгих — доктору медицинских наук, профессору, заслуженному деятелю науки Российской Федерации.

Владимир Терентьевич Долгих родился 28 января 1948 г. в Омской области (Тарский район). С отличием окончил педиатрический факультет Омского медицинского института (ОГМИ). В 1975 г., как аспирант, досрочно защитил кандидатскую диссертацию. С 1979 г. по 1985 г. В. Т. Долгих заведовал Центральной научно-исследовательской лабораторией (ЦНИЛ) ОГМИ. В этот период в ЦНИЛе сформировался мощный научный коллектив, были развернуты новые лаборатории: иммунологии, электронной микроскопии, радиоизотопных исследований.

В 1986 г. Владимир Терентьевич успешно защитил докторскую диссертацию на тему «Повреждение и защита сердца при острой смертельной кровопотере». Научными консультантами докторской диссертации В. Т. Долгих были академик АМН СССР, Лауреат Государственных премий СССР В. А. Неговский и Заслуженный деятель науки Республики Казахстан, профессор В. Г. Корпачев.

Наряду с деятельностью ученого, Владимир Терентьевич проявил себя как прекрасный педагог и организатор здравоохранения. С 1985 г. в течение 33 лет заведовал кафедрой патофизиологии с курсом клинической патофизиологии, в течение 7 лет был проректором по научной работе ОГМИ.

В 1989 г. В. Т. Долгих присвоено ученое звание профессора по кафедре патофизиологии. Под его руководством защищено 72 кандидатских диссертаций, а при консультативной помощи — 22 докторских диссертации.

Профессор В. Т. Долгих создал в России авторитетную научную школу патофизиологов, основным направлением которой является изучение молекулярных механизмов повреждения сердечно-сосудистой и центральной нервной системы при критических и постреанимационных состояниях, а также разработка эффективных методов их коррекции и профилактики. Ученики профессора Долгих В. Т. работают в различных регионах России и возглавляют научные и врачебные коллективы в Москве, Екатеринбурге, Омске, Сургуте, Ханты-Мансийске, Нижнем Новгороде.

25 октября 1995 г. профессор В. Т. Долгих был избран членом-корреспондентом Сибирского отделения Международной академии наук высшей школы, а в 1998 г. — действительным членом Российской академии медико-технических наук. В 2006 г. за особый вклад в изучение медицины критических состояний профессор В. Т. Долгих был награжден серебряной медалью Европейской Академии естественных наук и включен в список ведущих ученых России в области здравоохранения и медицины. В 2010 г. Владимиру Терентьевичу было присвоено почетное звание «Заслуженный деятель науки Российской Федерации». Профессор В. Т. Долгих награжден Почетным знаком Минздрава России «Отличнику здравоохранения» и Почетной грамотой Минздрава России.

С 2018 г. профессор В. Т. Долгих живет в Москве и работает главным научным сотрудником лаборатории клинической патофизиологии критических состояний НИИ общей реаниматологии им. В. А. Неговского ФНКЦ РР и заведующим кафедрой общей патологии Института высшего и дополнительного профессионального образования ФНКЦ РР, является заместителем главного редактора журнала «Общая реаниматология».

Московское издательство «Юрайт» выпустило его лекции по патофизиологии в двух томах, отмеченные золотыми медалями на международных книжных выставках в Москве, Вене, Нью-Йорке, учебные пособия «Иммунопатология», «Боль и обезболивание», учебник «Сердечная недостаточность», «Тесты по патофизиологии и иммунологии», «Клиническая практика по патофизиологии».

Глубокоуважаемый Владимир Терентьевич! Коллектив НИИ общей реаниматологии им. В. А. Неговского ФНКЦ РР и редакция журнала «Общая реаниматология» поздравляют Вас с юбилеем, желают крепкого здоровья и долгих плодотворных лет жизни.

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Assessment of the Myocardial Stress Biomarker NT-proBNP in Real Clinical Practice

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Summary

The objective. To compare the clinical informativeness of NT-proBNP plasma concentrations measured using a domestic enzyme-linked immunoassay (ELISA) kit or commonly employed in clinical practice direct immunochemiluminescence assay (ICLA).

Subjects and Methods. The study involved 35 vascular surgery patients of varying degrees of cardiological risk. Blood specimens were collected from each patient at 3 time points: 1. prior to surgery (NT-proBNP$_1$), 2 — after the procedure (NT-proBNP$_2$), 3 — before the discharge from the hospital (NT-proBNP$_3$). Each specimen was split into equal aliquots for biomarker quantification using two different techniques (ELISA using domestic reagents — for the 1st series of analyses, and ICLA using an imported kit — for the 2nd series). Perioperative cardiovascular complications were recorded. The consistency of the measurement results obtained by two different methods was evaluated using the Bland–Altman technique. A discrimination ability of independent variables in relation to a binary dependent variable was studied using ROC analysis.

Results. In the 1st series, ranges of the biomarker were as follows: NT-proBNP$_1$ — 24–774 pg/mL, NT-proBNP$_2$ — 41.2–889.1 pg/mL, NT-proBNP$_3$ — 39.3–1013.3 pg/mL. In the 2nd series, NT-proBNP$_1$ was 31.2–2087.0 pg/mL, NT-proBNP$_2$ — 32.5–3754.0 pg/mL, NT-proBNP$_3$ — 34.1–2728.0 pg/mL. In the Bland–Altman analysis, 97.03% of the values fell within the lower and upper limits of consistency (±1.96 SD of the average difference), which indicated comparability of the results in the series, but the values of NT-proBNP in the 1st series were lower than in the 2nd ones. Cardiovascular complications were registered in 3 (8.5%) patients. In the 1st series, NT-proBNP$_1$ > 218 pg/mL predicted cardiovascular complications with a sensitivity of 66.7% and a specificity of 81.3% (AUC 0.844, 95% CI 0.681–0.944, P = 0.0003). In the 2nd series, NT-proBNP$_1$ > 315 pg/mL predicted cardiovascular complications with a sensitivity of 66.7% and a specificity of 75.0% (AUC 0.828, 95% CI 0.663–0.934, P = 0.001).

Conclusion. The domestic ELISA kit for solid-phase enzyme immunoassay proved its clinical informativeness for quantitation of NT-proBNP demonstrating its value for diagnostic and prognostic purposes, or scientific studies. The novel domestic technique provides consistently reproducible results, although with lower reference values as compared to the standard immunochemiluminescence assay.

Keywords: natriuretic peptides; NT-proBNP; non-cardiac surgery; cardiac complications

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

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Introduction

In recent years, there has been increasing interest in the use of various biomarkers, including B-type natriuretic peptides (BNP), in cardiology and critical care medicine [1–5]. BNP levels are assessed in plasma by determining the concentration of the active B-type natriuretic peptide (BNP) and the inactive N-terminal fragment of the prohormone molecule (NT-proBNP), which are produced by enzyme-dependent cleavage of polypeptide precursors and enter the blood stream simultaneously. These biochemically different biomarkers [6, 7] have quite comparable informative value. Therefore, various international and Russian regulatory documents include values of both BNP and NT-proBNP as diagnostic and prognostic biomarkers [4, 8–16].

Widespread implementation of B-type BNP monitoring in everyday medical practice directly depends on the availability of this laboratory test not only in secondary and tertiary care, but also in general hospitals, especially with the use of cost-effective and high-quality domestic (Russian-made) reagents. When introducing new biomarkers, it should be taken into account that the techniques for their measurement may not be fully standardized and have a different range of reference values [2, 17]. Taking into account such characteristics of another biomarker (cardiac troponin), the Fourth Universal Definition of Myocardial Infarction does not specify its range, but suggests to be guided by exceeding the 99th percentile of the upper limit of reference values, specifying the latter in each individual

case [18]. There are chemiluminescence and enzyme-linked immunosorbent assay methods for the quantitative determination of NT-proBNP [2, 7], which may influence the assay results. Therefore, when expanding the use of NT-proBNP using new kits for different immunoassay variants, not only the reference values should be considered, but also the screening levels of the biomarker with diagnostic and prognostic significance should be specified. Screening levels of NT-proBNP can vary widely and may be outside the normal reference range [2, 3, 19, 20]. This may hinder proper interpretation of test results and even lead to diagnostic errors.

The aim of the study was to evaluate the informative value of NT-proBNP levels in blood of post-surgery patients using Russian-made ELISA kit in a clinical setting.

Material and Methods

A single-center simple prospective observational study was performed after the approval of the ethical committee of Yaroslavl State Medical University (protocol 50/2021). Inclusion criteria for the study were:

— age 45–85 years;

— elective open vascular surgery under general anesthesia;

— written informed consent of patients to participate in the study.

— endoscopic interventions;

— surgery under a neuraxial block;

— elevated creatinine level (> 120 μmol/L);

— clinically significant cardiac malformations and defects;

— reduced left ventricular ejection fraction < 40%;

— morbid obesity with body mass index (BMI) > 40 kg/m^2.

Exclusion criteria:

— canceled surgery;

— severe intraoperative surgical complications;

— repeated surgical interventions during hospitalization;

— patient's refusal to participate during the study.

In accordance with the inclusion criteria, 37 patients were initially selected. Two patients were excluded from the study (canceled surgery and refusal from participation).

We examined 35 patients (21 men and 14 women) aged from 52 to 74 (Me [P25–P75]: 66 [61–83]; M±m: 64.4±5.4 years). Preoperative status of the patients was Class III–IV (3 [3–3]) according to the American Society of Anesthesiologists. The BMI varied within the range of 19.0–38.1 (Me [*P25–P75*]: 27.9 [25.1–30.1]; M±m: 27.7±4.5) kg/m^2, while BMI > 30 kg/m^2 was revealed in 9 (25.7%) patients.

Patients underwent vascular surgery with varying levels of cardiac risk, including vertebral artery reconstruction in 8 (22.9%) cases, carotid endarterectomy for asymptomatic disease in 12 (34.3%) patients, carotid endarterectomy for symptomatic disease in 9 (25.7%) patients, and aortic and major vascular surgery in 6 (17.1%) patients. Surgery was performed under multimodal general anesthesia with mechanical lung ventilation (MLV) and standard monitoring. The duration of anesthesia was 150–480 (180 [180–240]) minutes. After surgery, all patients were transferred to the intensive care unit.

Blood samples for NT-proBNP measurement were obtained 3 times: stage 1, before surgery (NT-proBNP$_1$); stage 2, in the morning of day 1 after surgery (12–16 h after surgery) (NT-proBNP$_2$); stage 3, 5–7 days after surgery before hospital discharge (NT-proBNP$_3$). A total of 105 samples were collected. Each sample was aliquoted into two portions to measure the level of the biomarker using different techniques.

The following series were collected:

— Series 1 analyses (*N*=105) performed by solid-phase immunoassay technique using the «NT-proBNP-IFA-BEST» reagent kit (AO Vector-BEST, Russia) on a «LASURIT automatic» immunoassay analyzer (Dynex Tec., USA);

— Series 2 analyses (*N*=105) performed by chemiluminescence immunoassay using a set of reagents in a cassette for quantitative determination of NT-proBNP in serum and plasma (Roche Diagnostics GmbH, Germany) using a «Cobas e411» immunochemical analyzer (Roche, Switzerland).

Perioperative cardiovascular complications (CVC) included cardiac mortality, non-fatal myocardial infarction, transient myocardial ischemia, development of acute or decompensated chronic heart failure, acute cerebrovascular accident, hypotension requiring sympathomimetic vasopressor administration, clinically significant arrhythmia. One or more CVCs were considered as a composite endpoint for which the sensitivity and specificity of prognosis based on NT-proBNP assessment were evaluated.

A database created in Microsoft Office Excel was used to store and process the data. Detailed statistical analysis was performed using the Microsoft Office Excel and MedCalc software packages, version 19.4.1. The sample size of the study was not predefined.

Data distribution was analyzed using the Shapiro–Wilk and DeAgostini–Pearson criteria. All data were described as minimum (min) and maximum (max) values, median (*Me*) and interquartile range (*Q25; Q75*). For data with normal distribution, mean (*M*) and error of mean (*m*) were additionally calculated.

The agreement of measurements obtained by two different methods was assessed by the

Table 1. Changes in NT-proBNP (pg/mL) levels during the study based on tests of the 1st and 2nd series.

Parameter	Series 1	Series 2	*P-value*
NT-proBNP$_1$	79.7 [45–257]	154.6 [89.5–382.9]	0.028
NT-proBNP$_2$	194.5 [123–370.2]	274.2 [154.3–568.5]	0.189
NT-proBNP$_3$	206 [72.8–474.9]	243.2[107–531]	0.263

Bland–Altman method. We calculated the standard deviation of the difference and its 95% confidence interval (95% CI) and the statistical significance (*P* value), the mean difference between the measurements (bias) and its 95% CI. The scatterplot (Bland–Altman plot) characterizing the dependence of the difference between measurements on the mean of the measurements was constructed.

Significance of differences between unrelated samples was assessed using the Mann–Whitney test, while differences between related samples were assessed using the Wilcoxon criterion with Bonferroni correction for multiple comparisons.

The discriminative power of independent variables with respect to the binary coded dependent variable (present/absent) was assessed using ROC analysis. ROC curve characteristics were assessed by calculating area under the curve (AUC), 95% CI, and *P* value. Model quality was defined as excellent (AUC > 0.9), very good (AUC 0.89–0.8), good (AUC 0.79–0.7), fair (AUC 0.69–0.6), or poor (AUC < 0.6). The cut-off value of a variable was determined by the Youden index (maximum sum of sensitivity and specificity required), the requirement for test sensitivity approaching 80%, and the requirement for balance between sensitivity and specificity (minimum difference between these values). The value that best met all three requirements was used as the cut-off.

The following ROC analyses were performed

— NT-proBNP$_1$ series 1 and 2 values (independent variables) versus the composite endpoint indicating the presence of CVC (dependent variable);

— NT-proBNP$_1$ series 1 levels (independent variable) vs. NT-proBNP$_1$ series 2 levels > 350 pg/mL (dependent variable);

— NT-proBNP$_1$ series 1 values (independent variable) vs. NT-proBNP$_1$ series 2 values > 125 pg/mL (dependent variable).

Results of statistical analysis were considered significant at $P<0.05$.

Results and Discussion

In series 1, the range of NT-proBNP$_1$ was 24 to 774 pg/mL, NT-proBNP$_2$ was 41.2 to 889.1 pg/mL, and NT-proBNP$_3$ was 39.3 to 1013.3 pg/mL. In series 2, NT-proBNP$_1$ was 31.2 to 2087.0 pg/mL, NT-proBNP$_2$ was 32.5 to 3754.0 pg/mL, and NT-proB-NP$_3$ was 34.1 to 2728.0 pg/mL.

Using Bland-Altman analysis (Fig. 1), we found that the mean difference between NT-proBNP values in series 1 and 2 reached 157.65 pg/mL (95% CI, 80.27 to 235.03; $P=0.0001$). Most values (97.03%) fell within the lower and upper limits of consistency, which were –602.8 (95% CI, –735.37 to –470.07) and 918.1 (95% CI, 785.37 to 1050.74) pg/mL, respectively. The findings indicated that, on the one hand, NT-proBNP values in series 1 were lower than those in series 2, while on the other hand, more than 95% of the values were within ± 1.96 SD of the mean difference, indicating that the results in the series were comparable.

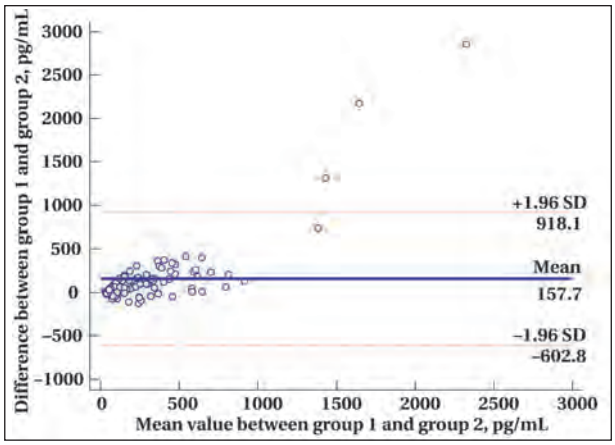

Fig 1. Bland-Altman plot for assessment of comparability of the test results of the series 1 and 2.

In view of the quantitative differences in the biomarker values between series 1 and 2 obtained in the Bland–Altman analysis, the informative value of measuring the biomarker level using solid-phase immunoassay was further studied in various clinical settings.

A stepwise analysis of perioperative data was performed. The median NT-proBNP values in the stage 1 (Table 1) were significantly lower in series 1 than those in series 2. During the other stages, the differences in the values in the series did not reach significance.

In series 1, the biomarker values in stages 2 ($P=0.004$) and 3 ($P=0.010$) were significantly higher than those in stage 1. Stage 2 and 3 values did not differ ($P=1.0$). In the series 2 of tests, NT-proBNP level tended to increase ($P=0.076$) during stage 2 and increased ($P=0.016$) during stage 3 compared with stage 1. There were no significant differences between stages 2 and 3 ($P=1.0$). In a stepwise analysis vs the values of stage 1, taken as 100% (Fig. 2), we found that the rate of increase in the biomarker during stage 2 in both series was almost the same, i. e., 50% and 41%. During stage 3, the rate of increase also did not differ significantly.

Table 2. Discriminating power of the preoperative level of NT-proBNP (pg/mL) for perioperative cardiovascular complication.

Series	AUC	95% CI	*P*-value	Cut-off value	Sensitivity, %	Specificity, %
1	0.844	0.681–0.944	0.0003	>218	66.7	81.3
2	0.828	0.663–0.934	0.001	>315	66.7	75.0

Thus, despite certain quantitative differences, the methodology based on domestic reagents was not inferior to international methods in assessing the changes in NT-proBNP in response to such factors as surgical trauma. This indicates feasibility of using solid-phase immunoassay technique both for scientific and for practical purposes, e. g., to assess the effectiveness of cardiac protection in «BNP-guided» cardiac therapy, etc. [2, 5].

During the next stage, we evaluated the discriminating power of the data obtained in both series prior to surgery (NT-proBNP$_1$) with regard to perioperative cardiovascular complications (CVC). The latter were recorded in 3 (8.5%) patients. There were no deaths due to CVCs. The CVCs included transient myocardial ischemia in 1 (2.9%) patient and hypotension requiring prescription of sympathomimetic vasopressors in 2 (5.7%) patients.

The AUCs of NT-proBNP$_1$ (Fig. 3) in both series were extremely close and corresponded to very good quality models. The difference in AUC was 0.016 (*P*=0.714). The cut-off values of the biomarker in the series exhibited similar values of sensitivity and rather closed values of specificity that, however, differed significantly (Table 2).

The cut-off values of NT-proBNP$_1$ in series 2 were close to the level of the biomarker (300–350 pg/mL), which is usually referred to as a predictor of CVC in noncardiac surgery [14–16]. NT-proBNP$_1$ was 1.5 times lower in series 1, which required further detailed discussion.

In the international guidelines on risk reduction in noncardiac surgery, NT-proBNP values determined by internationally used immunochemical techniques are given. With the latter, the upper limit of the biomarker reference values is 300–350 pg/mL or even slightly higher, depending on age [7]. However, in a meta-analysis [20] combining the results of NT-proBNP measurement using three different commercially available techniques, the cut-off of the biomarker, indicating a high risk of perioperative CVC, varied in the range 201–791 pg/mL. The authors did not provide an unambiguous explanation for this variability.

According to our data, the NT-proBNP$_1$ cut-off of series 1 almost coincided with the upper limit of normal values (up to 200 pg/mL), which was indicated by the developers of the domestic (Russian-made) solid phase enzyme immunoassay kit in the enclosed instructions. Obviously, at this level of reference values, one would expect a lower screening value for predicting CVCs in noncardiac surgery. To

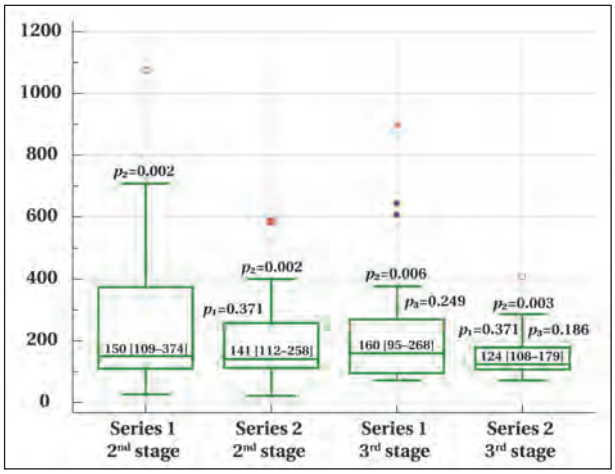

Fig. 2. Changes in the NT-proBNP level in the series 1 and 2 in relation to the stage 1 level taken as 100%.

Note. The vertical axis shows % in relation to the values of stage 1, which is assumed to be 100%. P_1 — significance of differences between the data of series 1 and 2 by Mann–Whitney test; P_2 — significance of differences between the data of the stages 2 and 1 by Wilcoxon test with Bonferroni correction; P_3 — significance of differences between the data of stages 3 and 1 by Wilcoxon test with Bonferroni correction.

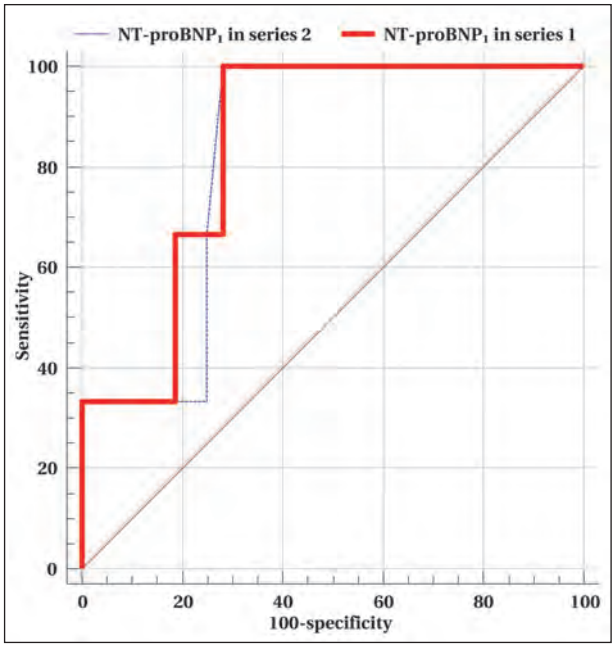

Fig. 3. ROC curves showing the discriminating power of NT-proBNP$_1$ for perioperative cardiovascular complications.

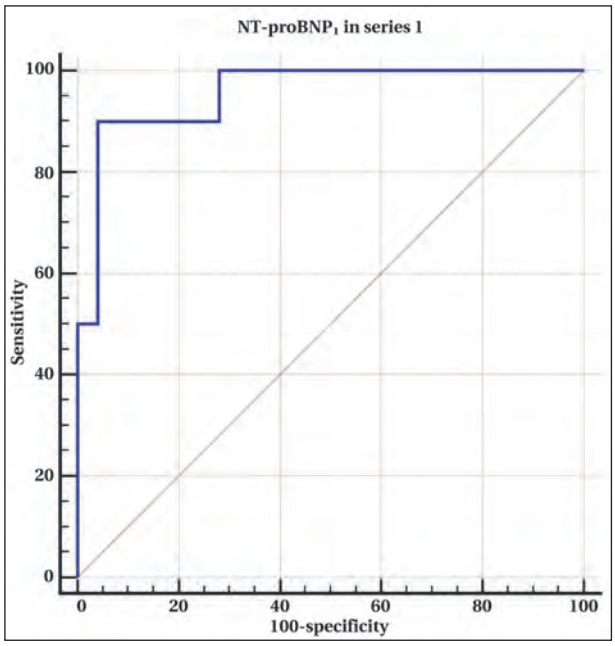

Fig. 4. ROC curve showing the discriminating power of series 1 NT-proBNP$_1$ vs series 2 NT-proBNP$_1$ values >350 pg/mL.

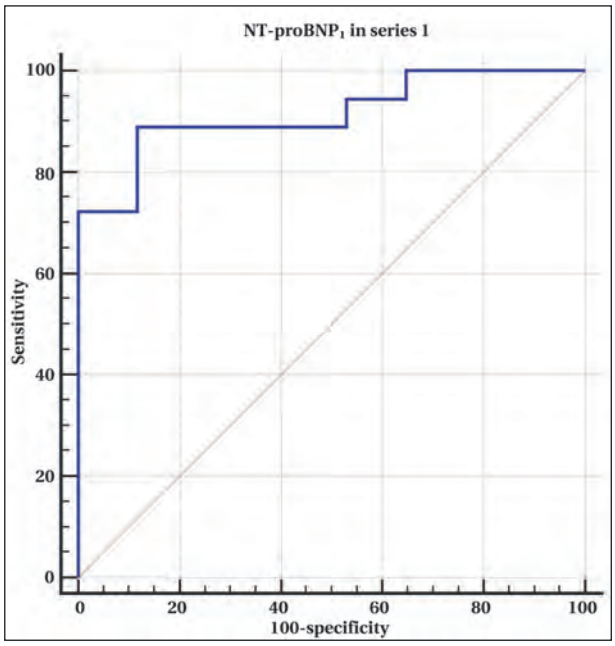

Fig. 5. ROC curve showing the discriminating power of series 1 NT-proBNP$_1$ vs series 2 NT-proBNP$_1$ values >125 pg/mL.

confirm this suggestion, we performed a ROC analysis of NT-proBNP$_1$ series 1 values versus series 2 values > 350 pg/mL (Fig. 4). The AUC was 0.958 (95% CI, 0.898–0.988; *P*<0.0001), which was consistent with an excellent quality model. The biomarker value in series 2 > 350 pg/mL was predicted by a cut-off of NT-proBNP$_1$ series 1 > 206 pg/mL with a sensitivity of 91.4% (95% CI, 76.9–98.2%) and specificity of 89.1% (95% CI, 78.8–95.5%). This cut-off was almost identical to the one obtained for the prediction of CVCs in everyday clinical practice (see Table 2).

The results suggest that the screening value of > 350 pg/mL, given in the international guidelines, corresponds to a level of about 200 pg/mL when using a Russian-made enzyme immunoassay kit. Undoubtedly, further extensive studies are needed to clarify the NT-proBNP cut-off for reliable discrimination of patients with high risk of CVC in noncardiac surgery. These values should be included in relevant national guidelines.

This is an extremely important aspect of implementation of B-type natriuretic peptide monitoring in real clinical practice, taking into account that screening values of biomarkers established in the international studies are often incorporated into the national clinical guidelines. In this case, not only significant discrepancy of quantitative characteristics of NT-proBNP, but also wrong interpretation of the results may occur.

Thus, in the guidelines on perioperative management of patients with chronic heart failure (CHF) [13], the level of BNP is quite reasonably recommended to be measured «to determine the risk of adverse events in the perioperative period». However, the authors specified 125 pg/mL as a «limit of normal reference range of NT-proBNP level», which is indicated in international and Russian guidelines on the diagnosis and treatment of CHF [4, 8–12] as a screening value (not the upper limit of reference values) when NT-proBNP level below 125 pg/mL indicates the absence of CHF in patients with relevant complaints (dyspnea, etc.). Unfortunately, the mentioned misconceptions in estimation of normal reference range of B-type NT-proBNP, as well as incorrect interpretation of screening biomarker values are quite widespread and can lead to diagnostic errors.

The use of domestic immunoassay kit provides grounds for inaccurate interpretation of NT-proBNP level not only by anesthesiologists, but also in cardiological practice. There is reason to believe that NT-proBNP level of 125 pg/mL, recommended as an important diagnostic criterion of CHF [11, 12], will correspond to a significantly lower value when using the kits of different manufacturers.

To test this hypothesis, we performed ROC analyses of series 1 NT-proBNP$_1$ values versus series 2 values > 125 pg/mL (Fig. 5). The AUC was 0.915 (95% CI, 0.770–0.982; *P*<0.0001), consistent with an excellent quality model. The biomarker value in series 2 > 125 pg/mL was predicted by a cut-off of NT-proBNP$_1$ series 1 at > 56 pg/mL, sensitivity of 88.9% (95% CI, 65.3–98.6%) and specificity of 88.2% (95% CI, 63.6–98.5%).

These preliminary data confirming our hypothesis are valuable for the correct diagnosis of CHF. Undoubtedly, further extensive targeted studies clarifying diagnostic limits of BNP detection in cardiology using domestic reagents are necessary.

Another debatable aspect of the interpretation of BNP test results may be the correlation of BNP and NT-proBNP levels in the same blood sample. The level of NT-proBNP in a sample should always be significantly higher than that of the active hormone [2, 4, 6]. Equalization of concentrations or even inversion of their ratio is most often due to preanalytical errors [2]. Presumably, lower reference values when using enzyme-linked immunosorbent assays can also lead to «paradoxical» results, when the concentration of NT-proBNP in the sample is lower than that of BNP. Such data should not be interpreted as a consistent pattern.

Obviously, in the present study the lower values of NT-proBNP in series 1 in Bland-Altman analysis, as well as in the assessment of perioperative changes in the biomarker levels and its prognostic significance regarding CVC were due to the differences in the analytical methods used. However, the comprehensive study has shown good reproducibility and undoubted clinical significance of biomarker measurement using solid-phase immunoassay method.

Several recommendations may be formulated for the implementation of laboratory testing of NT-proBNP using a domestic solid-phase immunoassay reagent kit in the daily practice of anesthesiology and intensive care.

1. The range of normal biomarker values should be established before clinical interpretation of the assay results.

2. A comparative analysis of results obtained by enzyme-linked immunosorbent assay (ELISA) and chemiluminescence immunoassay (CLIA) is not appropriate.

3. The NT-proBNP values from different laboratories should not be correlated unless accurate information about the reference values of the techniques used is available.

4. If the reference range of the biomarker according to the domestic manufacturer is 0–200 pg/mL, the screening values of the biomarker given in the international guidelines should not be used.

5. If the upper limit of normal NT-proBNP values is 200 pg/mL, blood levels > 200 pg/mL can be used as a tentative screening biomarker level indicating an increased risk of CVC in noncardiac surgery, given that this value needs further research and final validation.

Conclusion

The measurement of NT-proBNP using a domestic solid-phase enzyme immunoassay kit has undoubted clinical informative value and can be used for diagnostic and prognostic purposes as well as for scientific research. The technique provides consistent reproducible results, but has lower reference values compared with the international technique based on chemiluminescence immunoassay. As a result, the quantitative values of screening biomarkers (including diagnostic and prognostic values) may be lower than those reported in international studies and clinical guidelines. The identified quantitative differences require extensive studies using the national methodology in different clinical situations. Furthermore, several practical considerations should be taken into account when interpreting the results in order to avoid diagnostic errors and misleading conclusions.

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Comparing the Inspiratory Capacity Measurements Obtained by Incentive Spirometry and Ultrasonic Spirography in the Early Postoperative Period in Cardiac Surgery Patients

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Summary

Incentive spirometry is one of the most common methods used for respiratory rehabilitation in the early period after cardiac surgery. Inspiratory capacity values, obtained by a patient using spirometer, are not reliably trusted.

Objectives. To compare volumetric parameters measured with incentive spirometer and results obtained with bedside ultrasound-based spirometer to assure the feasibility of the use of incentive spirometry to assess the inspiratory capacity and effectiveness of postoperative respiratory rehabilitation.

Materials and methods. The study included 50 patients after elective cardiac surgery. Pulmonary rehabilitation involved the use of various respiratory therapy methods. Spirography was performed before and after each session. Both approaches were used simultaneously to obtain the spirometry maximum inspiratory capacity (SMIC) with a bedside ultrasonic spirography and maximum inspiratory capacity (MIC) index using an incentive spirometer. Patient's discomfort and adverse events during the procedures were recorded.

Results. The absolute values of the MIC measured before and after each session by the two methods were dissimilar, however, the average increment values (△) did not show statistically significant differences. The correlation analysis revealed a strong positive statistically significant relationship between △ SMIC and △ MIC ($R = 0.74$ before the session, $R = 0.79$ after the session, $R = 0.77$ across the whole data set, $P < 0.01$), also consistent with the Bland–Altman analysis, evidencing that more than 95% of all values fell within ± 1.96 SD of the mean difference. The inspiratory spirometry method showed good diagnostic accuracy (sensitivity 87%, specificity 85%, area under the curve (AUC) 0.8 (95% CI: [0.76; 0.83]), $P < 0.001$). Refusals of procedure were more often documented with ultrasonic spirography.

Conclusion. The increment in the inspiratory capacity index measured with incentive spirometer shows good agreement with ultrasonic spirography measurements. Therefore, incentive spirometry can be reliably used to assess the effectiveness of respiratory rehabilitation interventions in cardiac surgery patients during early postoperative period.

Keywords: respiratory rehabilitation; incentive spirometry; spirography; inspiratory capacity; lung drainage function

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

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Introduction

Cardiac surgery is associated with a high risk of respiratory complications in the immediate postoperative period due to the need for cardiopulmonary bypass and circulatory arrest, mechanical lung injury, relatively large blood loss and blood transfusion, prolonged «hard» mode mechanical lung ventilation (MLV), thoracic damage, drug-induced suppression of the respiratory center, respiratory muscle weakness, etc. [1–4].

All of the above may lead to impaired drainage function of the tracheobronchial tree, development of atelectasis, decreased number of ventilated alveoli, reduced lung vital capacity and respiratory failure.

Various methods of respiratory physical therapy are used to prevent and treat respiratory complications in the postoperative period. These include vibroacoustic lung massage, positive expiratory pressure (PEP) vibration therapy, and chest therapeutic massage using high-frequency compression devices (vests) [5–10]. The most common physiotherapeutic methods used in the postoperative period include incentive spirometry [11], which is based on measuring changes in inspiratory volume using a special device equipped with a piston and graded in ml. Thus, the patient can independently control the inspiratory volume during postoperative rehabilitation and strive to achieve target values, although, strictly speaking, incentive spirometry is not a measuring device. Meanwhile, the main effects of incentive spirometry include respiratory muscle training, improved expectoration and ventilatory parameters.

Aim of the study. To compare the volumetric parameters measured by incentive spirometry with the results of bedside ultrasound spirometry and to evaluate the feasibility of using incentive spirometry to assess inspiratory capacity and the effectiveness of postoperative respiratory physiotherapy.

Material and Methods

The study was conducted as a part of the «Evaluation of clinical and economic efficiency of various vibration therapy methods with regard to their effect on gas exchange, respiratory function parameters and expectoration in cardiac surgery patients in early postoperative period for prevention and treatment of postoperative respiratory complications» prospective randomized study conducted in Petrovsky Russian National Research Center for Cardiovascular Surgery. The trial record number on ClinicalTrials.gov is NCT05159401. The study was approved by the local ethics committee (protocol 12 dated 10/28/2021).

Inclusion criteria were as follows: age 18–80 years, spontaneous breathing after tracheal extubation, ability to maintain adequate gas exchange on inhaled oxygen, clear consciousness and good communication with the patient, adequate pain relief (⩽3 points) on a 10-point pain visual analog scale (VAS). Exclusion criteria were the need for mechanical ventilation, non-invasive mask ventilation or high-flow oxygen therapy, acute cerebrovascular accident, shock of various etiologies, ongoing bleeding, use of extracorporeal blood purification, neuromuscular diseases, pneumothorax, hydrothorax or hemothorax.

The analyzed group included 50 patients who underwent elective surgery, including valve replacement (mitral, aortic) (N = 15), plastic valve surgery (N = 7), septal myectomy (N = 10), aortic valve replacement combined with septal myectomy (N = 2), myocardial revascularization (N = 14, including 4 surgeries performed in combination with valve replacement), and combined ascending aorta reconstruction and aortic valve replacement (N = 2). Surgery was performed under cardiopulmonary bypass at room temperature or moderate hypothermia in 48 patients. Postoperative analgesia for VAS greater than 3 was administered with drugs that do not affect respiratory function (intravenous acetaminophen at a dose of 1 g; or tramadol, 50–100 mg; or intramuscular ketoprofen, 100 mg; or oral tapentadol, 50 mg).

During surgery, balanced multicomponent anesthesia (intravenous propofol, midazolam, ketamine, fentanyl, inhalational sevoflurane) was used. Muscle relaxation was maintained by intermittent intravenous boluses of pipecuronium bromide. Del Nido (or blood or Custodiol) cardioplegia was used for myocardial protection.

Spirometry was performed with a Spiro Scout portable ultrasonic spirometer (Schiller, Switzerland) according to the device manual and the Russian Respiratory Society guidelines for spirometry [12, 13]. Before the study, the patient was instructed on the correct examination technique. The investigator explained and demonstrated the correct grip of the mouthpiece and the breathing maneuver (at least four cycles of quiet inhalation and exhalation, followed by maximal deep inhalation and maximal deep exhalation, performed strictly at the request of the investigator, with the completion of the breathing maneuver after the subject's return to normal breathing). The measurements were performed three times, the criterion for a successful performance was the value of the vital lung capacity (VLC) within 150 ml of the maximum value obtained during the given test session. Several parameters were measured, but for the purpose of the study we used maximal inspiratory capacity (MIC), which is the sum of tidal volume (V_t) in ml and inspiratory reserve volume (IRV) in ml.

The studies were performed 10–12 hours after tracheal extubation, 3 times a day for the next 72 hours, before and after the use of different vibration techniques, such as vibroacoustic lung massage with the BARK VibroLUNG device, oscillating PEP therapy with the Acapella Duet Green, mechanical cough stimulation with the Comfort Cough Plus mechanical aspirator, and classical therapeutic manual chest massage with percussion and verbal cough stimulation together with chest compressions. A detailed description of each method is given in our previous publications [14–17].

During these phases of the study, we performed an incentive spirometry session (Coach-2 spirometer by SmithsMedical, USA). The following procedure was used. After instruction and under the control of the intensive care physician, the patient inhales through the spirometer mouthpiece and exhales into the ambient air. The tidal volume (V_t) value is recorded. The patient then places the mouthpiece in his/her mouth and slowly inhales as deeply as possible. The value of maximum inspiratory capacity (MIC), which is the sum of tidal volume and inspiratory reserve volume, is recorded. The measurement was performed three times and then the average value of this parameter was calculated. In this study, we analyzed 812 MIC and spirometric MIC (SMIC) measurements (406 each). Any adverse events and discomfort during these procedures were also recorded. The tests were performed by 6 specially trained physicians.

Statistical analysis was performed using Statistica 10.0 software (StatSoft, Inc.). The results obtained during the study were evaluated for normality of distribution using the Shapiro–Wilk criterion. Parametric and nonparametric methods of analysis were used. Arithmetic means (M) and standard de-

Table 1. The results of the measurement of the inspiratory capacity before and after respiratory physiotherapy sessions (median, 10 and 90 percentiles or *M*±*SD*).

№	Parameter (ml)	Before the therapy	*P-value*	After the therapy	*P-value*	Average △	*P-value*
1	MIC	1000 [500–2500]	0.01	1250 [600–3000]	0.04	200 [0–750]	0.38
	SMIC	1555±616		1735±666		180±270	
2	MIC	1200 [500–2750]	0.53	1694±893	0.88	203±280	0.35
	SMIC	1473±593		1587±591		95 [–225–510]	
3	MIC	1400 [750–3000]	1.00	1500 [750–3100]	0.46	125 [–100–300]	0.06
	SMIC	1519±578		1594±578		90 [–260–440]	
4	MIC	1500 [600–3100]	0.92	1843±878	0.004	100 [–250–300]	1.00
	SMIC	1510±605		1598±655		105 [–215–350]	
5	MIC	1880±937	0.02	1922±853	0.03	10 [–200–350]	0.65
	SMIC	1640±617		1727±599		87±330	
6	MIC	1906±920	<0.001	2025±971	<0.001	50 [–100–500]	0.17
	SMIC	1588±499		1670±635		82±291	
7	MIC	2160±976	<0.001	2261±1042	<0.001	25 [–250–300]	0.77
	SMIC	1845±641		1855±675		10 [–250–300]	
8	MIC	2255±965	<0.001	2500 [1000–4000]	<0.001	50 [–100–400]	0.17
	SMIC	1893±653		1878±648		5 [–380–390]	
9	MIC	2321±961	<0.001	2443±1004	<0.001	50 [–100–500]	0.88
	SMIC	1970±628		2036±674		85 [–185–330]	

Note. Here and in Tables 1, 2 and Fig. 1, 2. MIC — maximum inspiratory capacity; SMIC — spirometric maximum inspiratory capacity.

viations (*SD*) were calculated for numerical parameters with normal distribution. Sets of numerical parameters with non-normal distribution were described using median (*Me*) and 10th and 90th percentile values. The frequency of events in the group was determined by Fisher's exact criterion. Differences were considered significant when $P < 0.05$. The Pearson correlation coefficient (*r*) was calculated to assess the correlation between the same parameters from two different devices. The Bland–Altman method was used to determine bias and outliers, as well as the agreement between all results and between the results of individual patients [18, 19]. Sensitivity and specificity of the methods were determined by ROC analysis [20, 21].

Results and Discussion

Spirometry-based assessment of ventilatory lung function plays an essential role in the diagnosis and management of respiratory diseases and is used to evaluate the effectiveness of various therapies and the results of clinical trials [22–24].

Spirometry is a rather complex test that includes training of participants, acceptability and reproducibility of maneuvers (appropriate patient performance), training of specialists, calibration of equipment, and processing of results. Performing spirometric studies in the early period after cardiac surgery is difficult for patients due to the complexity of their training, the severity of their condition, general weakness, residual effects of general anesthesia and pain. In this context, only resting spirometry, i. e., measurement of volumetric parameters, is used because most of these patients are unable to perform effort-related testing. According to the literature, portable or stationary spirometers measuring forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), FEV_1/FVC ratio, total lung capacity (TLC), peak expiratory flow, mean forced expiratory flow in the middle half of the FVC and other parameters have been used in most research studies to evaluate the effectiveness of respiratory physiotherapy [25, 26]. However, these studies were conducted in non-surgical patients who were in significantly better condition compared to cardiac surgery patients, and they did not have pain and fatigue.

Based on the results of previous studies [14–17], we proposed that to evaluate the efficiency of respiratory physiotherapy methods in cardiac surgery patients in the immediate postoperative period, we could use the measurement of MIC changes using an incentive spirometer, which were compared with the data obtained using a portable ultrasound spirometer. The values of the studied parameters before and after physiotherapy sessions are presented in Table 1.

As it is evident from the data, the mean absolute values of MIC and SMIC were different in most cases. The difference in the absolute values of the volumetric parameters of the compared methods can be explained by the different measurement conditions and characteristics of the devices. Unlike the ultrasonic spirometer, the incentive spirometer has considerable resistance and inertia. In addition, nasal leakage is possible during its use because the nose is not clamped during the measurement. However, according to our data, the MIC changes measured with an incentive spirometer can be used in the respiratory rehabilitation of patients. The mean changes of these parameters before and after rehabilitation (mean △) did not show significant differences. The error in measuring the maximum inspiratory capacity with the incentive spirometer in

Table 2. Results of △MIC and △SMIC measurement in relation to the direction of their change after respiratory physiotherapy sessions (*N*=406 for each method).

Direction of changes	Number of measurements	△MIC (ml)	△SMIC (ml)	*P-value*
△ ⩾ 0	341/256	200 [0–500]	175 [25–−510]	0.32
△ < 0	65/150	–200 [–500—100]	–117[–480–−20]	0.23

comparison with the «gold standard» data (conventional spirometry) before and after the sessions was 5.35% and 9.24%, respectively. Regarding the general changes in the measured inspiratory volumes, we observed a significant increase in the first 4 sessions, while in the 5th session the increase was less than 100 ml according to both methods (Fig. 1). This was due to the fact that by this time the respiratory function of the lungs had been restored and the maximum possible values for a particular patient had been reached. Depending on the direction of change of the evaluated parameters, we distinguished two groups: with decreased (△ < 0) and with increased or the same (△ ⩾ 0) respiratory volumes.

No significant differences were found when comparing the two methods (Table 2).

In order to assess the relationship between the measured parameters, we performed a correlation analysis by calculating Pearson's correlation coefficient, which showed a strong positive significant correlation (R = 0.74 before the session, R = 0.79 after the session, whole sample R = 0.77, P < 0.001).

Taking into account the fact that the Pearson correlation coefficient can only assess the linear dependence between the results obtained, the level of agreement between the two measurement methods was assessed using the Bland–Altman method (Fig. 2). This showed a mean difference of 216.9 mL between the measurement pairs (limits of agreement: –1021.3; 1455) with an outlier of 4.06% (33/812). Thus, more than 95% of the values were within ± 1.96 SD of the mean difference, indicating good agreement between the two methods.

To determine the diagnostic efficacy of incentive spirometry in measuring inspiratory capacity, its diagnostic sensitivity and specificity relative to the spirography method (reference standard) were evaluated. The ROC curve is a graph of the frequency of true positives (sensitivity) versus the frequency of false positives (100 — specificity). The area under the ROC curve (AUC) was 0.8 (95% CI: [0.76; 0.83]), sensitivity was 87% and specificity was 85%, P < 0.001.

Thus, the incentive spirometry method showed a good diagnostic accuracy compared to the reference method, which, in our opinion, allows its use in assessing changes in maximal inspiratory capacity in the postoperative period in cardiac surgical patients in the intensive care unit.

We performed a comparative analysis of the side effects, tolerability and comfort of the incentive spirometer and the bedside spirometer when performing measurements in cardiac surgical patients. The results of this analysis are shown in Table 3.

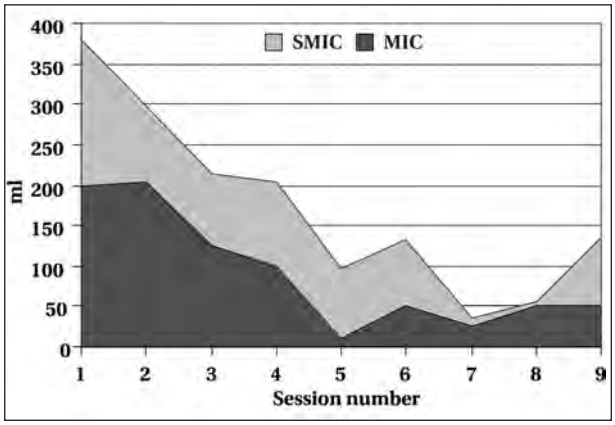

Fig. 1. Changes in the increase of the average values of the inspiratory capacity (△ MIC and △ SMIC) before and after respiratory rehabilitation sessions in ml.

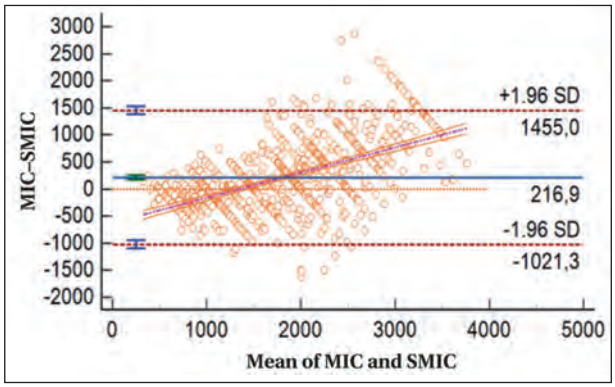

Fig. 2. Comparison of maximum inspiratory capacity and spirometric maximum inspiratory capacity values using the Bland–Altman method.
Note. X-axis shows the average value for two methods in one test (MIC and SMIC in ml), Y-axis shows the difference of values in one test, «mean» is the average value (shown by continuous middle line), upper and lower limits of agreement are represented by upper and lower dashed lines, respectively.

As can be seen from the Table 3, when performing measurements on a bedside spirograph (mainly in the first two days of the postoperative period), various complaints appeared (a total of 18 events in 8 patients, which is 16%), which made it impossible to perform further spirography, while using an incentive spirometer in the same patients did not cause such sensations [27, 28].

Table 3. Side effects during spirometry in cardiac surgery patients.

Side effects	Incentive Spirometer	Bedside Ultrasonic Spirometer	*P-value*
Nausea	0	3	0.08
Dizziness	0	3	0.08
Weakness	0	8	< 0.001
Palpitations	0	4	0.05
Total	0	18	< 0.001

The vast majority of cardiac surgery patients (44 out of 50 patients, 88%), despite performing all the tests, reported discomfort and difficulties in spirography due to the use of mouthpiece, nasal clip, incomplete understanding of the test itself, which required repeated instructions from the physician-researcher and prolonged the measurement process. Thus, we conclude that the use of the incentive spirometer is perceived by the patients as a simpler and easier procedure to perform.

Conclusion

Comparative evaluation of changes in inspiratory capacity using the incentive spirometer showed good agreement with the method of ultrasound spirography.

The incentive spirometer can be used to assess the increase in respiratory capacity parameters during rehabilitation of cardiac surgery patients in the early postoperative period.

The majority of postoperative cardiac surgery patients rated incentive spirometry as a more comfortable procedure compared with conventional spirography.

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Predictors of Clinical Efficacy of Cytokine Hemoadsorption in COVID-19 (Clinical Trial)

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Summary

Aim of the study. To evaluate the value of predictors of hemoadsorption clinical efficacy in patients with COVID-19.

Materials and methods. This study analyzed the results of treatment of 62 patients with severe COVID-19 in the intensive care unit using selective hemoadsorption of cytokines. All patients with severe COVID-19 were admitted to the intensive care unit within 14 days from the disease onset were subdivided into two groups. Group 1 patients (n=32) received on a top of standard treatment the hemoperfusion (HP) procedure for 4 hours, for 2–3 days in a row, using a cytokine sorption column composed of mesoporous styrene-divinylbenzene copolymer matrix. Group 2 patients were not subjected to extracorporeal blood purification. All patients received IL-6 inhibitors at a baseline in accordance to the temporary guidelines. We evaluated factors of unfavorable outcomes by analyzing changes in biochemical markers of systemic inflammatory response and mortality rates in patients of both groups.

Results. Initiation of HP later than 10 days from NCI onset ($P < 0.001$), length of stay in the ICU, extent of lung damage ($P = 0.036$) and the SOFA (Sequential Organ Failure Assessment) score ($P = 0.009$) were the most powerful predictors of unfavorable outcome. Levels of systemic inflammatory response markers (interleukin-6, CRP, D-dimer) in both groups did not significantly affect the survival rates and length of hospital stay ($P > 0.05$). HP group demonstrated better survival ($P < 0.05$). Mean hospital stay was 31 and 27 days, ICU stay — 11 and 8 days for Groups 1 and 2, respectively ($P < 0.05$).

Conclusion. Treatment of severe COVID-19 patients with HP using novel hemoperfusion device composed of styrene-divinylbenzene copolymer resulted in decrease in CRP levels on the first day after application and, with early onset, contributed to a significant increase in survival and decreased hospital and ICU stay. Additional studies are warranted to clarify the optimal timing of the initiation of HP in severe COVID-19 patients.

Keywords: hemoadsorption, cytokines; COVID-19; styrene-divinylbenzene copolymer matrix; Efferon CT

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

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Introduction

Recent experience with intensive therapy of severe novel coronavirus infection COVID-19 highlights the importance of pathogenetic treatment (including efferent therapy), which is particularly relevant given the lack of evidence for clinical efficacy of available etiologic treatments [1, 2]. High levels of circulating cytokines («cytokine storm») are important pathophysiological elements of COVID-19 progression, play a significant role in the development of multiple organ failure and poor outcome, and are associated with persistent post-COVID disease [2]. Cytokine adsorption and other methods of extracorporeal detoxification have been proposed in current version of temporary clinical guidelines to control cytokine storm when medical therapy is unsuccessful and respiratory failure progresses [3]. There are several reports in the literature on the successful use of cytokine adsorption alone and in combination with other efferent therapies in the treatment of severe COVID-19 [4, 5]. However, the actual use of these methods in infectious disease clinics is limited due to the lack of a clear understanding of the optimal timing, duration, and frequency of cytokine adsorption. In our study, we evaluated the changes in systemic inflammatory response and treatment outcomes in ICU patients with severe COVID-19 who underwent hemoperfusion to remove cytokines from the circulation in relation on the timing of the procedure.

Aim. To determine the significance of predictors of clinical efficacy of cytokine hemoperfusion in patients with COVID-19.

Material and Methods

A retrospective, single-center, case-control clinical study was conducted to evaluate the efficacy of extracorporeal anti-cytokine hemoperfusion (EACH) in combination with interleukin-6 receptor antibody therapy for severe COVID-19.

The study included 62 patients with severe and critical COVID-19 (7 or more points on the NEWS [National Early Warning Score] scale) admitted to the intensive care unit. In the first group, 32 patients each underwent a 4-hour hemoperfusion treatment using the Efferon® CT adsorber with styrene-divinylbenzene copolymer adsorbent beads. No other extracorporeal detoxification methods were used. Within this group, patients were divided into two subgroups: those who underwent hemoperfusion during the first 10 days after severe disease development and those with a longer duration of this period.

According to the temporary clinical guidelines, extracorporeal treatments are indicated for progressive respiratory or multiple organ failure due to cytokine storm that persists despite pharmacotherapy [3]. Vascular access was established with a dual lumen central venous dialysis catheter. The circuit was stabilized by microjet injection of sodium citrate (ACD-A). The procedure was repeated for 2–3 consecutive days (depending on patient condition, reduction of inflammatory mediator levels, oxygen and inotropic requirements).

In the second subgroup of 30 retrospectively selected patients («control»), no extracorporeal detoxification was performed.

At baseline and during intensive therapy, we evaluated changes in laboratory parameters such as ferritin, C-reactive protein, IL-6, D-dimer. All patients received anticytokine therapy (with recombinant humanized monoclonal antibodies against the human interleukin-6 receptor, such as tocilizumab 400–800 mg, sarilumab 400–800 mg, or levilimab 648–1296 mg) and anti-inflammatory therapy (dexamethasone up to 24 mg/day) according to current temporary clinical guidelines. Plasma cytokine levels were measured by enzyme-linked immunosorbent assay. Analysis of mortality, ICU and total hospital length of stay for patients was performed. The characteristics of the patients in the groups are shown in Table 1.

The clinical efficacy of EACH was evaluated statistically by intergroup differences. Parametric and non-parametric statistical methods were applied. Data collection, correction, primary processing, and presentation were performed using MS Office Excel 2010. Statistical analysis was conducted using Jamovi Desktop software (version 2.3.18) with assessment of distribution normality by the Shapiro-Wilk method, determination of mean values, mean square deviation, medians, lower and upper quartiles, maximum and minimum values. The values in the two independent groups were compared using the Mann–Whitney test. In addition, regression analysis with OR (odds ratio) estimation and survival analysis with competing risks curve plotting were used to assess the significance of the differences between the groups. The *P-value* < 0.05 was used as the threshold for significance.

Results and Discussion

Several patterns were observed when evaluating the impact of various predictors on the clinical efficacy of EACH therapy (Table 2). Significantly elevated

Table 1. Baseline patient characteristics.

Parameter	Values in groups		*P-value*
	Control, *N*=30	EACH, *N*=32	
Sex (male), %	57	58	1
Age, years	61 (56–69)	64 (54–68)	0.86
Body weight, kg	94 (82–00)	87 (78–93)	0.06
SOFA score, points	3 (3–4)	3 (2.5–4)	0.21
CRP, mg/l	41 (10–165)	122 (84–200)	0.09
IL-6, pg/ml	416 (280–600)	423 (230–820)	0.67
Ferritin, µg/l	1190 (660–1850)	800 (437–1770)	0.38
D-dimer, ng/ml	590 (330–970)	510 (330–1730)	0.75

Table 2. Ranking of predictors of clinical efficacy of EACH therapy in COVID-19 patients.

Parameter	OR	95% CI	*P-value* (LR)	50% survival		AUC
Age, years	1.007	(0.97–1.07)	0.33			
Body weight, kg	0.997	(0.99–1.02)	0.75			
CRP, mg/l	0.996	(0.98–1.01)	0.13			
D-dimer, ng/ml	1.000	(1.00–1.00)	0.25			
Ferritin, µg/l	1.000	(1.00–1.00)	0.35			
IL-6, pg/ml	1.001	(0.99–1.01)	0.086	⩽	522	0.62
Severity of lung involvement, %	1.14	(1.01–1.25)	0.036	⩽	77%	0.60
SOFA score, points	3.261	(1.39–7.61)	0.009	⩽	3	0.66
ICU stay, days	1.11	(1.07–1.16)	<0.001	⩽	16	0.75
Time to adsorption*, days	0.76**	(0.54–0.96)	0.016	⩽	7	0.58
Model based on both significant parameters						
Time to adsorption*	0.79**	(0.69–0.90)	<0.001			0.85
ICU stay, days	1.31	(1.28–1.34)	<0.001			

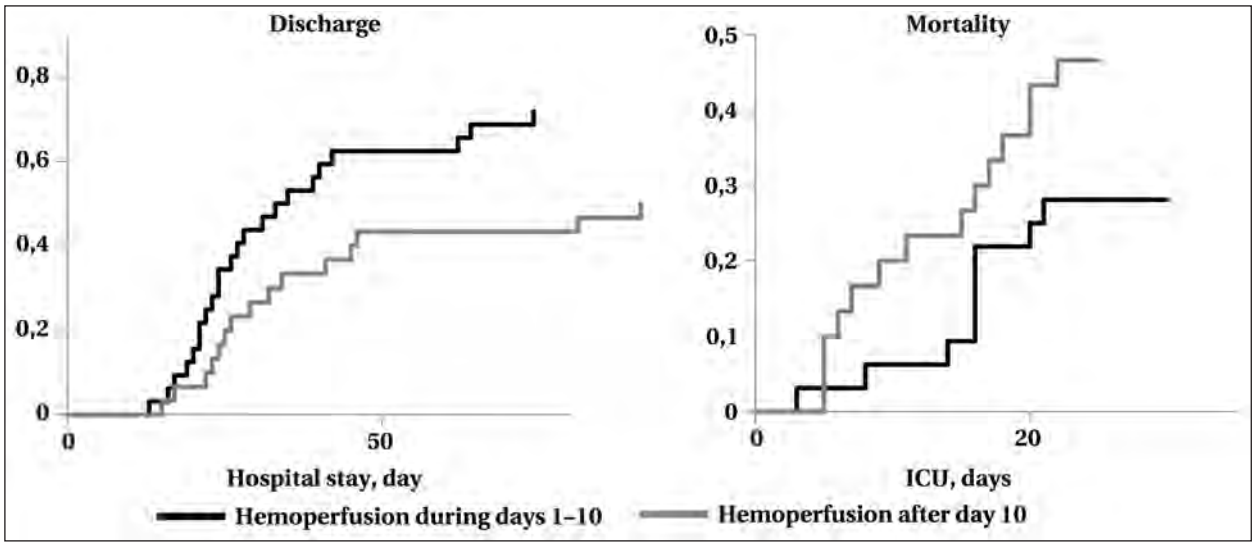

Fig. 1. Incidence curves of competing risks.

Table 3. Treatment results.

Parameter	Values in groups		*P-value*
	Control	Hemoperfusion	
Survival	53%	72%	0.19
ICU stay in survivors, days	8	11	0.45
Hospital stay, days	27	31	0.028

Table 4. Cox's competing risk model based on a length of hospital stay prior to the EACH treatment initiation

Event	SHR (day 10)	*P-value* (χ^2, df=1)	SHR (1/t)	95% CI	χ^2 (Wald)
Transfer	1.18	0.002	4.8	(1.8-12)	9.6
Discharge	1.17	0.002	5.2	(1.9-14.6)	9.8
Death	0.80	0.042	0.11	(0.013-0.92)	4

Note. SHR — sub-distributed hazard ratio.

levels of CRP, D-dimer, ferritin, and interleukin-6, traditionally used in the clinic to initiate adsorption therapy, had a less significant effect on the likelihood of discharge than did baseline disease severity as assessed by the SOFA scale (P = 0.009) and the severity of lung involvement (P = 0.036) (Table 2). However, there was a significant increase in adverse outcomes when the watchful waiting strategy was used and extracorporeal therapy was initiated at a later stage of the disease (P < 0.001), when inflammatory markers were significantly elevated and further deterioration of patients with progression of multiple organ failure was observed.

Notably, delaying extracorporeal detoxification until anti-inflammatory therapy has failed is not specified in the temporary clinical guidelines [3].

The results of treatment of patients are shown in Table 3. Analysis of the data characterizing the effect of extracorporeal procedures on mortality and duration of hospitalization in patients with COVID-19 allowed us to determine the most favorable period of EACH initiation from the onset of disease manifestations and hospitalization. Figure 1 shows mortality rates in relation to the time of initiation of EACH treatment and the onset of clinically significant signs and symptoms.

The interval of 1–10 days from the manifestation of the disease to the beginning of EACH treatment was optimal. The clinical outcome of EACH started within this period of hospitalization and the overall treatment efficacy are shown in Table 4.

Data demonstrate that patients who started EACH during the first 10 days were:

- 18% more likely to be discharged from the ICU to the ward (P = 0.002)
- 17% more likely to be discharged from the ICU to home (P = 0.002)
- 20% less likely to die (P = 0.042)

Literature data exist on the importance of timely initiation of efferent therapy. For example, Amir Ahmad Nassiri et al. (2021) observed the relationship between mortality and the timing of hemoadsorption initiation [6], while Ali Esmaeili Vardanjani et al. (2021) evaluated the efficacy of the procedure during the early period of ICU stay [7] (not based on specific time limits, but rather on the course of the disease, i.e. before clinical deterioration or need for mechanical ventilation). In the study

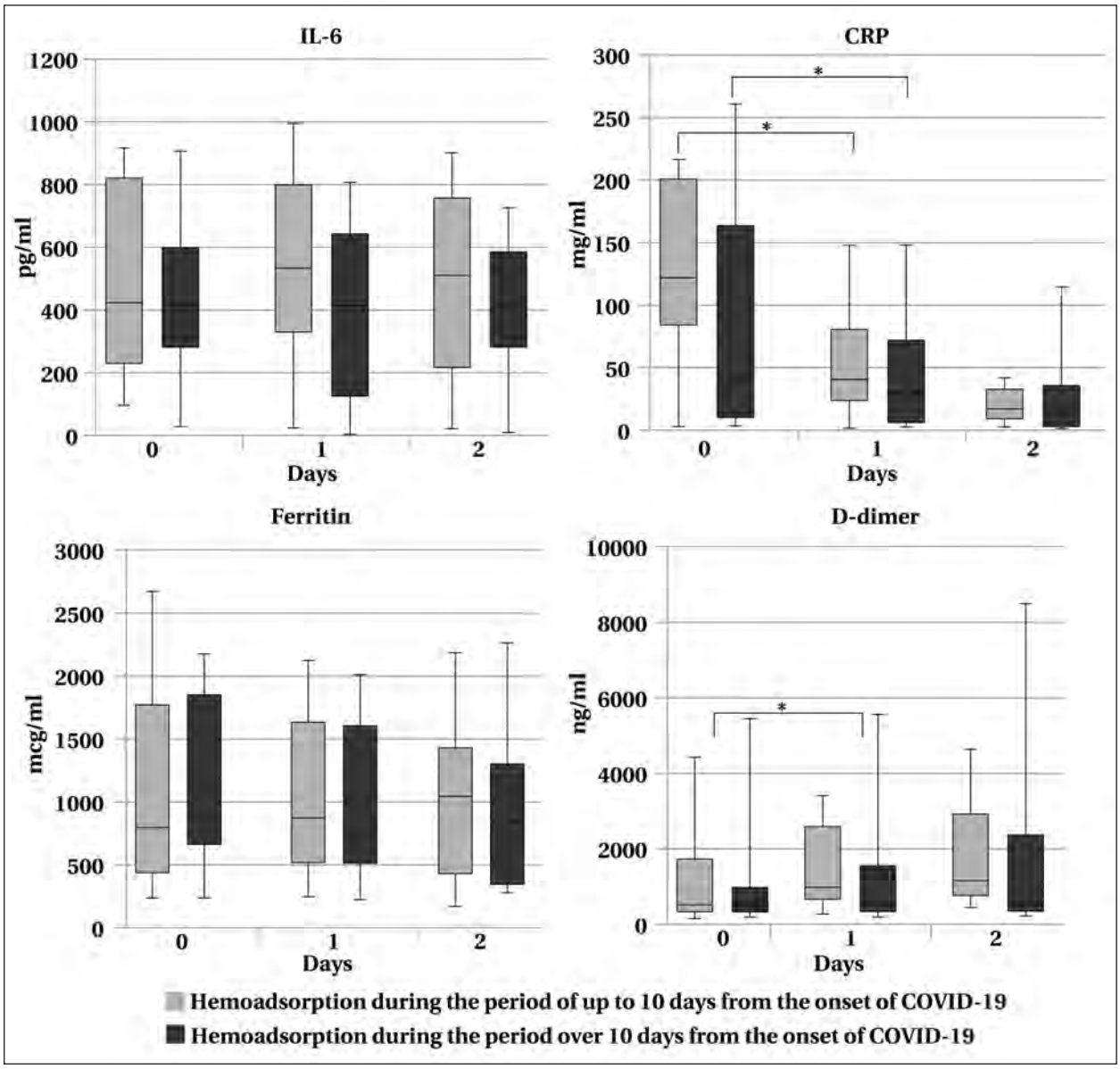

Fig. 2. Changes in systemic inflammatory response and coagulation parameters during ECH.

by Haleh Mikaeili et al. (20–21), evaluating the efficacy of cytokine adsorption in comparison with a control group of patients without efferent therapy, the average time of treatment initiation was 7 days after the onset of signs and symptoms [8], which confirms our findings.

Notably, several authors report the efficacy of early hemoperfusion to remove cytokines from the circulation [6–10], but the available data do not provide sufficient information on the timing of treatment initiation. Only one of these papers reports that patients were in the ICU for 9 days, without specifying the time from admission to hemoperfusion [6].

In order to exclude the influence of other factors on the described effect of the time of initiation of EACH, which reduce the effectiveness of the procedure when performed later, a comparative analysis of the changes in SIR (systemic inflammatory response) markers was made in the subgroups of timely and late extracorporeal blood purification (Fig. 2).

In both subgroups, there was a rapid and significant decrease in IL-6 and C-reactive protein after each EACH procedure, which is consistent with the literature [4, 5], but no significant differences were found between patients who received hemoperfusion within 10 days of disease onset and those who received it later. As expected, CRP levels decreased significantly after the first session and correlated strongly with interleukin-6 levels (K=0.89). These results reflect a significant contribution of adsorption to the control of SIR and provide a rationale for its use, including in combination with biological therapy.

Since coagulopathy in patients with COVID-19 is a predictor of disease severity, whereas coagulation

parameters are traditionally associated with the evolution of SIR syndrome, we examined the changes in D-dimer and fibrinogen levels in both groups [11, 12]. Evaluating the temporal changes in D-dimer (Fig. 2), we observed an increase in this parameter in the subgroup of patients with early EACH initiation.

Such a trend has been described in the literature and is probably associated with severe disease and progressive coagulopathy [13], as well as with an imbalance of factors controlling systemic fibrinolysis, which could also be due to their removal with adsorption.

In addition, the mean fibrinogen level decreased with treatment in both subgroups (from 6.4 g/l to 4.25 g/l), which can be considered an additional indicator of effective correction of systemic inflammation [14].

The significant increase in the probability of death in the subgroup of patients who started treatment at a later stage of the disease is also noteworthy. The subgroup differences in the likelihood of discharge from the ICU to the ward (18% higher, $P = 0.002$), the likelihood of discharge to home (17% higher, $P = 0.002$) and the likelihood of death (20% lower, $P = 0.042$) start to emerge after day 10 of disease onset, suggesting that this period can be considered critical for the decision to start cytokine adsorption.

Hypercytokinemia is a potentially detrimental factor leading to the onset and progression of multiple organ failure (MOF) [15–19]. According to the available data, cytokines directly or indirectly stimulate coagulopathy, endothelial destruction and increased catabolism. Their levels correlate with the severity of COVID-19 and prognosis and influence the efficacy of medical therapy [20–24]. Biologic therapy only partially solves this problem because it selectively targets a specific group of cytokines and their receptors without affecting other equally important inflammatory factors, does not prevent further production of cytokines and their new receptors, and has a long-term immunosuppressive effect, especially with repeated use, as well as significantly increases the cost of treatment.

Cytokine adsorption alone and in combination with immunobiologic therapy can be an important adjunct in the treatment of patients with both COVID-associated sepsis and infection-related organ dysfunction of other etiologies, but as shown by our and similar studies, should be initiated in a timely manner [7, 25, 26]. In particular, we did not differentiate the contribution of adsorption and biological drugs in the regression of systemic inflammation, because we believe that these methods should be used together.

Our study has several limitations. We conducted a single-center, nonrandomized study. The delay in EACH initiation may have been influenced by exacerbating factors (e. g., hematoma development, thrombocytopenia, etc.), which may have worsened the treatment outcome. Further studies are needed to better understand the indications for optimal initiation of EACH procedure in COVID-19 patients.

Conclusion

Cytokine adsorption with the Efferon® CT extracorporeal adsorber has shown its clinical efficacy in patients with severe COVID-19 when performed earlier (up to 10 days) after the onset of the disease, reducing mortality and shortening the duration of hospitalization.

The most important predictors of adverse outcome are the later initiation of EACH treatment (10 days and later after the onset of coronavirus infection) and the severity of multiple organ failure.

The level of CRP decreased significantly after the first hemoperfusion session and correlated strongly with the level of interleukin-6.

In the follow-up period, the levels of IL-6, CRP, ferritin, D-dimer did not change significantly in the course of anti-inflammatory medical therapy after the EACH.

Initiation of EACH therapy should be considered in combination with conservative anti-inflammatory treatment, but not as an alternative or «last resort» method.

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Achieving and Maintaining Effective Plasma Concentration of Lithium After Oral Administration

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Summary

The aim of the study. To study the achievability and contingency to maintain an effective plasma lithium concentration in the perioperative period in patients undergoing carotid endarterectomy (CEAE) with oral intake of lithium carbonate pills.

Materials and methods. It was a prospective study, as a preparatory stage of the multicenter «BINOS» (NCT05126238) RCT. The sample included 15 patients undergoing elective CEAE. In the course of this study, patients were administered oral lithium carbonate, 900 mg per day during 4 perioperative days: two days before the procedure, in the day of surgery and in the 1st postoperative day. Plasma lithium concentration was monitored every 24 hours during all 4 days from the onset of treatment.

Results. Increased plasma lithium concentrations were found in blood samples taken at 48 hours (0.68 mmol/l [0.53–0.84], $P = 0.004$) and 72 hours (0.68 mmol/l [0.62–0.90], $P < 0.001$), as compared with the initial values (0.14 mmol/l [0.11–0.17]).While during the period between 48 and 72 hours from the onset of treatment the plasma lithium concentration remained in the therapeutic range (0.4–1.2 mmol/l) in 100% of patients.

Conclusion. Oral intake of lithium carbonate pills at a dose of 900 mg/day during 2 preoperative days provided an effective and safe plasma lithium concentration in 100% of patients enrolled in the study.

Keywords: carotid endarterectomy; lithium; pharmacokinetics; drug administration regimen; plasma lithium concentration

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

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Introduction

Approximately 10.3 million cases of cerebral infarction (CI) are reported worldwide each year, with ischemic CI accounting for about 80% [1, 2]. In Russia, more than 450,000 cases of stroke are reported annually, and the 30-day mortality rate exceeds 25%. In the following 12 months, about half of the remaining patients die, which is more than 200,000 people [3]. Stroke sequelae are the leading cause of disability [4].

The main cause of most strokes is atherosclerosis with predominant lesions in the carotid arteries [2]. In this context, carotid endarterectomy is considered by current guidelines as the main method for the prevention and treatment of CI [5, 6]. However, despite improved diagnostic methods and techniques of carotid surgery, perioperative cerebral ischemic stroke remains a significant challenge. The incidence of major ischemic stroke after carotid endarterectomy (CEAE) is reported to be 2–2.5%, while the rate of major adverse cardiovascular and cerebrovascular events (MACCE) (composite outcome including death, myocardial infarction, and acute cerebrovascular accident) reaches 5–7% [7, 8].

Neurocognitive disorders manifesting as postoperative delirium or cognitive dysfunction are another serious problem of the postoperative period [9, 10]. In some cases, postoperative delirium is the earliest and sometimes the only manifestation of latent CI [11]. The consequences of postoperative delirium and POCD are not as benign as they may have seemed until recently. Postoperative delirium is associated with a twofold increase in mortality and prolonged ICU and hospital stay [12], while POCD requires prolonged medical and social rehabilitation [13].

Lithium salts have been used in psychiatry for more than 50 years and remain the «gold standard» in the treatment of bipolar disorder [14–16]. However, only recently have researchers drawn attention to a reduced risk of stroke in patients with bipolar disorder taking lithium compared with patients treated with modern antidepressants, antipsychotics, and anticonvulsants [17]. This observation was supported by the results of two independent RCTs showing faster recovery from stroke in patients treated with lithium compared with placebo [18, 19]. In both studies, the target blood concentration of lithium ions was 0.4–0.8 mmol/L [18, 19]. However, there is currently no consensus on the therapeutic concentration of lithium preparations in blood plasma. Thus, a literature review aimed at identifying the therapeutic concentration of lithium ions concluded that the most acceptable range is 0.4–1.2 mmol/L [20]. In the German guidelines, the therapeutic range is also 0.4 to 1.2 mmol/L [21]. At the same time, in the Canadian recommendations, the therapeutic concentration is 0.8–1.2 mmol/L, but the lower limit of this range is reduced to 0.4 mmol/L in elderly patients [22].

Wider use of lithium salts, particularly in anesthesia (for stroke prevention in CEAE) and intensive care (for stroke treatment), is hampered by the lack of a soluble form of the drug. However, achieving and maintaining an effective concentration of lithium salts in the blood using a tablet form of the drug in an acute situation, although quite challenging, is not impossible based on theoretical assumptions. At least, such a possibility has never been investigated.

The aim of this study was to investigate the possibility of achieving and maintaining an effective concentration of lithium ions in the blood of patients in the perioperative period when performing CEAE using a per os preparation containing lithium carbonate.

Material and Methods

This was a preliminary study of the multicenter RCT «BINOS» (NCT05126238). The study was approved by the Ethics Committee of the Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology (protocol 3/21/6, dated June 27, 2021).

Inclusion criteria were age 18 years and older, signed informed consent, prescription of Sedalit® (lithium carbonate) by the medical team.

Exclusion criteria were known allergy to lithium preparations, neuromuscular diseases specified in the ICD-11, epilepsy, history of leukemia, glomerular filtration rate less than 30 mL/min/1.73 m^2, left ventricular ejection fraction less than 30%, chronic heart failure NYHA class 3–4, known pregnancy at the time of enrollment.

The primary endpoint of the study was the patients' blood lithium salt concentrations on the day of surgery and the day after surgery.

Consecutively, 15 patients who were admitted to the inpatient department of City Clinical Hospital No. 68 for elective CEAE and who met the eligibility criteria were offered to participate in the study. Patients who signed the informed consent and were approved by the medical team were offered initial blood sampling, followed by prescription of Sedalit 300 mg three times a day (total daily dose was 900 mg) two days before the date of surgery. The drug was continued in the postoperative period immediately after the permission to eat solid food on the day of surgery and the first postoperative day.

To study the concentration of lithium ions in the blood, a blood sample of 6.0 ml was taken from an upper extremity vein in the morning before the next dose of Sedalit. Each blood tube was centrifuged, and 2.0 mL of plasma was collected from each blood sample for analysis of lithium ion concentration. Blood samples were collected at 5 time points for each patient: 1 — period between the patient's enrollment in the study and the start of Sedalit, 2 — 24 hours after the start of Sedalit, 3 — 48 hours after the start of Sedalit, 4 — 72 hours after the start of Sedalit, 5 — 96 hours after the start of Sedalit. Time point 1 reflected the initial concentration of lithium ions in the patients' blood, while the other points indicated the accumulation of lithium ions in the patients' blood while taking Sedalit. Time point 3 also reflected the blood level of lithium ions prior to surgery.

Plasma lithium concentrations were determined using an AVL 9180 electrolyte analyzer from Roche Diagnostics at the Moscow Research Institute, a branch of the Serbsky National Medical Research Center for Psychiatry and Narcology of the Ministry of Health of the Russian Federation.

Data analysis was performed according to the «as treated» principle. Thus, if a patient stopped taking Sedalit, subsequent blood test results were excluded from the statistical analysis, as they did not reflect the process of lithium ion accumulation in the blood.

Data distribution was assessed using the Shapiro–Wilk criterion. Quantitative data were presented as medians and interquartile ranges with 5^{th}, 10^{th}, and 90^{th} percentiles; frequencies were presented as percentages. To assess the significance of differences over time, Friedman's rank dispersion analysis was used for paired samples, and Nemenyi's post hoc test was used for multiple comparisons. Box plots were used to visualize the data. All statistical tests were performed using the IBM SPSS Statistics 26.0 software package. Tableau Desktop Software 2019.1 was used for visualization. The significance level was set at 0.05.

Results

A total of 15 patients were included in the study (Fig. 1). The mean age was 57.5 (66; 81) years, and 7 (46.7%) patients were female.

The patients included in the study had a history of comorbidities and were taking medications, as shown in Table 1.

During the study, one patient refused to take Sedalit 24 hours after the start of the study for reasons unrelated to the side effects of the lithium drug. Another patient had hemolysis of a blood sample on day 3 (point 4 — 72 hours) during centrifugation, which prevented evaluation of the lithium concentration in his sample.

The changes in the concentration of lithium ions in the blood of the patients are shown in Table 2.

The changes over time were significant ($P < 0.001$) according to Friedman's non-parametric criterion. The results of a posthoc test showed that the patients had higher blood lithium concentrations on day 2 (0.68 [0.53–0.84] vs. 0.14 [0.11–0.17], $P = 0.004$), day 3 (0.68 [0.62–0.90] vs. 0.14 [0.11–0.17], $P < 0.001$), and day 4 (0.79 [0.67–1.15] vs. 0.14 [0.11–0.17], $P < 0.001$) compared to baseline (Tables 2, 3). In addition, the increase in lithium ion concentration was significant on days 3 ($P = 0.043$) and 4 ($P = 0.002$) compared with day 1 (Table 3).

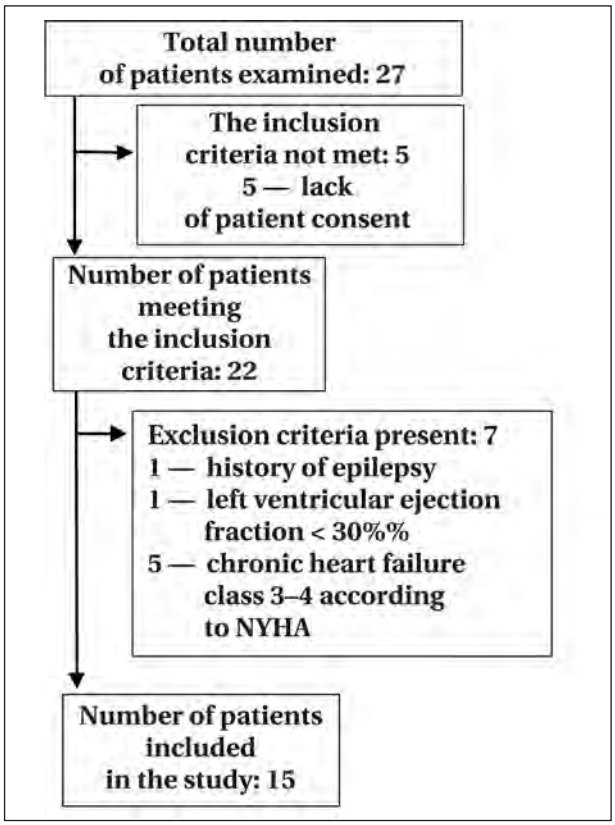

Fig. 1. Flowchart illustrating the process for enrolling patients into the study.

Table 1. Frequency of comorbidities and medications used by patients.

Chronic comorbidities		Medications	
Condition	**Number of patients, *N* (%)**	**Group**	**Number of patients, *N* (%)**
Coronary heart disease	1 (6.67)	β-blockers	4 (26.67)
Myocardial infarction	3 (20.00)	ACE inhibitors	2 (13.33)
Stroke	2 (13.33)	ARBs	6 (40)
Stable angina	2 (13.33)	Calcium channel blockers	2 (13.33)
Atrial fibrillation	1 (6.67)	Antiplatelet drugs	1 (6.67)
Chronic heart failure	2 (13.33)	Anticoagulants	1 (6.67)
Hypertension	13 (86.67)	Statins	5 (33.33)
Diabetes mellitus	5 (33.33)	Antiarrhythmic drugs	1 (6.67)
Bronchial asthma	1 (6.67)	Diuretics	1 (6.67)
Chronic obstructive pulmonary disease	1 (6.67)	Insulin	1 (6.67)
Chronic kidney disease	2 (13.33)	Other hypoglycemic drugs	4 (26.67)
		α-blockers	1 (6.67)
		Neuroprotectors	2 (13.33)

Note. ACE — angiotensin-converting enzyme; ARBs — angiotensin receptor blockers.

Table 2. Concentrations of lithium ions in the blood of patients at different time points.

Parameter	Baseline	Days			
		1	2	3	4
N	15	15	14	13	14
Median (mmol/L)	0.14	0.49	0.68	0.68	0.79
Minimum (mmol/L)	0.00	0.31	0.47	0.55	0.55
Maximum (mmol/L)	0.19	0.81	0.94	1.10	1.77
Percentile					
5	0.00	00.31	0.47	0.55	0.55
10	0.00	00.36	0.48	0.57	0.57
25	0.11	00.45	0.53	0.62	0.67
50	0.14	00.49	0.68	0.68	0.79
75	0.17	00.61	0.84	0.90	1.15
90	0.19	00.73	0.91	1.08	1.66

Table 3. Pairwise comparisons of patients' lithium concentrations at different time points (Nemenyi's posthoc test).

Pairwise comparison	Coefficient	*P-value*
Baseline — Day 1	1.231	0.472
Baseline — Day 2	2.192	0.004*
Baseline — Day 3	3.000	< 0.001*
Baseline — Day 4	–3.577	< 0.001*
Day 1 — Day 2	–0.962	1.000
Day 1 — Day 3	–1.769	0.043*
Day 1 — Day 4	–2.346	0.002*
Day 2 — Day 3	–0.808	1.000
Day 2 — Day 4	–1.385	0.256
Day 3 — Day 4	–0.577	1.000

Note. * — differences are significant.

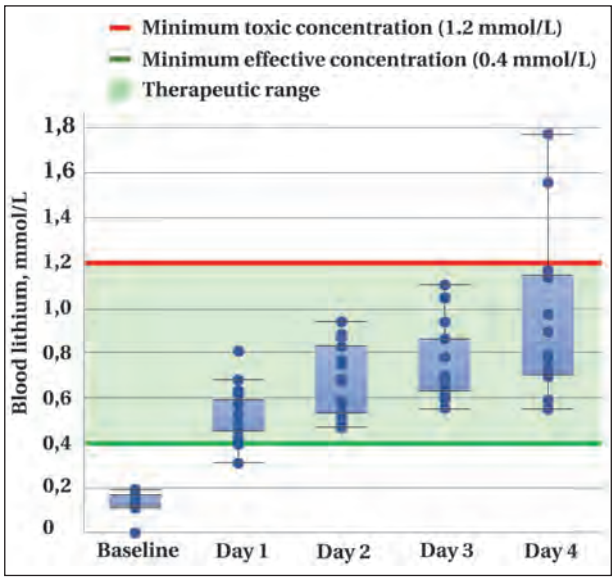

Fig. 2. Changes in the concentration of lithium ions in the blood of patients at different stages of the study (box plot).

Figure 2 shows the changes in lithium ion concentrations in patients' blood at various time points, indicating the minimum effective concentration (0.4 mmol/L), the minimum toxic concentration (1.2 mmol/L), and the therapeutic range (0.4–1.2 mmol/L).

Table 4 compares the percentages of patients relative to the minimum effective and minimum toxic concentrations of lithium ions in the blood.

According to the results of the analysis, the optimal period in terms of pharmacokinetics is 2–3 days (48–72 hours) after starting Sedalit 300 mg 3 times a day, because 100% of patients had lithium concentration values within the therapeutic range, and none of them had values below the minimum effective concentration (0.4 mmol/L) or above the minimum toxic concentration (1.2 mmol/L).

Discussion

A recent study by O. V. Forlenza et al. showed that long-term lithium administration for 2 years at doses ranging from 150 mg to 600 mg per day and reaching plasma concentrations (0.25–0.5 mmol/L) attenuated cognitive and functional impairment in elderly patients with moderate cognitive impairment in the memory domain, which is associated with high risk of Alzheimer's disease.

In the study by S. E. Mohammadianinejad et al., the target plasma lithium ion concentration was 0.4–0.8 mmol/L. It is important to note that the upper limit was considered to be 1.2 mmol/L, which served as a criterion for post-randomization exclusion in this study. These values of lithium ion concentration in blood plasma fully correlate with the limits used in our study.

The lithium drug regimen (300 mg lithium carbonate twice daily) in the study by S. E. Mohammadianinejad et al. differs from that in our study. The lower daily dose of the drug was probably the reason why the average plasma concentrations of lithium ions in the study of S. E. Mohammadianinejad et al. were not reached until day 5. The dosing regimen used by S. E. Mohammadianinejad et al. worked well for long-term dosing in patients with cerebral infarction, but it is difficult to use in perioperative medicine because of the very long time required to reach the target concentration. The dosing regimen of our study allows for faster achievement of therapeutic concentration and its maintenance during the perioperative period.

In another study by Y. R. Sun et al., the target plasma concentration of lithium ions was also 0.4–0.8 mmol/L. This paper is important in comparing lithium dosing regimens. Lithium carbonate doses of 300 mg or more per day were shown to correlate with improved cognitive function compared with those of less than 300 mg per day.

The key finding of our study is that 100% of patients achieved target therapeutic concentrations

Table 4. Number and percentage of patients relative to the minimum effective and minimum toxic concentrations of lithium ions in the blood.

Parameter	Baseline, *N* (%)	Day, *N* (%)				Total, *N* (%)
		1	2	3	4	
Concentration of lithium ions in blood, mmol/L						
<0.4	15 (100)	2 (13.3)	0 (0.0)	0 (0.0)	0 (0.0)	17 (23.9)
0.4–1.2	0 (0.0)	13 (86.7)	14 (100)	13 (100)	12 (85.7)	52 (73.2)
>1.2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (14.3)	2 (2.8)
Total	**15**	**15**	**14**	**13**	**14**	**71**

on days two and three on a 900 mg daily dose of lithium carbonate. In addition, not a single patient had a blood lithium concentration below 0.4 mmol/L, which is the minimum effective concentration of the drug according to literature data [20, 21]. In addition, none of the patients reached the minimum toxic concentration specified in the German and Canadian recommendations [21, 22].

Limitations

Overall, the study was conducted according to the principles of good clinical practice and evidence-based medicine. Perhaps the specific pharmacokinetics of Sedalit in patients with renal and cardiac failure should have been studied. However, given the nature of this work as a preliminary study to the main trial and the inclusion/exclusion criteria for the main study, the authors considered such detail unnecessary.

The authors restricted the study to 15 patients. This was due to the financial resources of the clinic. Theoretically, the study could have been expanded, but the clear result obtained in 15 patients confirmed the correctness of the authors' original position.

Conclusion

Oral lithium carbonate 900 mg/day administered for 2 preoperative days can help achieve effective and safe blood lithium concentrations in 100% of the patients enrolled.

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3D EEG and Clinical Evidence of Brain Dying. Preliminary Report

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Summary

Determination of brain dying means reversible or irreversible injury to the brain, including the brainstem. Current guidelines rely on clinical examination including the proof of coma, absent brain stem reflexes, and apnoea test. Neurophysiological testing using electroencephalography and evoked potentials — somatosensory evoked potentials and brainstem auditory evoked potential could have been helpful in the final diagnostic brain death conclusion, but the diagnostic accuracy of these methods in the last years has revealed controversies. Here, we present data on quantitative EEG signal evaluation (qEEG) by a 3-dimensional brain mapping (3D BM) as developing tool to clarify whether the transverse and anterior posterior coherences such as connectivity indices may demonstrate connection in transversal or anterior posterior dimensions with «wavelet transformation» and if the 3D BM visualization of the of representative EEG signals may improve informative value of EEG signals quantification when evaluating the brain dying.

The purpose of our work is to provide an update on the evidence and controversies on the use of EEG for determining brain dying and raise discussion on EEG applications to improve the transplantation program.

Results. We analyzed the EEG records of 10 patients admitted for cardiopulmonary resuscitation (CPR) during September, 2017 — August, 2018. Data from one patient, ŽM, 33 years old, after haemorrhagic shock (August 2018) were analyzed in details. Quantitative EEG dynamics by images and clinical course of brain dying were monitored prior and after the amantadine sulfate intravenous administration for brain revival. Data demonstrated the ability of brain to survive; the cause of final brain death was heart failure.

Conclusion. Data confirm the hope for survival of the brain in a coma and demonstrate brain capability to keep functionally optimal state as a potential for a good social adaptation.

Keywords: electroencephalography; brain dying; quantitative EEG; 3D brain mapping, longitudinal and transversal coherencies, wavelet transformation, resuscitation

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

Introduction

The brain stem controls the essential functions necessary for survival, such as breathing, blood pressure, and heart rate. Currently, despite the differences in clinical practice in individual countries [1] the standard diagnosis of brain dying depends on three cardinal neurological features: coma, lack of brain stem reflexes, and apnoea [2].

Brain dying, briefly speaking, is referred to the incompletely reversible state leading to complete, irreversible, and permanent loss of all brain and brainstem functions. Brain dying implements also the possible termination of a human's life; correspondingly, the diagnosis of the dynamic process «brain dying» resulting in brain death is very important (Ad hoc committee of the Harvard medical school to examine the definition of brain death, 1968). However, some social disagreements or different diagnosis criteria in clinical practice are still remain around the world. Some standard tests to determine the brain death are widely used, such as the apnoea test or brainstem function examination [1]. Notably, it is commonly agreed that EEG might serve as an auxiliary and useful aid in the confirmatory tests common for adults and children [3–5]. Typically, isoelectric EEG recording is required for the brain death condition at least 30 min and may last 3–24 h [1]; the positive response of EEG tests suggests functioning of the brain. Consequently, the patient in deep coma — «brain dying» condition — might show some EEG electro-activity, while the brain-dead patient will not. It is not known what to do with a quantitatively positive EEG signal test such as a three-dimensional brain mapping (3D BM) exhibiting the presence of oscillations in many cases, where the classic isoelectric EEG long lasting registrations are not visually seen. Are the 3D BM signals real? Whether this problem represents a fairy tale

lasting for many years, or an imaginable phantasy of our innate intelligent soul in the era of a computer intelligence? It seems to be a crucial challenge for neuroscience in the 21st century. A quantitative evaluation of «qualia», the internal and subjective component of sense perceptions from stimulation of senses by the computer intelligence, in our case, might become a main goal for current neuroscience.

Novadays, the evaluation of EEG patterns by means of a power spectral analysis has become a major challenge for predicting enhanced or non-changeable neurological status beside the discharge of the patient from cardio-pulmonary resuscitation (CPR). EEG is employed to measure electrical potentials at the surface of the scalp to detect cortical activity that commonly refer as «brain waves». The analysis of the quantitative EEG (qEEG) in a digital format is considered as a «Brain Mapping». The qEEG is an extension of the analysis of the visual EEG interpretation, which may assist and even augment our understanding of the EEG and brain function. the procedure of qEEG records EEG activity using a multi-electrode recording with the aid of a computer. Multi-channel EEG data are processed using various algorithms, such as the classic «Fourier» algorithm, or in a more modern format as a cross-spectral «wavelet» analysis. The digital data are statistically analyzed, sometimes comparing values with «normative» database reference values. The processed EEG data are usually converted into color maps of the functioning brain called «Brain maps». EEG information and derived qEEG data can be interpreted and used by experts as a clinical tool to monitor and evaluate the brain function changes following various interventions such as neuro-feedback or medications, as well as survival-dying or brain death data.

Various analytic approaches include commercial databases or database-free methodology, such as EEG phenotype analysis, or classic EEG Vigilance model (Bente, 1964) [6] are used in modern clinical application of the EEG/qEEG. The use of advanced techniques such as Independent Component Analysis (ICA) and neuro-imaging techniques such as Low Resolution Electro-magnetic Tomography (LORETA) can map the actual sources of the cortical rhythms.

The purpose of our work is to provide an update on the evidence and controversies on the use of EEG for determining brain dying and raise discussion on EEG applications to improve the transplantation program.

Oscillations coming of ECG signal, natural respiration pacing signal, and blood pressure are interpreted as an important natural oscillations that affect the EEG signal generation by «cross-coupling» mechanism modulating EEG signal frequency, amplitude and even the phase.

Interpreting EEG with a high sensitivity required for the diagnosis of brain dying and brain death, can pose a diagnostic challenge. Furthermore, EEG is frequently affected by physiologic variables and drugs. However, no consensus exists for minimal requirements for blood pressure, oxygen saturation, body temperature during the EEG recording, minimal time for observation after the brain injury or re-warming from hypothermia, and determining the brain death when the findings of electro-cerebral inactivity (ECI) is equivocal. Therefore, there is a strong need in establishing detailed guidelines for performing EEG to determine brain dying [7].

We would like to clarify, in which functional module, or in which of basic functional modules, the oscillator of individual frequency bands is situated as a sign of possible spontaneous or provoked activity using functional restoration with amantadine sulphate (by intravenous (IV) administration at a dose of 200 mg, 5 injections), and whether these quantitative indicators of brain vital basic function e.g. consciousness (carriers of lucidity, vigilance, aware cognition, aware consciousness) are present [8].

ECI is required to confirm cessation of brain function, but this does not ensure either the irreversibility or loss of whole brain function.

If sedative medication used before the diagnosis of brain dying-brain death, the French guidelines recommend using the techniques based on the study of intra-cerebral blood flow such as cerebral angiography, which was not influenced by the medications.

The cause of sufficiency of a single EEG described in the American EEG guidelines is that no patients survived for more than a short period after an EEG showed ECI, excluding the cases, which were due to overdosing with CNS depressants. Therefore, single EEG demonstrates that ECI is a highly reliable tool for determining cortical dying and death.

Materials and Methods

In the Clinic of Anaesthesiology and Intensive Medicine we analyzed the EEG records of 10 patients admitted for cardiopulmonary resuscitation (CPR) during September, 2017 — August, 2018. Data from one patient, ŽM, 33 years old, after haemorrhagic shock (August 2018) were analyzed in details. For detection of EEG signal we used NEURON SPECTRUM AM with specialized software. By processing EEG signals, we evaluated the classic EEG line signal in reference, transversal and longitudinal montages. Data recording were performed during 20–30 minutes. After that, the analysis of EEG line signal was continued by means of classic visual evaluation, rapid Fourier´s transform, cross-spectral analysis, and 3D BM in colors. Our aim was to exclude the current wave within the frequency frame of 0.1–40 Hz with an amplitude below 2μV that

represented a classic criterion for definition of «brain death» by EEG signal. Brain dying resulted in appearance of a flat EEG curve with an amplitude above 2μV but with a progressive decrease in power measured by the amplitude. We consider this pattern as that demonstrating the ECH electro-cerebral hypoactivity.

The EEG/qEEG procedure was performed twice or trice as a standard advance for diagnosing brain dying and brain death.

Many natural oscillation as determined by ECG, BP, pacing respiration could serve as the secondary natural sources of EEG signal transforming to its frame through cross-coupling of frequency, amplitude and even a phase of both particular EEG band oscillations and extra-cerebral biological rhythms [9, 10].

Brain Mapping (BM-pEEG). The map shows the amplitude distribution of the EEG signal frequency band potentials. The essence of the BM consists of coding the numerical values of the signals into the color scale and its iterative interpolation, even for the areas where the signal values have not been really measured. The goal of interpolation is to obtain spatial image (raster) from a discrete image [11].

The procedure of 3D BM. These data constituted a 19-channel EEG recording in accordance with the international 10–20 system, referenced to the Cz electrode, sampled at 500 Hz and band-pass filtered at 0.5–45 Hz. After the visual evaluation, we designated an optimal 5–8 s section of the EEG signal that was a subject of a further digital power cross-spectral analysis, the results of which we iteratively interpolated to the color sperctrum and obtained a spatial 3D image (raster) from a discrete image.

Case report. Patient Ż. M., woman, 33 years old, was admitted to the Clinic of Anaesthesiology and Intensive Medicine on August, 7, 2018 and hospitalized untill August, 24, 2018. The patient was transferred from the District Hospital after Caesarean section and unexpected womb bleeding, after which she was underwent cardiopulmonary resuscitation. During August 02–07, 2018 patient was treated because of post-Cesarian section hemorrhagic shock in the District Hospital.

Neurologic examination done in the August, 7, 2018 at 5.00 p.m. states: the patient does not respond to the nociceptive stimulus, comatose state GCS 3 points, insufficient spontaneous breathing activity and cough reflex are present, photoreaction bilaterally is absent, ciliospinal dilatation of the pupils is revealed, after the illumination of the eyes, a moderate mydriasis appears, corneal reflex is bilaterally positive but significantly weakened, masseter reflex is absent. Gag-reflex, tendon-jerk reflexes (C8-S2 responses) are absent. Skeletal muscles are flaccid, pathologic exteroceptive reflexes absent, and limbs are passively situated along the somatic trunk. Sclerae are light icteric, conjunctiva is pale, eyeballs are in a middle position and motionless, nystagmus is absent. Blood pressure 70/50 mmHg, HR 85/min. Continuous medication: catecholamine (Noradrenaline) and Terlipressin (Remestyp). Peripheral oxygen saturation 99%. Continuous administration of anti-arrhythmic drug Amiodarone and orotracheal intubation are performed. The urinary catheter drains concentrated, thick, deep yellow-colored urine.

On the day of admission, the patient was after the fourth hemodialysis. The abdominal wound after the cesarian section was covered, not overflowed, the intestine and the stomach peristalsis was audible.

The following day, August 8, 2018, the consecutive neurologic and nephrologic examinations, EEG investigation, CT-scan of the brain and + 3D reconstruction were performed. Diagnosis: coma. State after bleeding shock, CNS structures with no sign of intracranial middle line shift. Ventricular system and SA without signs of extension, without convincing pathological changes supratentorial and infra-tentorial. No signs of intracranial haemorrhage, without fresh focal ischemic changes. No evidence for a malignant brain edema.

Neurological examination on August 9, 2018: Hypoxemic-anoxic multiorgan damage in severe post-haemorrhagic shock, hepato-renal syndrome. Brain stem reflexes are absent, GCS 3. Tracheostomy in August 09. 2018 was performed, it was revised in August 14. 2018. Laparoscopic cholecystectomy performed in August 23, 2018 concluded: thick-walled gall bladder with gangrene of the mucosa. According to the anaesthesist's report, surgery with no any anaesthesia complication. During the entire ICU stay, the patient was monitored daily by a gynaecologist, neurologist, surgeon, cardiologist, dialysis physician, and endocrinology specialist. The course of the entire hospitalization and the treatment was conducted and managed according to all current laboratory parameters (biochemistry, hematology) of the patient's clinical condition and recommendations of all consultants. Due to the variability of the clinical neurological state (undulating state of consciousness, GCS 5–7 after amantadine sulphate administration), the patient gradually disconnected from the ventilator (weaning) intermittently fixed her gaze, primitively responded to a simple verbal challenge and responded by face flushing on arrival of her husband. This neurological condition persisted until 24.08.2018, when early in the morning hemodynamic and cardiac instability progressed, and the doses of drugs with vasoactive support were increased.

That day, starting from 1.30 p.m. and transfer to haemodialysis, the vital functions failed, and widespread CPR was initiated. ECG demonstrated ventricular fibrillation, and defibrillation was performed. ECG monitoring showed asystole, and significantly pale skin color and anemic conjunctiva appeared. The advanced life support continued. Subsequently, the rhythm changed again to asystole and at 2.15 p.m. due to the length of CPR (45 minutes) and general condition of the patient, the CPR was terminated.

Results

EEG evaluation (investigation) during the hospitalization.

Neurologic examination revealed coma GCS 3 on admission, extinction of brain stem reflexes, tendon-jerk areflexia, skeletal muscles flaccidity. Between

08.08.2018 — 14. 08.2018 EEG investigations revealed the following patterns shown in Figures 1–6.

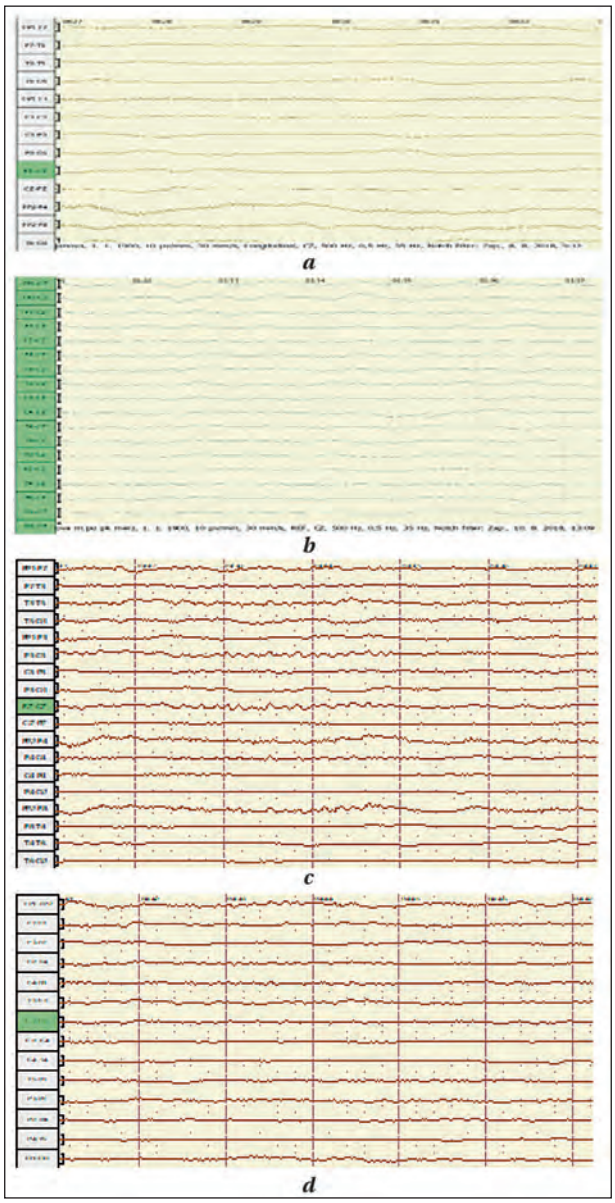

Fig. 1. Ž M, 33 years, EEG.
***a* — 08.08.2018,** without amantadine sulphate. Longitudinal montage of EEG signal, sensitivity 10 μV/mm, 6 seconds lasting EEG. Here and in b and c: cross-spectral analysis of the signal followed by 3D BM color-scale quantification of particular EEG frequency bands was performed. Flat EEG show low voltage activity in rare grids above 2μV of amplitude (AP), with rare higher voltage, demonstrating «brain dying» pattern.
***b* — 10.08.2018,** here and in c and d: following the amantadine sulphate, 200 mg each dose, IV administered. EEG signal, sensitivity 10μV/mm, 6.5 seconds lasting EEG sample. Clinical state: coma; GCS values: 3–4 scores. EEG signal is flat with a low voltage activity (slightly above 2μV).
***c* — 14.08.2018,** EEG signal at a frequency of 8 Hz in a longitudinal montage. The alpha frequency was situated in six channels of frontal regions showing distinct arousal effect with an AP increase up to 20 μV. GCS values at that time increased to 5–7 scores.
***d* — 14.08.2018,** Transversal montage illustrates arousal effect namely in frontal region as not continual but dispersed alpha waves with AP approximately 10–20 μV.

August 14, 2018: Following the 5th administration of amantadine sulphate, 200 mg, i. v. GCS increased from 3–4 to 5–7 scores. The patient was able to perform simple motor tasks: close and open her eyes, even on command, gaze a person near the bed. She reacted very vividly to the presence of her husband, tendon-jerk reflexes were present in a range of C8-S1, light reaction and abdominal reflexes were assessed.

The autopsy material of the brain neuropil and myocardial tissue (Fig. 7).

Excerpt from the autopsy protocol (a macroprint of the brain):

The brain mass is 1.582 g, it is enlarged compared to the norm, the entire brain tissue is soft, dough like, disintegrating by hand (the respiratory brain in the initial stage?). The sulci are smooth, the gyri are flattened, the border of the grey and the white matter can be distinguished on the cut, the tissue is aqueous and adherent to the knife. The brain ventricles are almost extinct, filled with a small amount of clear cerebrospinal fluid, the lining of the ventricles is fine, glossy, the choroid plexus are of a purple color.

Brain stem structures — conus compressions: The pons, the cerebellum and the medulla are intact with no changes in the anatomical integration, soft dough-like consistency. The frontal, temporal, and occipital herniations are highlighted — aqueous brain.

Brain microscopic features: in the cortex, the evidence of vacuolar degeneration of the pyramidal cells, a resorption reaction around the cells due to granular cells and the microglia multiplication. Peri-capillary and peri-neurocytes swelling. Thal-

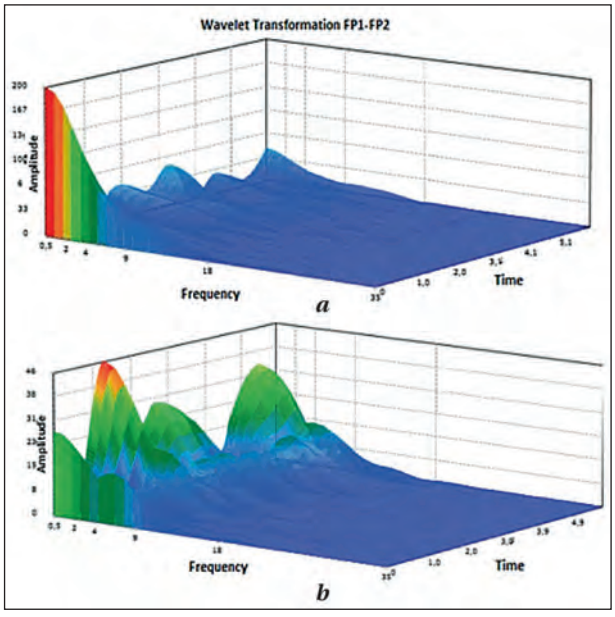

Fig. 2. Wavelet transformation of EEG signal.
Note. *a* — 10.08.2018: wavelet transform from transversal montage following amantadine sulphate administration, leading electrodes FP1-FP2 in 6 seconds lasting window.
***b* — 14.08.2018:** following the 5th dose of amantadine sulphate, 200 mg each dose, IV administration. Wavelet transformation of EEG signal from Fig. 1, *d*.

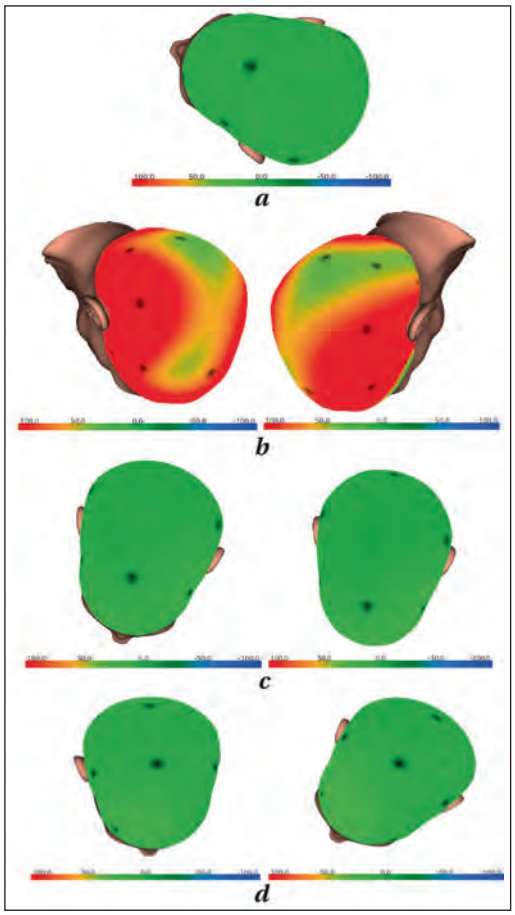

Fig. 3. Ž M, 33 years, 08.08.2018, without amantadine sulphate.
a — gamma frequency band BM in a longitudinal montage with a power value of 0.0 μV/mm.
b — delta frequency; longitudinal montage of powerful bilateral temporo-frontal oscillations and without power in occipital and parieto-centromotor parasagital regions. It means a presence of a «pacemaker activity» in brain structures.
c — Beta-LF to the left, beta-HF to the right BM in a longitudinal montage. No any power oscillation over the whole neurocranium means unconsciousness without any motor and mental performances.
d — Theta rhythm left, alpha rhythm right BM with 0.0 μV AP power; longitudinal montage.

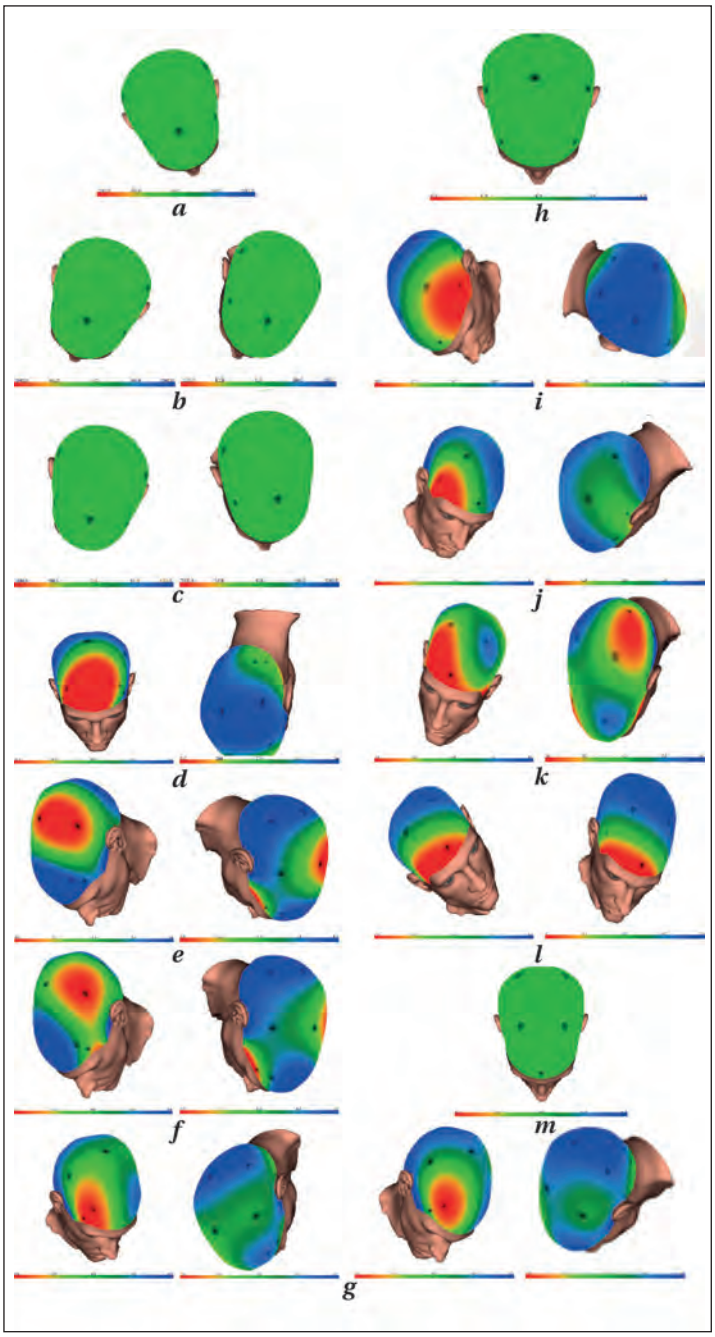

Fig. 4. Ž M, 33 years, following the amantadine sulphate administrations on 10.08.2018 and 14.08.2018.
10.08.2018, with amantadine sulphate, 200 mg, IV administration:
a — gamma rhythm is without any arousal effect without any power in reference montage;
b — without any signs of arousal in theta rhythm left, and alpha rhythm right 3D BM — reference montage;
c — without any signs of arousal effect in EEG signal – beta-LF left, beta-HF right 3D BM — reference montage.
14. 08.2018, after the 5th dose of amantadine sulphate, 200 mg each dose, IV administration:
d — delta frequency in a longitudinal montage; 3D BM shows very intense delta oscillations in bifrontal-prefrontal-central-motor regions;
e — theta frequency in a longitudinal montage; 3D BM shows very intense oscillations in central-motor-parietal-left with covering vertex region and lightly right parasagittal prefrontal-central-motor and parietal regions;
f — alpha frequency oscillator-raster picture is situated in parietal left covering partial parietal vertex region, and frontal-prefrontal opercular left regions;
g — Beta-LF(two pictures left), beta-HF (two pictures right). Both oscillations pictures are situated in similar positions;
h — gamma rhythm without any change in performance showing 0.0 power value;
i — delta rhythm oscillations in left frontal-prefrontal-anterior-temporal regions — transversal montage;
j — strong theta rhythm oscillations located to the frontal-prefrontal regions (right) and light theta rhythm oscillations located to the temporal-parietal regions and parietal-occipital boundary (left); transversal montage;
k — ehere are two strong alpha oscillations: frontal-prefrontal — central motor regions (right) and occipital-parietal regions (left). Possible our-self interpretation: Right hemisphere is working with decreased lucidity and vigilance, vice versa the left hemisphere works with high lucidity and vigilance — functional dissociation of quantitative parameters in consciousness – transversal montage;
l — beta-LF oscillations (to the left) and beta-HF oscillations (to the right) are only slightly different in location, size, power and shape due to 3D BM raster; transversal montage;
m — gamma frequency oscillator does not exist because of 0.0 power; transversal montage.

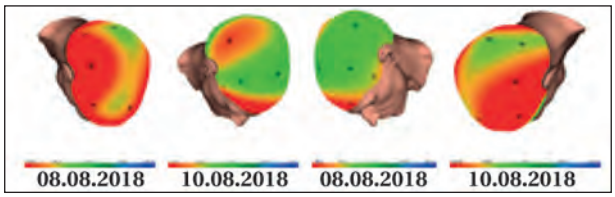

Fig. 5. Ž M, 33 years old, no amantadine (8.08.2018) versus amantadine sulphate, 200 mg, IV administration (10.08.2018).
Note. Comparison of 3D BM delta frequency power with arousal effect on August 10 in delta frequency power as resulted from delta band disinhibition. Substantial reduction of delta power inhibitory rhythm over the left and the right hemispheres. It is arousal positive due to disinhibition; reference montage.

amus: necrobiotic changes and neural cell necrosis, presence of granular (resorption making) cells, peri-capillary swelling.

Discussion

Decreasing delta rhythm performance (disinhibition, «pacemaker» activity transmission into the EEG signal) over both hemispheres, and namely over the left hemisphere under the influence of amantadine sulphate as observed on August 10, 2018, demonstrated disinhibition of delta frequency

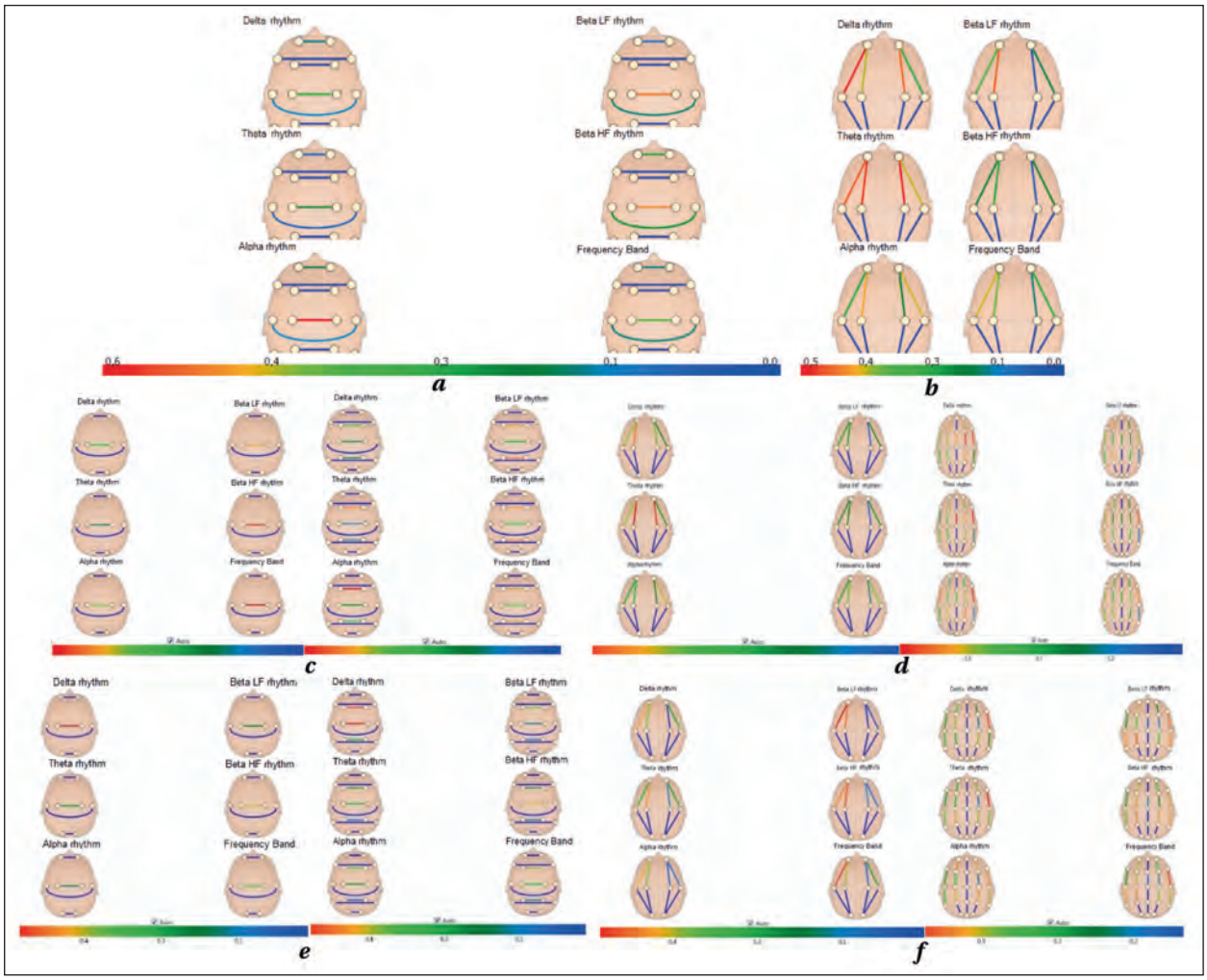

Fig. 6. Brain maps.
a — Brain maps of interhemispheric coherencies-indexes of connectivity in particular frequency bands show frontal and occipital split brain condition, only central-motor connectivity in alpha, beta-LF, and beta-HF is preserved; transversal montage.
b — Brain maps of the anterior-posterior coherencies-indexes of connectivity in particular frequency bands show total posterior hemispheric part disconnection and only some anterior hemispheric regions are connected in delta, theta, alfa bands and partially in beta LF, and beta HF; longitudinal montage.
Ž M, 33 years old:
c — 10.08.2018: following amantadine sulphate, 200 mg, IV administration. Brain maps of inter-hemispheric coherencies, indexes of connectivity in particular frequency bands show in 4 and 8 channel registrations frontal and occipital split-brain situation. Notice: the long distance of registration electrodes false-interrupts bi-prefrontal, bi-temporal, and bi-occipital connections; transversal montage.
d — 14.08.2018: after the 5th dose of amantadine sulphate, 200 mg each dose, IV administration. Brain maps in anterior-posterior direction show in color the coherencies – indexes of connectivity in 8 and 16 channels dispersion split, namely in bi-parietal-occipital regions; longitudinal montage.
e — 14.08.2018: after the 5th dose of amantadine sulphate, 200 mg each dose, IV administration. Brain maps in transversal direction.
f — 14.08.2018: after the 5th dose of amantadine sulphate, 200 mg each dose, IV administration. Brain maps in longitudinal montage.
Disconnection in 4 vertex bipolar montages of 16 channel mode presumably means decisive disconnections in cingulate gyrus supporting/generating the aware human consciousness as a product of default mode network [12].

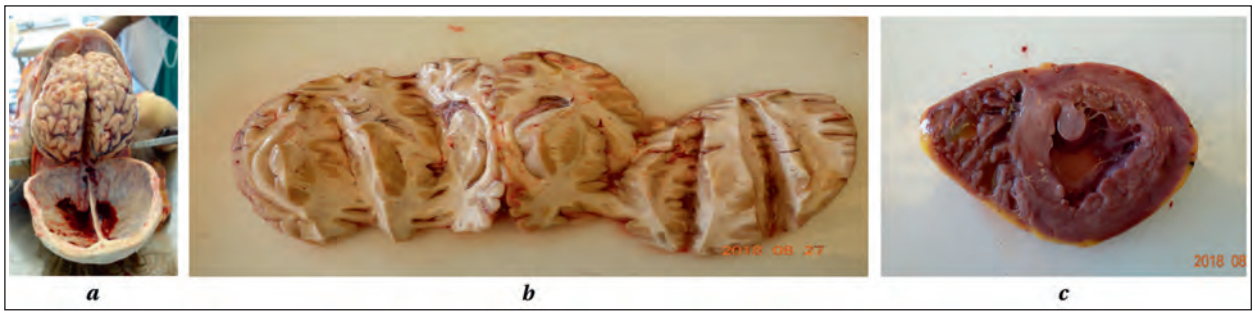

Fig. 7. Convexity of both hemispheres. Aqueous brain flows out of the intracranial space (*a*). Sagittal cuts through brain hemispheres (*b*). Crossed heart section. Dilation of the left heart ventricle with wall hypertrophy, acute cardiomyopathy (*c*).

band, e. g. the first electric prodromal sign of incoming arousal performance in aware conscious regulating brain structures.

There were no changes of EEG gamma band output over the entire neurocranium on August 10, 2018. It probably correlated with disconnection over the cingulate gyres as the decisive part of default mode resting state network, DMRSN [12].

There was no change in the alpha and theta output on August 10, 2018 after the IV administration of a 5th dose of amantadine sulphate, 200 mg per dose, that showed strong extinction of occipital and hippocampal allo-cortical oscillation activities in 3D BM, which were evident around 10μV in a basic EEG signal. That patterns were completely changed in August 14, 2018, when the AP of alpha rhythm increased in prevailing grids to 10–20μV/mm in a basic EEG signal and oscillators of alpha and theta rhythms created in 3D BM (Figure 4, *j, k*) images of powerful signal. The same situation was observed with beta-LF and beta-HF (Figure 4, *l*). The gamma rhythm was not detected as the last one during the period of progressive worsening of the comatose state and during general anaesthesia [12]. However, we did not see any gamma rhythm changes because we did not use the eLORETA program, which is capable to detect EEG signals from low resolution area, the cingulate gyrus, for technical reasons.

The images of the above-mentioned oscillators, except for the gamma frequency band, were not displayed due to the low power of the EEG signal from August 8, 2018 untill August 14, 2018. When the arousal reaction to the 5th dose of amantadine sulphate supported brain electrogenesis in AP of EEG signal, it increased from lightly below 10 μV/mm to predominantly 10–20 μV/mm. Then, the 3D BM revealed in a raster mode high oscillator performance in these regions that meant functional neuronal adequacy for starting lucid consciousness. The 3D BM raster pictures from August 14, 2018, correlated with pupil light-reaction, brain stem reflexes revitalization, behavioral activation, and a sign of gazing observation, an attention.

From August 8 to August 10, 2018 the patient exhibited patterns of a brain dying process according to clinical picture and pEEG, extinction of the brainstem reflexes, tendon-jerk areflexia and pacing of heart and respiration decrease. However, after the 5th administration of amantadine sulphate at a dose of 200 mg the surprising revitalization was observed that lasted from August 14, 2018, until the August 28, 2018, when the secondary post-ischemic lesions (due to excitotoxicity resulted form kidney failure) and brain stem alterations were added to the primary ischemic neocortex and allocortex lesions as illustrated by pEEG and completed total brain destruction. Since August 14, 2018, brain neuropil tissue showed signs of competence to renew the complete human aware consciousness, and also the highest mental, emotional, and social levels of aware human consciousness that we repeatedly observed in similar cases in the past [8].

Brain dying but not brain death as demonstrated by basic EEG signal and some pEEG tools was correlated with the clinical extinction of brain stem functions and reflexes as revealed during period from August, 8 to August 10, 2018. This feature followed by surprising revitalization in basic visual mode — joint attention, behavioural samples, brain stem reflexes, and pEEG. The observed revitalization occurred in brain stem functions - mesencephalon, pons, medulla, brain stem reflexes, but 18 days later the heart pacemaker and breathing pacing failed. Whether the subsequent, post-ischemic brain tissue lesions due to excitotoxicity resulted in a unfavourable fate of our female patient? No! It was the myocardial destruction due to heart arrest that led to a secondary death of the brain. Clinical restoration of stem reflexes and lucid and vigilant consciousness, revival of visual contacts (attention to nursing staff and especially to her husband after the administration of the 5th dose of amantadine sulphate at a dose of 200 mg) provided a prerequisite for optimistic definitive exit from brain dying toward functional adjustment of mental and psychomotor functions. The brain was capable of revitalization because it retained delta activity that had been recognized as a sign of vital performances (blood pressure, ventilation rhythm, ECG oscillating at a <0.10Hz frequency band, transformed in one constant segment as illustrated by 3D BM and wavelet transformation). There is a well-known classical principle in the evaluation of EEG signal in the diagnosis of brain death, which states that if there is only one

frequency band of the EEG signal, the brain cannot be considered dead. A number of EEG and fMRI studies in mammals have demonstrated that spontaneous low frequency oscillations in cerebral activity at <0.1 Hz represent a fundamental component of brain activity [13, 14]. Areas involved in this intrinsic activity including the posterior cingulate cortex/praecuneus, medial prefrontal cortex, and bilateral temporo-parietal junction are known as the «default mode resting state network, DMRSN» [15].

The DMRSN is a resting state network that is active during passive moments and deactivated when one engages in a mental task [16]. However, the majority of energy utilized in the brain can be attributed to DMRSN activity [17]. The decrease in connectivity levels measured by mean squared of coherences in the gamma frequency band above DMRSN is considered a robust measure of decreased lucidity of consciousness during general anaesthesia as an example to surpass the brain death model [12, 18, 19].

From August 8 to August 10, 2018, and until the outcome on August 28, 2018, the secondary post-ischemic brain stem lesions along with the primary ischemic neocortex and allocortex lesions as shown by pEEG have completed the total brain destruction exhibiting dough-like aqueous brain structure on a postmortem investigation. It was only a matter of time when heart pacemaker and breathing pacing would disappear due to multiple inner organs failure after exsanguination due to massive hemorrhage occurred in the patient.

Finally, our data warrant the opening a discussion on weather the 3 DM BM in color might be well suited to monitoring dying and definitive brain death. We suggest that it's worth to explore the 3D BM informative value — with optimistic expectations.

Conclusions

The 3D brain mapping is a promising, up-to-date electrophysiologic and dynamic quantitative method employing automatic PC-aided statistic programs for dynamic evaluation of digital signals of dying brain that may impact the intensive care medicine.

To determine brain dying, electro-cerebral hypoactivity (ECH) should be demonstrated on scalp EEG, which is recorded considering the following criteria:

(a) sensitivity of 10μV/mm; The arbitrarily accepted electrologic life-death threshold is AP value 2 μV of EEG waves registered from the skull surface;

(b) inter-electrode distances less than 10 cm;

(c) covering over all major brain areas including midline area;

(d) recording for at least 30 minutes;

(e) during the application of amantadine sulphate as five i. v. administrations at a dose of 200 mg each, there was a revival of the EEG signal in the baseline curve and in the 3D BM, associated with the revival of brain stem reflexes including the light reaction.

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3D Spheroids — a Cellular Model for Studying the Effects of Hypoxia on the Epicardial Microenvironment

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Summary

Fundamental research in recent years has allowed us to reassess the molecular and cellular mechanisms of cardiac ontogenesis and its repair after damage. The epicardium, the outer, tightly adjoining layer of the cardiac wall formed by epicardial mesothelial cells, collagen and elastic fibers, has gained special relevance as an important participant of reparative processes. Better insight into poorly understood epicardial function is challenged due to anatomical issues and lack of relevant cellular models.

The aim of this study was to develop a spheroid 3D model of the epicardial microenvironment and determine responses of spheroids to hypoxia.

Materials and methods. Spheroids were harvested in V-shaped culture dishes with a low adhesion coating. Immunofluorescent staining of cryosections, histological methods and real-time PCR were used for characterization of cultured spheroids.

Results. We demonstrated that cultivation of cells under low adhesion conditions in V-shaped culture dishes resulted in the formation of spheroids with an average size of 136+21 μm and cell viability rates of over 98%. The cells in the spheroids cultured under normoxic conditions formed tight junctions and were characterized by a low level of proliferation and the ability to synthesize extracellular matrix proteins. Under hypoxia cells in the spheroids showed partial loss of intercellular contacts, acquired a spindle shape, started to express HIF1a, SNAIL, COL1Al and accumulate collagen. All these features demonstrated the activation of mesothelial(endothelial)-mesenchymal transition strongly resembling epicardial cellular responses to ischemia in vivo.

Conclusion. An epicardial spheroid cell culture model suitable for study cellular responses to hypoxic environment was developed. This model can be used to clarify mechanisms regulating epicardial microenvironment and test new targeted candidate drugs.

Keywords: spheroid; hypoxia; cardiac repair

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

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Introduction

For several decades, cardiovascular diseases have been the leading cause of morbidity and mortality in Russia and worldwide [1]. The most important factor in the progression of most of these diseases is fibrosis associated with excessive deposition of extracellular matrix proteins, especially fibrillar collagen, leading to increased myocardial stiffness, loss of systolic function, and significant structural and morphological changes [2, 3]. Recently, there has been evidence that the activation of fibrosis can be caused by various factors, which have different effects on the cells and determine the characteristics and rate of the pathological process [4]. The main trigger of fibrosis is hypoxia [5, 6]. It causes stabilization of hypoxia-induced factors (HIF) in cells differentiating into fibroblasts, especially in epicardial cells, provides their activation, fibroblast formation and fibrosis progression [7–9]. However, the mechanisms of such regulation remain poorly understood due to anatomical limitations in accessing the epicardium and the lack of relevant cellular models.

The aim of this study was to develop a 3D model of the epicardial microenvironment and to evaluate the effect of hypoxia on its characteristics.

Material and Methods

Animals.

C57b/6 mice (male, 8 weeks old) were kept in the vivarium of the Yevgeny Chazov National Medical Research Center for Cardiology (Moscow, Russia). The study design was approved by the Ethics Committee of the Institute of Experimental Cardiology.

Simulation of myocardial infarction.

Experimental myocardial infarction in mice was induced according to the previously described protocol [10].

Generation of epicardial mesothelial cell culture.

Epicardial cells were harvested from murine hearts according to the protocol described previously [11].

Assembly of murine epicardial cell spheroids.

For the assembly of epicardial spheroids, we used the GravityTRAPTM ULA Plate (Insphero, USA) V-shaped cups with low adhesion. To obtain spheroids, a cell suspension (5000 cells) was plated into the wells of the plate, precipitated by centrifugation (200 g, 2 min), and cultured for 72 h (in IMDM medium supplemented with 1% fetal calf serum) under standard incubation conditions (37°C, 5% CO_2).

Evaluation of cell viability in spheroids.

The viability of cells forming spheroids was assessed using a commercially available LIVE/DEAD™ Viability/Cytotoxicity Kit (Invitrogen, USA).

Normoxia/hypoxia simulation.

A New Brunswick TM Scientific incubator (Eppendorf, USA) was used to simulate normoxia and hypoxia. Spheroids were cultured under conditions of normoxia and hypoxia (3% O_2) for 72 hours.

Characterization of heart cryosections and spheroids.

To assess the structure of the spheroids, they were stained according to the previously described protocol [12]. Cryosections of spheroids were used for spheroid immunophenotyping experiments. Sections were fixed in 3. 7% para-formaldehyde solution, washed in phosphate-salt buffer solution, preincubated in secondary antibody donor serum solution, and stained with antibodies against the proliferation marker Ki-67 (Abcam, USA), ZO-1 (Abcam, USA), collagen type 1 (Abcam, USA), TCF21 (Abcam, USA), and HIF1a (Abcam, USA) for 1 hour, washed, and stained with antibodies conjugated to Alexa Fluor 488 or 594 (Invitrogen, USA). Cell nuclei were stained with DAPI (Sigma, USA). Morphometric analysis of spheroids was performed using Image J software (NIH, USA).

Preparation of cDNA samples and real-time PCR.

RNA was isolated from cells using a Quiagen kit (Quiagen). Reverse transcription was performed using the Maxima First Strand cDNA Synthesis Kit (Thermo Fisher Scientific). Real-time PCR was performed on a Step One Plus Real-Time PCR System Amplifier (Thermo Fisher Scientific) using a standard protocol with the following primers: SNAIL (ACATCCGAAGCCACACG; GTCAGCAAAAGCACGGTTG), ACTA2 (CCCAGACATCAGGGAGTAATGG; TCTATCGGATACTTCAGCGTCA), FN1 (GGAATGGACCTGCAAACCTA; GTAGGGCTTTCCCAGGTCT), beta actin (CTAAGGCCAACCGTGAAAG; ACCAGAGGCATACAGGGACA), Col1A1 (CCGCTGGTCAAGATGGTC; CTCCAGCCTTTCCTAGGTTCT).

Microscopy and image analysis.

Myocardial cells and cryosections were analyzed using an Axiovert 200 M fluorescence microscope (Carl Zeiss, USA) and AxioVision 4.8 software (Carl Zeiss, USA).

Statistical analysis.

Statistical significance of differences between samples was assessed using the non-parametric Mann–Whitney test. Statistical analysis of the results was performed using Statistica 8.0 software (StatSoft, Inc.). Data were presented as mean±standard deviation (*M*±*SD*).

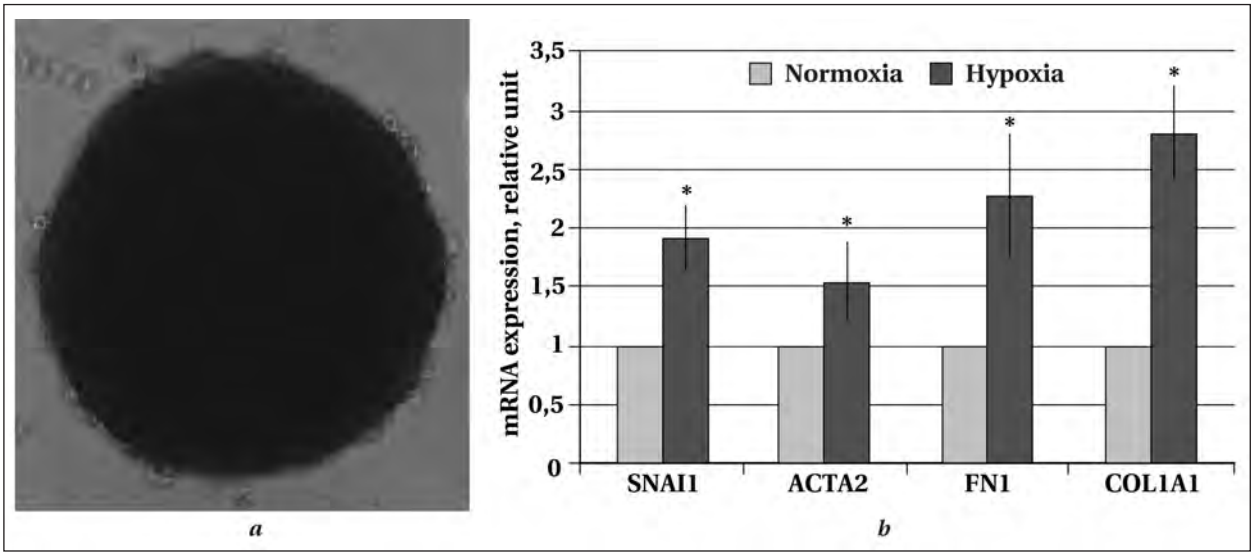

Fig. 1. Characteristics of spheroids created on the basis of epicardial cells.
Note. *a* — Representative image of spheroid created on the basis of murine epicardial cells. *b* — Graphs of quantitative evaluation of SNAI1, ACTA2, FN1, COL1A1 gene expression after spheroid culture under normoxia and hypoxia, * — $P < 0.05$.

Results

Our study showed that culturing cell suspensions under low-adhesion conditions (V-cups with low-adhesion GravityTRAPTM ULA Plate) resulted in accelerated aggregate formation and self-organization of cells into spheroids. We found that cells go through several stages in the process of spheroid assembly: first, a cell cluster is formed, which subsequently compacts to form a globular structure (Fig. 1 *a*). Disappearance of cell processes on the spheroid

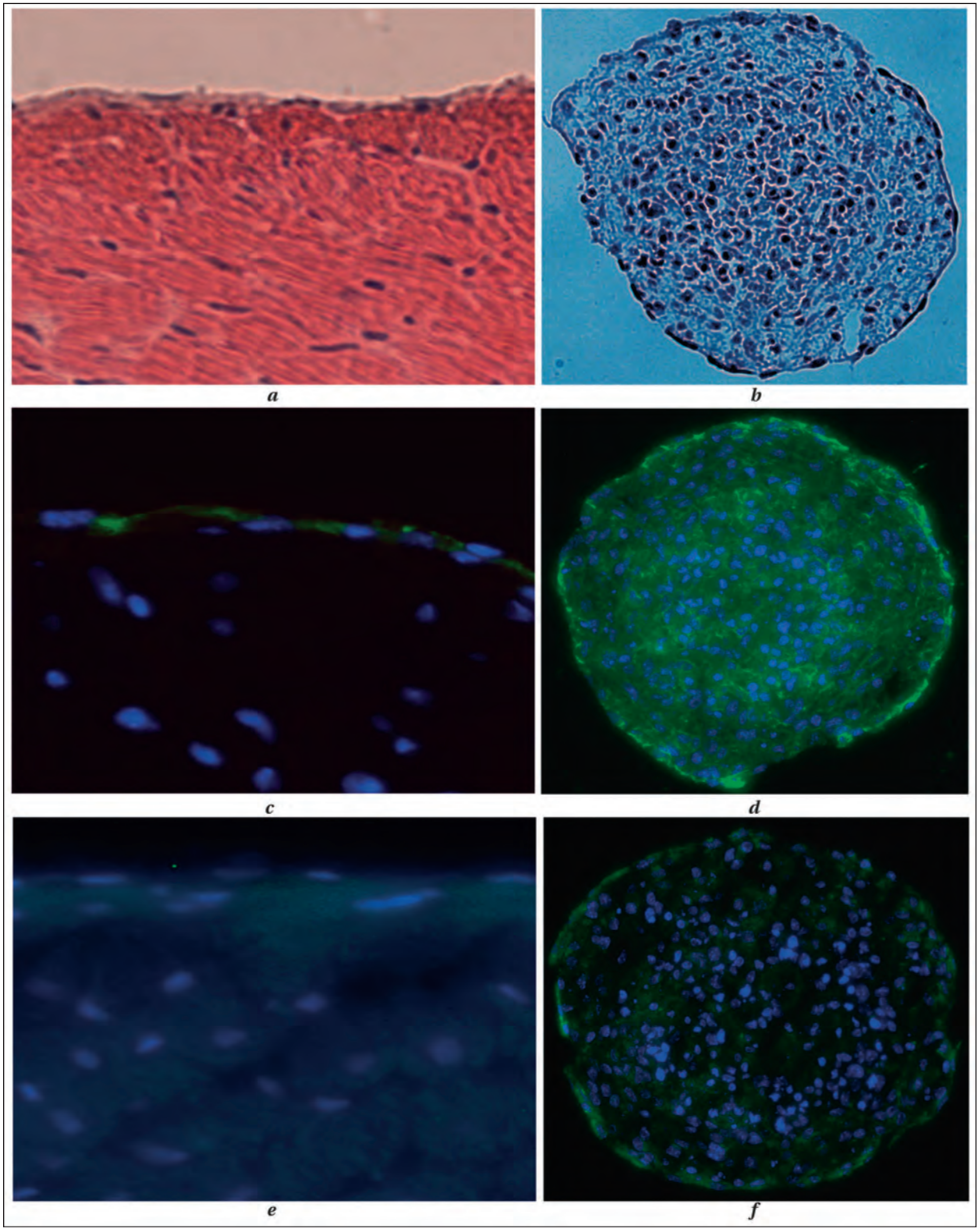

Fig. 2. Comparative characterization of epicardial zone organization in intact heart and spheroid.
Note. Representative images of cryosections of the epicardial zone in the intact heart and spheroid stained with hematoxylin-eosin (*a, b*), antibodies against dense contact protein ZO1 (*c, d, green*), collagen 1 (*e, f, green*). Nuclei were stained with DAPI (*blue*).

surface and formation of a relatively regular spheroid structure occurs 72 hours after plating the cell suspension, indicating the end of spheroid assembly and readiness for subsequent testing. The final size of the formed spheroids was 136+21 μm, and the viability of the cells within them was over 98%.

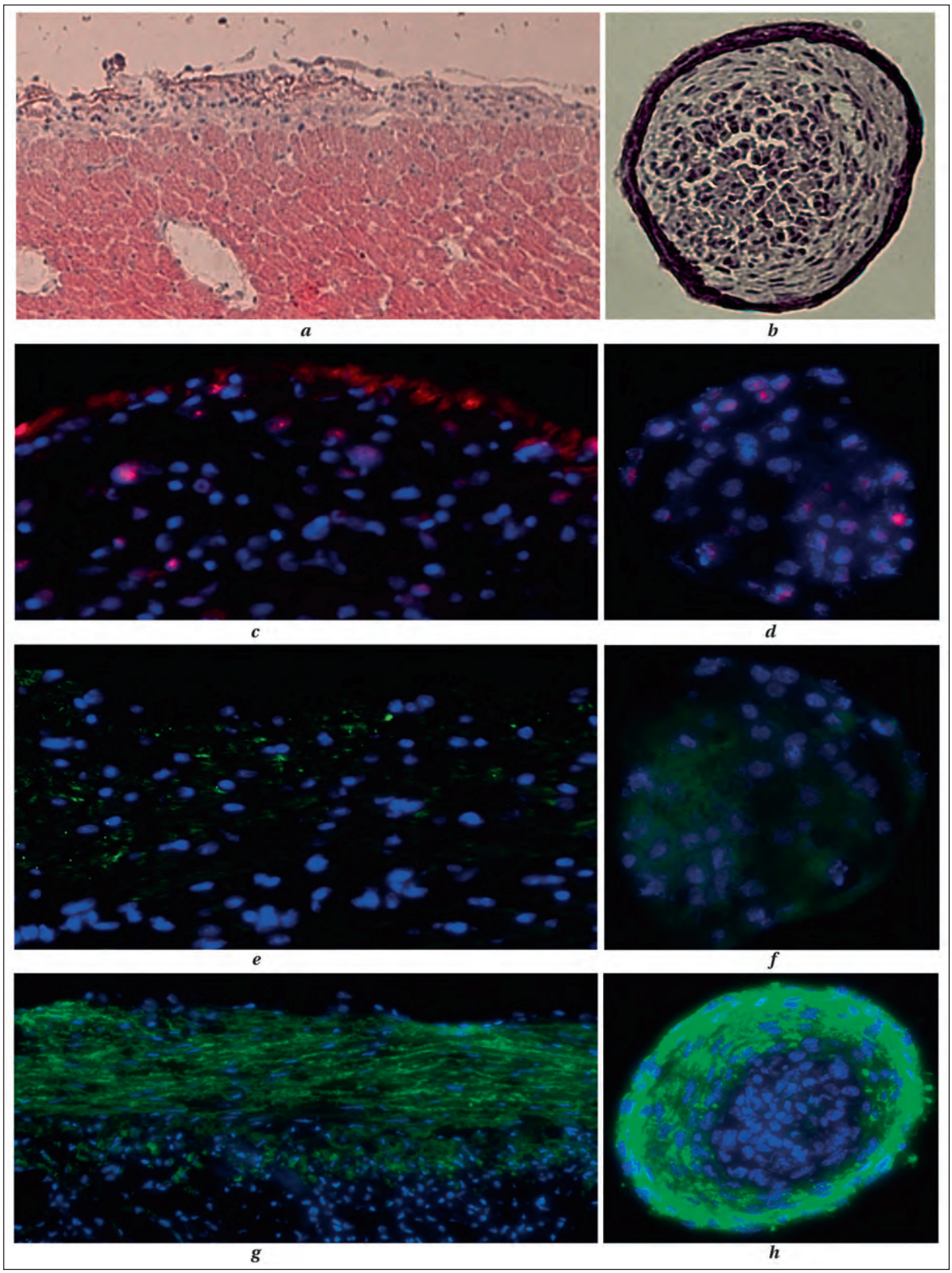

Fig. 3. Comparative characterization of epicardial zone organization in postinfarction heart and in spheroid after hypoxic exposure.
Note. Representative images of cryosections of epicardial zone in intact heart and spheroid stained with hematoxylin-eosin (*a, b*), antibodies against hypoxia marker HIF1a (*c, d, green*), ZO-1 (*e, f, green*), collagen 1 (*g, h, green*). Nuclei were stained with DAPI (*blue*).

The developed model of the epicardial microenvironment should, with a certain degree of assumption, match the pattern of organization of the intact epicardial zone. For this purpose, we compared the structural organization of the epicardial zone in the intact/undamaged heart and in the spheroid (Fig. 2). The spheroid was found to be represented by epicardial cells interacting with each other through ZO-1+ dense contacts, with a low level of expression of fibroblast markers (Fig. 2 *c, d*) and collagen matrix (Fig. 2 *e, f*), which is similar to the organization of the epicardial zone in the intact heart. Simulation of the experimental infarction resulted in an extensive ischemic zone and the appearance of cells expressing HIF1a in the epicardial/subepicardial zone (Fig. 3 *c, d*). After acute ischemic exposure, we observed disorganization of dense contacts between epicardial cells, redistribution, migration of mesothelium into the underlying layers of the cardiac wall, accompanied by thickening of the epicardial area, accumulation of fibroblasts, and increased collagen production (Fig. 3 *e, g*). Similar changes were observed in the generated spheroids cultured under hypoxic conditions. Hypoxic exposure caused loss of intercellular contacts (Fig. 3 *e*), cells acquired a spindle shape (Fig. 3 *b*), expressed HIF1a and accumulated collagen. These changes were accompanied by increased expression of genes associated with activation of the mesothelial-mesenchymal transition (MMT) (SNAI1, ACTA2, FN1, COL1A1) and their differentiation towards fibroblasts/myofibroblasts (Fig. 1 *b*).

Discussion

In the intact heart, epicardial cells are predominantly in a «quiescent» state with low levels of proliferation, no signs of MMT, and a reduced ability to produce extracellular matrix proteins. In contrast, acute ischemic injury has an activating effect on the epicardial cell pool, leading to the initiation of their MMT, increased secretory activity and their migration to the underlying regions of the cardiac wall to participate in repair. Despite the great practical interest in studying the mechanisms of the epicardial regenerative response to damage, its study is difficult due to the lack of relevant models. Currently, the only model described in the scientific literature is based on three-dimensional organotypic epicardial sections of the porcine heart [13], which has significant limitations for its widespread use due to its complex construction, short ex vivo lifespan, and inability to model hypoxic effects. The cell model proposed in this work does not have the above-mentioned drawbacks. The 3D model can be easily generated using commercially available materials/reagents and is able to reproduce, with some assumptions, the changes that occur in the epicardial area under normoxia and hypoxia. Initially, the spheroid is orchestrated by epicardial mesothelial cells interacting through dense ZO-1-containing contacts and exhibiting low levels of expression of fibroblast and collagen matrix markers, which corresponds to the organization of the epicardial zone in the intact heart. Under hypoxia, HIF1a stabilization occurs, epicardial mesothelial cells undergo MMT, acquire fibroblast-like properties and activate the production of extracellular matrix proteins, which correlates with the regenerative response of epicardial cells occurring in the acute phase of cardiac ischemic injury. These findings correlate with those of other researchers who have shown that hypoxia is an important regulator of tissue fibrosis. By acting through the HIF-1 signaling mechanism, hypoxia induces MMT activation, which leads to the loss of E-cadherin-based intercellular contacts, reorganization of the cytoskeleton, and ultimately the production of fibroblast-like cells [14–17]. In contrast, suppression of HIF-1α expression prevented fibroblast formation and reduced ICM accumulation [18]. In addition to its effect on MMT, hypoxia may stimulate fibrogenesis through transcriptional regulation of the expression of genes related to ICM metabolism. Hypoxia induces type I collagen formation, decreases matrix metalloproteinase 2 (MMP-2) levels, and increases the expression of plasminogen activator inhibitor-1 (PAI-1), tissue inhibitor of metalloproteinase-1 (TIMP-1), and connective tissue growth factor (CTGF) through HIF-dependent mechanisms [19–21].

Conclusion

Thus, we have developed and characterized a 3D cellular model of the epicardium capable to exert the cellular responses to hypoxia and be employed in studies of the mechanisms of regulation of the epicardial microenvironment and targeted drugs testing.

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Microwave Radiothermometry in Evaluating Brain Temperature Changes (Review)

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Summary

Aim. This review aims to inform physicians of different specialties (anesthesiologists, intensivists, neurologists, neurosurgeons, oncologists) about the diagnostic capabilities of microwave radiothermometry, which enables to identify and analyze features of alterations of cerebral temperature in brain damage.

The review displays a critical analysis of 80 recent Russian and foreign open access publications found by keywords.

The review presents major clinical features and pathophysiological mechanisms of cerebral thermal balance disruptions in brain lesions. Slow responsiveness and vulnerability of cerebral thermal homeostasis regulation mechanisms that underlie development of different temperature heterogeneity levels in the cerebral cortex in healthy brain and brain lesions are highlighted. The authors postulate their concept about the critical role of hyperthermia in the pathogenesis of brain damage and disruption of interconnections in the global central regulation system. A body of evidence explaining direct association between the depth of consciousness impairment and degree of cerebral cortex temperature heterogeneity manifestation is presented. It is emphasized that a significant increase in temperature heterogeneity with areas of focal hyperthermia accompanies an acute period of ischemic stroke, while in post-comatose state usually associated with prolonged impairment of consciousness, the temperature heterogeneity significantly subsides. It has been suggested that lowering of an increased and rising of the reduced temperature heterogeneity, for example by using temperature exposure, can improve altered level of consciousness in patients with brain damage. The diagnostic capabilities of various technologies used for cerebral temperature measurement, including microwave radiothermometry (MWR), are evaluated. Data on high accuracy of MWR in measurement of the cerebral cortex temperature in comparison with invasive methods are presented.

Conclusion. In healthy individuals MWR revealed a distinct daily rhythmic changes of the cerebral cortex temperature, and badly violated circadian rhythms in patients with brain lesions. Since MWR is an easy-to-perform, non-invasive and objective diagnostic tool, it is feasible to use this technology to detect latent cerebral hyperthermia and assess the level of temperature heterogeneity disruption, as well as to study the circadian rhythm of temperature changes.

Key words: brain temperature balance; cerebral lesions; microwave radiothermometry; MWR

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

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Introduction

Body temperature is an essential integral parameter of general body condition, its functional activity and regulatory status. Temperature homeostasis in warm-blooded animals is characterized by very high thermal heterogeneity, typical for both homoeothermic core and thermal envelope sections [1]. The temperature of surface tissues largely depends on the ambient temperature, while in the compartments of the thermal center, including internal organs, spinal cord and brain, the differences in temperature are determined by local metabolic activity and the intensity of blood flow, which provides elimination of excess heat into the external environment [2]. The circulatory system levels out the internal temperature gradients in the major arteries such as aorta and pulmonary artery to 37±0.1°C in the normal ranges at rest and under thermoneutral conditions, which does not exclude internal thermal heterogeneity most evident in the brain [3].

Cerebral blood flow is mostly autoregulated, and its changes in response to inner requirements are relatively independent of the systemic circulation within certain limits of arterial pressure variations [4]. The relative independence of the cerebral blood flow from the systemic circulation underlies such independence of cerebral and basal temperature regulation, the values of which can differ significantly [5, 6].

Temperature differences between deep and superficial brain structures, as well as excited and relatively quiescent areas, can be as high as several degrees [7].

Temperature recording is a valuable tool for diagnosis and prognosis in various brain diseases

[8]. In neurogenic fever, latent cerebral hyperthermia without increase in the basal temperature often develops, which may result in underestimation of its impact on disease severity and outcome [9, 10]. Thermal balance disorders are associated with the severity of brain damage, and cerebral temperature is an important marker of the latter [11, 12].

Methodological issues may limit the use of cerebral thermometry in clinical practice. The use of invasive thermometry techniques is acceptable only in neurosurgical patients. It is the most accurate method of temperature measurement, but implantable thermoresistors provide temperature data only in the area of measurement, making it impossible to assess the severity of the thermal imbalance throughout the brain [13]. In addition to thermoresistors, technologies based on radio-emission detection sensors [14] and fiber-optic methods [15], which are still under development, can be employed for invasive temperature sensing.

The most advanced and informative method is proton NMR spectroscopy [16], which provides non-invasive data on brain temperature. However, this technology is labor-intensive and not suitable for monitoring [17]. A previously developed method of thermoencephaloscopy based on registration of infrared electromagnetic radiation (EMR) from the scalp allows the identification of warmer and cooler areas of cortical projections, but gives no idea of the true temperature [18]. Radiometric thermometry using sensors placed on the skin of the forehead has been developed, but still requires careful validation [19].

Microwave radiation thermometry (RTM) is a simpler and more informative method of temperature measurement based on the determination of the intrinsic EMR power of deep tissues [20]. The RTM allows EMR measurements in any body region and at different time intervals [21, 22]. The technique is safe and has no adverse impact on the patient. At present, it is used in a limited way for research purposes to diagnose diseases associated with local temperature elevation [23] and to control the depth of therapeutic hypothermia [24].

The aim of the review is to update specialists in various fields (anesthesiology, intensive care, neurology, neurosurgery, oncology) on the diagnostic performance of microwave radiation thermometry, which allows the identification and analysis of cerebral thermoregulatory disorders in brain injury.

Microwave Radiation Thermometry in Medicine

The first microwave radiation thermometers were developed for radio astronomy in the mid-twentieth century [25], and the principle of radiation thermometry was soon used in medicine for the early diagnosis of breast cancer [26].

In contrast to conventional infrared thermography, which can only estimate temperature changes in superficial skin layers [27], measuring the EMR power of human tissues in the microwave range (λ = 3–60 cm, frequency 109–1010 Hz) allows the determination of internal temperature values.

In the radio range, the intensity of radiation is directly proportional to temperature. Therefore, with the measured power of EMR registered by special antennas placed directly on the skin surface of a biological object, it is possible to obtain information by non-invasive estimation of the internal temperature.

In the medical literature, the terms «brightness» or «core» temperature, which correspond to the true thermodynamic temperature, are most commonly used [28]. When calculating the brightness temperature values, the dielectric permittivity values of the biological object tissues, which determine the attenuation of electromagnetic wave propagation, are taken into account and determine the depth of measurement.

Tissues with low water content are characterized by low dielectric permittivity and minor radiation power losses. In this context, brain membranes, flat skull bones, periosteum and aponeurosis are conventionally considered to be «radio-transparent» tissues that distort the recorded signals to the least extent.

Tissues with high water content, such as blood, muscle tissue, internal organs, skin, and brain matter, are characterized by high values of dielectric permittivity and signal attenuation [29].

Radiation propagation in biological tissues depends on its frequency. In particular, the depth of temperature measurement of internal tissues in the centimeter range of about 3 GHz reaches 5–7 centimeters. Measurement accuracy, tested against implanted thermosensors, is ±0.2°C [30].

Performing RTM with an antenna of about 30 mm in diameter allows to register EMR in a tissue volume reaching 1500 1800 mm³, and the calculated temperature values correspond to the average temperature in the whole volume. Implanted thermosensors provide information about the temperature in a much smaller volume of tissue, which seems to underlie the above discrepancies in results.

In modern computerized instruments, such as RTM-01-RES (OOO RTM-Diagnostics, Russia), the brightness temperature is automatically calculated based on the numerical solution of Maxwell's equation [31]. The measurement procedure is quite simple. The antenna is installed by pressing it firmly against the skin surface in the projection of the target tissue or organ. The measurement takes 3–5 seconds and the data is displayed in °C. The position of the antenna can be changed successively, so that measurements can be made in specific areas and a profile of the internal temperature distribution can be obtained within the resolution.

The RTM as a diagnostic and research tool is becoming increasingly popular in the study of brain temperature [32, 33], as well as in various conditions manifested by increased heat production [34]. In particular, RTM technology has been successfully used in the diagnosis of breast cancer and other malignant neoplasms [28].

Since inflammation is one of the key links in the onset, development and progression of atherosclerosis, the use of RTM allows the detection of high temperature heterogeneity in affected carotid arteries [35, 36]. Increased heat production in the inflammatory focus of pyelonephritis, kidney stone disease and inflammatory prostate disease can be detected by RTM [37, 38]. The RTM can be used for early diagnosis and monitoring of various inflammatory conditions [39], including pneumonia in COVID-19 [40]. Correlation between pain level and RTM results has been observed in the diagnosis of joint and muscle diseases, musculoskeletal disorders, and headache in degenerative disc disease of the cervical spine [41, 42].

The use of RTM showed that under normal conditions and at rest, the cortical temperature is lower than the basal temperature, while during physical activity it increases and exceeds the axial temperature by 0.3–1.0°C. After mild traumatic brain injury (TBI) in competitive boxers, focal hyperthermia with the temperature of 37.5–39°C was registered [43].

Patterns of EMR wave attenuation in tissues limit the resolution of the method when recording brain temperature, allowing only to estimate the temperature of the cortex of the cerebral hemisphere.

The Regulation of Brain Thermal Balance

Brain temperature is largely determined by the core temperature level, but the mechanisms of cerebral thermoregulation have specific features that distinguish them from regulation in other organs of the body heat center. High levels of heat production and limited passive ways of heat elimination provide conditions for heat accumulation in the brain, which is especially evident in physical hyperthermia, fever and brain diseases [44, 45].

The brain mass is about 2% of the adult body weight, while its contribution to the total body heat production reaches 20% in the normal resting state [7]. Basic cerebral metabolism is provided by the consumption of almost 20% of total glucose, oxygen and cardiac output [46].

Cerebral blood flow is heterogeneous: to adequately supply gray matter, approximately 80 ml of blood per 100 g/min is required, while white matter requires about 20 mL/100 g/min, with an average hemodynamic supply of the entire brain of 50–65 mL/100 g/min. In excitation, cerebral blood flow can increase significantly, reaching 140 ml/100 g/min, which supports the growing demand for oxygen and substrates, as well as the removal of excess metabolic heat [47].

The temperature of blood entering the brain is 0.2–0.3°C lower than in the aorta, and that of blood leaving the brain is 0.2–0.3°C higher [48]. The incoming blood is cooled by countercurrent heat exchange through dense contacts of the internal carotid arteries and the vessels of the jugular venous system, which collect blood cooled in the external environment from the mucous membranes of the upper respiratory tract and nasopharynx, as well as the skin of the head and neck. In addition, the emissary veins deliver cooled blood from the scalp to the dural sinuses directly to the brain surface [49]. This cools the surface of the cerebral cortex, protecting this universal «biological computer» from overheating.

Cerebral blood flow largely compensates for local heat release in some parts of the brain and enhances its accumulation in other parts [50, 51]. The heat release associated with excitation is a dynamic but rather inert process. The evoked temperature response to sensory stimulation develops at a frequency of approximately 0.005–0.008 Hz [52].

Any excitatory process that accompanies eating and sexual behavior, emotion, affect, pain, sensory stimulation, increases cerebral temperature, primarily of the cerebral cortex, and provides an increase in temperature heterogeneity [53]. Radial and interhemispheric gradients during stimulation can reach 1.5–2.5°C [54].

The use of implanted thermosensors in experiments revealed significant differences in cerebral and core temperatures, with the temperature of subcortical structures being 0.1–0.5°C higher than body temperature, with the highest values in the hippocampus [53, 55, 56]. According to proton NMR spectroscopy, the cortical temperature in healthy humans is lower than the temperature of the oral cavity, the tympanic membrane, and the skin over the temporal artery [57]. Comparing theoretical models with data from clinical and experimental studies, a clear dependence of heat release processes and heat accumulation on the intensity of local blood flow has been demonstrated [58].

In TBI, ischemic and hemorrhagic stroke, neurogenic fever commonly develops, which may be latent without changes in core temperature and worsens the prognosis and outcome of the disease [59–61]. In TBI, brain temperature is 1–3°C higher than core temperature [62].

The thermal response of the brain to injury is initiated by excitotoxic reactions and the development of local neurogenic inflammation. The release of proinflammatory cytokines at the site of injury affects the neurons of the hypothalamic thermoregulatory centers, providing a «set point» adjustment

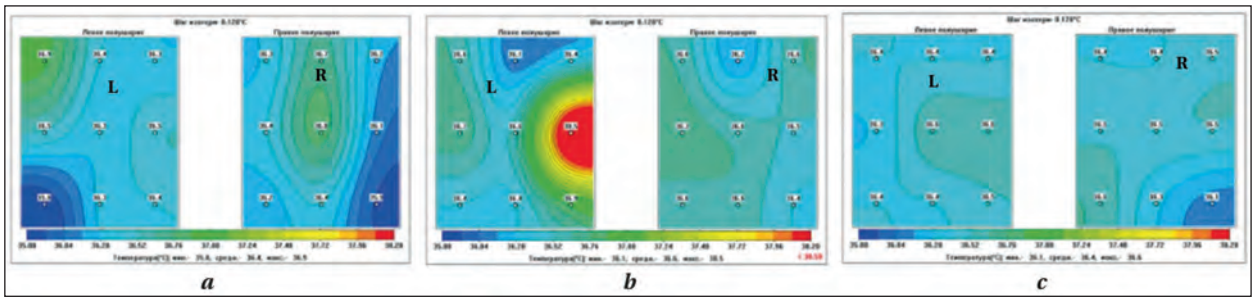

Figure. Examples of temperature distribution maps in the cortex of the left (L) and right (R) hemisphere of a healthy person at rest (*a*), a patient on the first day after an ischemic stroke (*b*) and a chronically critically ill patient (*c*) [69].

that tunes the body's thermostat to a higher level of regulation [63, 64].

Many factors are associated with the vulnerability of the brain's mechanisms for maintaining thermal homeostasis. The brain's nearly spherical shape favors heat accumulation, while its thermally isolated position in the skull prevents heat dissipation. The intensity of systemic and local blood flow is not determined by the increasing temperature, but rather by the internal demands associated with stimulation. In other words, the brain has no active thermoregulatory mechanisms. Pathways of passive cooling of the brain surface by blood flow through the emissary veins are unable to adequately compensate for the increase in heat production, and brain temperature does not affect the systemic circulatory responses involved in thermoregulation.

The structural, functional, and hemodynamic heterogeneity of the brain underlies its thermal heterogeneity, changes in which may indicate the development and severity of disease.

Brain Temperature Heterogeneity in Cerebral Disease

The use of proton NMR spectroscopy in cerebral infarction allowed the detection of an increase in temperature heterogeneity between the ischemic lesion and the contralateral intact regions [17]. Not only absolute temperature values, but also their diurnal variations, which are disrupted in stroke [65] and severe TBI [66], may have diagnostic relevance, as demonstrated by implanted thermosensors.

Daily fluctuations, temperature heterogeneity and its distribution over the brain surface can be studied using microwave RTM. In particular, RTM showed that healthy humans are characterized by a pronounced 24-hour circadian variation of cortical temperature with peaks at 12–16 hours and troughs at 0–6 hours. Correlation analysis revealed strong positive correlations between left and right hemisphere temperature changes, while moderate positive correlations were characteristic between diurnal variations of cortical and core temperature, emphasizing the relative independence of brain and body temperature regulation [67]. In severe brain injury patients with chronic disorders of consciousness (CDC), such as vegetative state (VS) and minimally conscious state (MCS), the diurnal variations of cortical temperature were absent, apparently reflecting the gross lesions of cerebral structures, including central circadian oscillators [68].

In order to study temperature heterogeneity, a technique of sequential temperature registration in 9 symmetrical regions of the cortex of the large hemisphere on the left and right side (18 registration areas) was developed, which allows the construction of brain surface temperature distribution maps (Fig.) [69].

The studies were performed in healthy subjects at rest, in patients with acute ischemic stroke, and in patients with CDC after severe brain injury (VS and MCS) [70].

These studies showed that in healthy individuals resting cortical temperature is heterogeneous, with areas of relatively elevated (up to 36.7–37.4°C) and decreased (down to 35.8–36.3°C) values, while the average temperature of left and right hemispheres does not differ, averaging 36.4–36.7°C. The maximum difference between relatively warm and cold regions (△T) does not exceed 2.0–2.5°C, and their location varies individually and may be situation-specific.

In patients on the first day after ischemic stroke, regardless of the area of infarction, the average temperature of the right and left hemispheres increases to 37.9–38.0°C. At the same time, cerebral hyperthermia occurs in one third of patients with normal core temperature, i.e. it is latent. Focal hyperthermia develops with foci of increased temperature up to 39–41°C. The △T between «warm» and «cold» areas increases sharply, reflecting marked thermal heterogeneity. Patients whose △T was greater than 3–4°C died within 7–10 days. Thus, elevated brain temperature and severe thermal heterogeneity can be considered predictors of poor outcome [71].

The development of CDC after recovery from coma [72] is accompanied by a decrease in neuronal activity, metabolic disorders, and low hemodynamic

support of the brain. These processes may alter the cerebral thermal balance. In this category of patients, with values of averaged cortical temperature close to normal, △T seems to be less than 2°C, which indicates low thermal heterogeneity.

Correlation analysis between temperature values of symmetrical cortical areas of the left and right hemispheres in healthy subjects, patients with acute ischemic stroke, and those in CDC revealed significant differences. Thus, healthy subjects were characterized by positive significant medium strength correlations between symmetrical regions of the left and right hemispheres, with correlation coefficients (CC) ranging from 0.504 to 0.747.

In patients on day 1 of acute focal cerebral ischemia, the pattern of correlations between temperatures of symmetric brain cortical areas varied significantly. The CC varied widely from negative (–0.370) to positive (0.848) values, indicating an increase in interhemispheric temperature heterogeneity.

Correlation analysis of brain temperature relations in symmetrical regions of the large hemisphere cortex in patients with CDC showed that the CCs were in a narrow range from 0.971 to 0.947, reflecting the presence of strong positive correlations and uniformity of temperature distribution across the large hemisphere cortex.

According to the theory of functional biological systems developed by Pyotr Anokhin [73], the elements of an effectively functioning system are linked by medium strength connections, which provides enhanced opportunities for adaptation due to the variability of adaptive reactions generated by a set of system elements. The adaptive reserve of the system, when strong (rigid) links are established between its elements, is reduced by limiting the variability of reactions and strong interdependence, while extra strong impacts on the system and its components can lead to the rupture of links between them and cause system collapse. In turn, weakening and changing the direction of interrelations between the elements of the system cause its destruction, leading to the cessation of integrated activity.

Excessive increase of interhemispheric thermal heterogeneity and, on the contrary, its decrease, demonstrating disturbed connections between elements of the system, in this case between symmetrical regions of the cortex of the large hemispheres, accompany severe brain injuries and conditions of decreased consciousness, which proved to be characteristic for acute ischemic stroke and post-coma chronic disorders of consciousness.

The characteristic pattern of changes in temperature heterogeneity is also observed in psychiatric patients. In particular, in patients with schizophrenia, low cortical temperature heterogeneity was associated with an increase in the activity of inflammatory blood markers and, in most cases, with a positive response of the patients to therapy. High cortical temperature heterogeneity appeared to be characteristic of patients with a deficient inflammatory proteolytic system and high levels of anti-brain antibodies. In these patients, the disease was more severe and resistance to therapy was observed in most cases [74]. Positive treatment results in patients with schizophrenia, acute focal cerebral ischemia and CDC were associated with an increase in decreased and a decrease in increased cortical temperature heterogeneity, respectively.

Despite a long history of research, the specific features of temperature homeostasis regulation remain largely unexplored. Recent data show that the temperature of subcortical brain structures can vary within a wide range in healthy individuals and in patients with TBI, and that both absolute values and circadian fluctuations of brain temperature are of diagnostic value, with abnormal diurnal changes being predictive of a significant increase in the probability of death in patients with severe TBI [75].

The pathogenetic role of cerebral hyperthermia, as well as the frequent occurrence of latent neurogenic fever, emphasize the importance of thermometry in the diagnosis, progression, and prediction of outcome of severe brain disease, with microwave RTM being the most convenient, simple, safe, and informative technique.

Moreover, the increase or decrease in temperature heterogeneity observed in severe brain injury may both be associated with the development of diseases and underlie the mechanisms of disturbed relationships between elements in the global systems of central regulation. This suggests that a reduction in the increased thermal heterogeneity or an increase in the decreased thermal heterogeneity may improve clinical outcome. The suggestion is supported by clinical observations showing that selective cooling of the brain helps to reduce the neurological deficit, mainly due to an increase in awareness, by controlling the thermal balance and reducing thermal heterogeneity in patients with acute ischemic stroke [76].

Conclusion

The RTM technology may be a helpful tool in the diagnosis of various brain disorders, including acute and chronic cerebrovascular disease and brain injury, psychiatric and neurological conditions, decreased consciousness and cognitive function.

Microwave RTM is a relatively new method of non-invasive deep tissue temperature assessment that has been used primarily for scientific purposes. However, the accumulated experience allows a prospective evaluation of its diagnostic performance, which definitely requires additional in-depth clinical and pathophysiological studies.

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Etiology and Pathogenesis of Postoperative Cognitive Dysfunction (Review)

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Summary

Impairment of higher mental functions can complicate the course of the postoperative period even after short and minimally invasive, including laparoscopic, surgical procedures. Postoperative cognitive dysfunction significantly challenges patients' quality of life, negating real success of surgical intervention and anesthetic support. In some cases, early postoperative cognitive dysfunction may be one of the main predictors of persistent cognitive impairment.

The purpose of the review. To contemplate etiology, pathogenesis and the current perspective of postoperative cognitive dysfunction.

We analyzed 96 publications in various databases (PubMed, Medline, RSCI and others), including 67 papers published over the past 5 years.

The review provides an overview of current definitions and classification of postoperative cognitive dysfunction, data on the prevalence, polyethyology and risk factors, potential impact of the type of anesthesia and surgical intervention on the development of postoperative cognitive dysfunction. Various pathogenetic mechanisms of higher mental functions impairment alongside with available effective pharmacotherapies to correct them were considered.

Conclusion. Numerous adverse factors of the perioperative period, such as neurotoxic effects of general anesthetics, neuroinflammation in response to operational stress and surgical trauma, impaired autoregulation of the cerebral blood flow, imperfect oxygen homeostasis, interactions of neurotransmitter, etc., can potentially cause postoperative cognitive dysfunction. Further deeper insights into etiology and pathogenesis of early postoperative cognitive dysfunction are relevant and necessary to improve prevention strategies and identify most effective pharmacotherapies to correct such disorders.

Keywords: postoperative cognitive dysfunction; higher mental functions; neuropsychological testing; cognitive disorders

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Introduction

Ensuring patient comfort in the perioperative period is a major challenge for modern anesthesia care [1, 2]. This issue has been interpreted in a broad sense, ranging from the elimination of emotional lability and anxiety in the preoperative period, adequate anesthetic support during surgery, effective postoperative anesthesia with early patient activation, avoidance of postoperative nausea and vomiting, muscle tremor, excessive sedation, to the prevention and elimination of cognitive dysfunction [3, 4].

Disorders of higher mental activity and development of postoperative cognitive dysfunction (POCD) significantly worsen the quality of life and negate the success of both the performed surgical intervention and the anesthetic aid. Disorders of higher mental functions (HMF) can complicate the postoperative period even after minimally invasive and short-term surgical procedures, including laparoscopic surgery. Several studies [5, 6] have shown that early POCD is one of the main predictors of persistent cognitive dysfunction.

Aim of the review. To discuss the ethology, pathogenesis, and current status of postoperative cognitive dysfunction.

Definition and Classification

In the postoperative period, patients who have undergone anesthesia and surgery may develop a variety of cognitive impairments ranging from POCD to delirium. Postoperative delirium can be defined as an acute confusion that may manifest as impaired consciousness, cognitive dysfunction, or changes in perception and behavior.

The duration of postoperative delirium can vary from a few hours to several days and should be distinguished from dementia and postoperative cognitive impairment [7].

According to L. S. Rasmussen (2001), postoperative cognitive dysfunction is a disorder that develops in the early and persists into the late postoperative period, manifesting as impaired memory, reasoning, language, and other higher cortical functions, and can be confirmed by neuropsychological

testing (NPT) as a decrease of at least 20% (or ±1SD) in postoperative scores compared to preoperative scores [8].

Currently, according to the definition of the International Working Party for Nomenclature of Perioperative Cognitive Disorders proposed at the 16th World Congress of Anaesthesiologists (Hong Kong, 2016) and subsequently endorsed in Geneva (Euroanaesthesia 2017), POCD is defined as cases in which the difference in NPT is at least ±1.96 SD from baseline values based on at least two tests from a battery of 5–10 tests [9].

Until recently, POCD was classified according to the duration of clinical manifestations as

— acute or short-term type (acute postoperative cognitive dysfunction or short-term cognitive disturbance) lasting up to 1 week after surgery;

— intermediate postoperative cognitive dysfunction lasting up to 3 months after hospital discharge;

— long-term cognitive decline or prolonged postoperative cognitive dysfunction with cognitive impairment lasting 1–2 years or longer.

Postoperative cognitive dysfunction can manifest as impaired memory and attention, speech, spatial and temporal orientation, counting, ability to think abstractly, development or worsening of depression, and can vary in severity [10, 11].

Mild cognitive impairment refers to minor changes in daily activities, primarily related to impaired memorization of new material. These «subjective» cognitive impairments do not significantly interfere with a person's daily life and may not be detected by tests because the parameters analyzed are within or slightly off the statistical average for the age group. Mild cognitive impairment is only perceived by the patient when he or she notices a deterioration in memory or responsiveness compared to his or her individual standard [12–14].

Gradually, with age, memory and thinking become weaker, and it becomes more difficult to focus attention and choose the right words. These changes are associated with natural aging and the development of moderate cognitive impairment. In some cases, they exceed the age-specific reference but do not reach the severe level of dementia. Self-referral to a doctor is one of the subjective criteria for distinguishing moderate cognitive impairment from mild dementia. When dementia develops, the patient is usually brought to the doctor by relatives. Moderate cognitive impairment significantly interferes with daily activities and memory is retained only for well-learned or personal information. The term «moderate cognitive impairment» has been included in ICD-10 as an independent entity. According to the ICD-10 recommendations, this diagnosis corresponds to:

— impaired memory, attention, or learning;

— increased fatigue with mental work;

— memory and other higher brain function abnormalities not associated with dementia or delirium;

— organic nature of the above disorders.

Moderate cognitive impairment occurs in 11–17% of older adults and is considered by neurologists to fall between the normal aging process and severe dementia. In many patients (up to 85%) with moderate cognitive impairment, memory impairment is the hallmark, but impairment of multiple cognitive functions (thinking, attention, language) can also be detected.

Moderate cognitive impairment is not a disease entity, but rather a syndrome. It may be due to different causes or a combination of them (age-related changes, neuronal death, vascular problems, metabolic disorders). Therefore, when a syndrome of moderate cognitive impairment appears, a thorough clinical and functional examination should be performed to identify its possible cause.

About half of patients complaining of memory disturbance have no evidence of cognitive impairment. The most common cause of symptoms without objective confirmation are emotional disorders such as increased anxiety or low mood, including depression [15, 16].

In severe cognitive impairment, patients are unable to remember new information or reproduce previously learned material. POCD may be reversible in some patients, and many authors consider the relationship between severe POCD and the development of dementia [17].

Dementia refers to the most severe cognitive impairment that results in an inability to function in daily life, is not associated with disorders of consciousness, and has a progressive course. Dementia is more common in the elderly, affecting at least 5% of people over the age of 65. Dementia manifests itself simultaneously in several cognitive areas, such as thinking, memory, attention, and language. Even in its early stages, the impairment is significant enough to adversely affect both daily life and work activities.

According to modern nomenclature, early POCD can be diagnosed from the 7th postoperative day. Cognitive impairment that persists up to 3 months after surgery (previously defined as «intermediate POCD») is referred to as delayed neurocognitive recovery [18].

Epidemiology

The first studies on the epidemiology of POCD were performed in 1955, when P. Bedford published in the Lancet data from a retrospective analysis of the postoperative period of 1193 elderly patients who underwent surgery under general anesthesia.

Cognitive impairment of varying severity was observed in approximately 10% of patients [19].

Similar data were obtained in a randomized study of the International Study of Post-Operative Cognitive Dysfunction (ISPOCD 1, 1998), which showed the persistence of cognitive deficit in 9.9% of patients during 3 months postoperatively. In older patients (over 75 years), persistent POCD was found in 14% of cases [20].

According to the results of the international multicenter study ISPOCD 2 (2000), the incidence of early POCD after non-cardiac surgery under general anesthesia was 19.2% in middle-aged patients (40–60 years old) and 21.4% in elderly patients, while the incidence of persistent POCD reached 6.2% [21].

In a study by T. Monk et al. [22], 1064 patients of different ages undergoing non-cardiac surgery were analyzed. NPT was performed preoperatively, at hospital discharge (4–10 days), and 3 months postoperatively according to the ISPOCD study methodology. In young patients (18–39 years) POCD was observed in 36.6% at hospital discharge and in 5.7% 3 months after surgery, in middle-aged patients (40–59 years) short-term POCD was observed in 30.4% of cases, intermediate POCD in 5.6%, while in elderly patients (60 years and older) the frequency of short-term and intermediate POCD was 41.4 and 12.7%, respectively. The authors paid special attention to the significant relationship between the history of POCD and patient survival: if the NPT indicated POCD both at hospital discharge and 3 months after surgery, mortality during the first year after surgery was significantly higher than without POCD at all study stages (10.6% vs. 2.1%, $P = 0.02$) (class of recommendations IIa, level of evidence B). The risk of persistence of POCD in the late postoperative period was higher in patients over 60 years of age, with a low level of education, and with a history of stroke [23].

A recent systematic review analyzed 7 papers with data from neuropsychological testing of 2796 patients. Tests were performed 7 days postoperatively, 3 months later, and in the long term (12–60 months). Early POCD developed in different categories of patients with a frequency ranging from 17% to 56% and a tendency to resolve later (3–34.2%). Risk factors for POCD were old age, insulin resistance and low educational level. The type of surgical procedure performed and anesthesia used did not affect the incidence of cognitive impairment [24]. In a randomized controlled trial of 60 elderly patients over 60 years of age undergoing knee replacement surgery under general anesthesia, the incidence of early POCD was 20% [25].

Etiology

Nowadays, POCD is considered to be multifactorial, with the main causes of HMF impairment being both anesthesia-related and patient-specific (including the nature of the surgery or mental/medical status) [26, 27]. In a review by N. Patel et al. [28] based on 130 randomized clinical trials, the major causes of POCD included anesthesia (15 studies), blood pressure variations (5), cerebral autoregulation disorders (4), systemic inflammatory response (26), hypothermia and rewarming (19 and 6, respectively). Other predictors of POCD include early age (less than 3 years) [29] and old age (more than 60 years), male sex, low level of education, baseline cognitive deficit, history of anxiety and depressive disorders, neurological diseases, especially of vascular etiology [30].

From the perspective of evidence-based medicine (recommendation class II, level of evidence A, B), the third trimester of pregnancy, alcoholism, genetic predisposition (epsilon 4 allele of apolipoprotein E) are also considered predictors of impaired postoperative HMF [31]. The incidence and severity of POCD are influenced by the duration and frequency of general anesthesia, especially when its duration exceeds 3.5–4 hours [32–34]. A meta-analysis of 21 randomized clinical trials by S. E. Mason et al. convincingly (OR = 1.34; 95% CI: 0.93–1.95) demonstrated an association between POCD and type of anesthesia. General anesthesia significantly increases the risk of cognitive decline compared to regional (or combined) anesthesia [35, 36]. The risk of developing cognitive impairment is significantly increased during carotid artery reconstruction, cardiac surgery [37], especially with the use of cardiopulmonary bypass. Studies by T. V. Klyp [38, 39] show the development of neurocognitive disorders of varying severity in 30–70% of patients after cardiac surgery.

Pathogenesis

Until the end of the last century, anesthetic neurotoxicity was considered the main element in the pathogenesis of brain damage. At the same time, it was noted that POCD occurs much more frequently in the elderly (over 60 years of age) than in younger patients and in children under 3 years of age. However, a large number of studies have shown that the neurotoxic effects of general anesthetic drugs are most severe in children, especially in the younger age group. The adverse effects of general anesthesia on brain structures in school-aged children result in impaired neuropsychological development both in the postoperative period and in the long term [40]. The pooled hazard ratio (HR) for children undergoing their first anesthesia before the age of four is 1.25 (95% CI: 1.13–1.38; $P < 0.001$) [41]. In 2016, the FDA indicated the potential risk of POCD with surgery lasting more than 3 hours or multiple anesthetics in children younger than 3 years and in women in the third trimester of pregnancy [42]. Recent studies have not shown a significant decrease in the incidence of POCD with

the use of modern anesthetics (sevoflurane, desflurane, etc.), which, according to most authors [43–45], have cerebro- and neuroprotective properties that outweigh possible neurotoxic effects, compared with the previous generation of anesthetics, as well as with the use of neuroaxial techniques.

Currently, the mechanism of postoperative disorders of HMF is considered to be multifactorial [46], developing under the influence of numerous unfavorable factors of the entire perioperative period [47]. The pathogenesis of POCD is based on a complex of pathophysiological changes in the central nervous system (CNS). The CNS structures where general anesthesia-induced neurodamage develops include medial septal nucleus, reticular formation, thalamic nuclei, hippocampus, neocortex (frontal, parietal, temporal, and occipital lobes), hypothalamus [48].

General anesthesia is accompanied by increased permeability of mitochondrial membranes, leading to their dysfunction, disturbs calcium homeostasis in neurons and inhibits energy processes [49]. Sevoflurane and isoflurane inhalation anesthetics can induce neuronal apoptosis due to caspase activation and aggregation toxicity of β-amyloid peptides [50]. General anesthesia for more than 1 hour causes hyperphosphorylation of tau protein, a major internal neuronal membrane protein, which directly induces brain cell death [51]. This pattern has been attributed to propofol and dexmedetomedine, which cause increased tau protein phosphorylation in the murine hippocampus in vitro [52]. In view of the above, the choice of anesthetic should clearly be aimed at minimizing its neurotoxicity. For this purpose, a comparative evaluation of different anesthetic techniques should be performed.

A meta-analysis of 15 randomized clinical trials (RCTs) involving 1854 elderly noncardiac patients showed that the incidence of early POCD was significantly lower after propofol anesthesia than after inhalational anesthesia (*RR* = 0.37; 95% CI: 0.15–0.88; *P* = 0.025), and NPT scores were significantly higher after propofol anesthesia than after inhalational anesthesia (SMD = 0.59; 95% CI: 0.07–1.11, *P* = 0.026) [53]. At the same time, in a meta-analysis of 28 RCTs with 4507 randomized participants over 60 years of age undergoing similar surgical procedures as in the previous study, there was no conclusive evidence of a benefit of propofol-based total intravenous anesthesia for reducing POCD (SMD = –0.52; 95% CI: 0.31–0.87) compared with inhalational anesthesia [54, 55].

In a Russian prospective randomized study (*N*=40) of carotid endarterectomy, cognitive decline of 2 or more MoCA (Montreal Cognitive Dysfunction Scale) points was observed in 55% (day 1) and 35% (day 5) of patients in the total intravenous propofol anesthesia group, which was significantly higher than in the sevoflurane inhalation anesthesia group, where the incidence of POCD was significantly lower (35% on day 1 and 5% on day 5) [56].

A meta-analysis of the use of ketamine as an adjunct to general anesthesia in 3 RCTs showed a lower risk of POCD (*OR* = 0.34; 95% CI: 0.15–0.73) compared with propofol-based total intravenous anesthesia [57]. A meta-analysis of 26 RCTs showed that the perioperative use of dexmedetomidine significantly reduced the incidence of POCD (OR = 0.59; 95% CI: 0.45–2.95) and improved neuropsychological test scores (MMSE) (SMD = 1.74; 95% CI: 0.43–3.05) compared to groups without its use [58].

A number of studies have examined the relationship between the incidence of POCD and the depth of hypnosis [59]. In a meta-analysis of 10 RCTs including 3142 patients, the incidence of POCD was significantly lower in the shallow anesthesia group than in the deep anesthesia group on day 1 (*RR* = 0.14; 95% CI: 0.04–0.45; *P* > 0.10) and 3 months after surgery (*RR* = 0.72; 95% CI: 0.54–0.96; *P* > 0.10) [60]. The opposite results were found in another RCT. In 66 elderly patients who underwent total knee replacement surgery under general anesthesia, the incidence of early POCD on postoperative day 7 was 20% with a bispectral index (BIS) of 40–50, whereas in the comparison group with a BIS of 55–65, the incidence was only 3.3% [61]. At the same time, a meta-analysis of 4 studies showed no significant correlation of POCD incidence between low and high BIS groups (*R* = 0.84; 95% CI: 0.21–3.45; *P* > 0.05) [62].

Some studies have analyzed the association of POCD with the quality of antinociceptive protection achieved during surgery. Antinociceptive failure leads to overexcitation and depletion of the energy balance of cortical and subcortical neurons responsible for an adequate level of consciousness [63, 64].

Intraoperative awakening may play a significant role in the development of postoperative cognitive dysfunction, which could significantly worsen patients' quality of life in the long term after surgery. Possible residual effects of components of general anesthesia, primarily anesthetics and their biotransformation products, on the CNS have been studied [65].

Studies on the effect of general anesthesia on HMF are intriguing. First of all, this concerns modern neuroaxial techniques, because in any variant of their use (alone or as a component of antinociceptive protection in combined anesthesia or for postoperative prolonged epidural analgesia), the doses of systemic drugs are significantly reduced. For example, seven RCTs involving 1,031 patients showed that the incidence of POCD was significantly lower in patients who received regional anesthesia than in those who received general anesthesia on days 1

and 3 after surgery ($P < 0.05$). However, no significant differences were found between the two types of anesthesia on day 7 and 3 months after surgery ($P > 0.05$) [66–68].

In a multicenter, randomized trial of patients over 60 years of age undergoing major noncardiac surgery, a significant reduction in POCD was found when neuroaxial anesthesia was used during the first week after surgery compared with general anesthesia. The advantages of epidural and spinal analgesia include adequate antinociceptive effect, reduced dose of general anesthetics, prevention of postoperative complications (cardiovascular, pulmonary, renal, thromboembolic, infectious), which both improve surgical treatment outcomes and contribute to the prevention of POCD and better quality of life of patients [69].

Recently, the role of neuroinflammation in the mechanisms of adverse effects of surgery on mental status has been increasingly recognized. It is caused by a systemic inflammatory response to surgical stress, inadequate postoperative anesthesia, invasive procedures, and drug therapy. The inflammatory response is accompanied by the release of potent pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) into the systemic circulation. They disrupt the integrity of the blood-brain barrier, promote the migration of macrophages and activated leukocytes into brain tissue, which is associated with the activation of microglia and astrocytes, resulting in the initiation of neuroinflammation with impaired neuronal function and the development of cognitive disorders [70–73]. This theory is supported by a meta-analysis of 13 studies showing an association between POCD and IL-6 and protein S-100, a marker of brain damage [74, 75]. In another meta-analysis of 15 RCTs involving 1854 elderly non-cardiac patients, IL-6 (SMD = –2.027; 95% CI: –3.748 to –0.307; $P = 0.021$) and TNF-α (SMD = –0.68; 95% CI: –0.93 to –0.43; $P < 0.001$) levels were significantly lower after propofol anesthesia than after inhalational anesthesia [76].

The use of dexmedetomidine contributed to the reduction in levels of key proinflammatory cytokines. A meta-analysis of 26 RCTs showed that perioperative use of dexmedetomidine significantly reduced IL-6 (SMD = –1.31; 95% CI: –1.87 to –0.75; $P < 0.001$) and TNF-α (SMD = –2.14; 95% CI: –3.14 to –1.14; $P < 0.001$) levels compared with the control group without its use [77].

Regarding the efficacy of clinical use of drugs with selective action on different brain structures, which refers to different neuroprotective agents, we did not find convincing evidence-based studies in the databases (PubMed, Medline). The results of some studies are of some practical interest and promising for the application and correction of HMF disorders caused by anesthesia and surgery.

First of all, this is true for cholinergic precursors (citicoline, gliatilin). The cholinergic system closely interacts with the dopaminergic and GABAergic systems in the CNS, providing and maintaining optimal levels of cognitive function, and its dysfunction plays a role in the development of POCD [78].

Citicoline is one of the few neuroprotectants with proven clinical efficacy that has been included in the European clinical guidelines for the treatment of ischemic stroke. A double-blind, placebo-controlled study was conducted to evaluate the efficacy of cerebral neuroprotection with citicoline during surgical procedures under general anesthesia. Neuropsychological testing on day 1 after surgery revealed POCD in 50% of patients in the comparison group, while cognitive impairment was observed in only 20% of patients in the main group ($P < 0.05$). On day 3 after surgery, long-term memory scores (according to the results of the 10-word memory test) were 56% better in the majority of patients in the study group than in the control group ($P < 0.05$) [79].

Some clinical experience is available with cytoflavin, a neurotropic antioxidant with metabolic activity. In an RCT of 60 operated school-aged children, the incidence of POCD in the cytoflavin group was 6.67% on day 1 of the postoperative period and 3.33% on day 7. In the group without cytoflavin, POCD developed in 13.79% and 27.59% of cases, respectively. The use of intraoperative metabolism-directed cerebral protection during total intravenous anesthesia based on propofol and fentanyl reduced the incidence of POCD in school-aged children by 8 times ($P < 0.01$) [40, 41].

Regarding the possible role of Cellex, a neuroprotectant with pronounced neuroplasticity, in the correction of early POCD, there are successful results of its use in patients with various neurological disorders [80, 81].

A possible imbalance of neurotransmitter (adrenergic, cholinergic, NMDA and GABAergic) interactions in the CNS, accumulation of excitatory mediators such as dopamine, seems interesting and promising [82]. Disturbed neurotransmitter interactions between dopamine and acetylcholine may cause dissociation of excitation-inhibition in the CNS. Altered production of key neurotransmitters can result from impaired delivery of neurotransmitter precursor amino acids to the brain. This can occur when the ratio of aromatic to non-aromatic amino acids in the blood changes, causing excitotoxicity of monoaminergic regulation [83]. The development of neurotransmitter disorders may potentiate the pharmacological neurotoxicity of general anesthetics. In some cases, this can lead to a a deficit of cholinergic activity with the development of central anticholinergic syndrome, which is a specific complication of general anesthesia, manifested by abnormal awakening with its slowing or severe psychomotor agitation

or intense muscle tremor, the pathogenesis of which is based on an acute deficit of central cholinergic activity. Anticholinergic drugs used in anesthesiology and intensive care mostly show selective antagonism against muscarinic receptors (atropine, scopolamine), but some have a mixed mechanism of action (antihistamines, antipsychotics, tricyclic antidepressants), while others reduce acetylcholine secretion (opiates, benzodiazepines, clonidine) [84, 85].

Surgical injury has recently been found to be capable of provoking a disturbance of iron homeostasis with its accumulation in the brain, mainly in the hippocampus. Such processes lead to cognitive impairment because excessive iron causes oxidative stress and impaired mitochondrial function. In addition, glucose metabolism is impaired and ATP production is reduced due to downregulation of key enzyme genes and protein synthesis, which can induce neuronal apoptosis [86].

POCD can develop as a result of the deleterious effects of both general (hypoxemia, reduced circulation) and local (decreased cerebral blood flow, its redistribution) hypoxia. For optimal transport and consumption of O_2 by neurons, an optimal cerebral perfusion should be maintained [87, 88]. The leading role in its maintenance belongs to cerebral perfusion pressure, the value of which is directly proportional to mean arterial pressure and inversely proportional to intracranial pressure. The latter tends to increase more frequently in severe neurosurgical situations and has a significant impact on cerebral blood flow much less frequently in routine surgical practice. Recently, several studies have addressed the impact of systemic blood pressure on cerebral perfusion and consequently on the development of POCD. A meta-analysis of 24 RCTs including 4317 patients (mean age 63 years) showed that hypertension was not significantly associated with the risk of POCD (OR = 1.01; 95% CI: 0.93 to 1.09; $P = 0.82$), although in 8 studies with participation of more than 75% of men, a 27% association of hypertension with increased risk of POCD was found (OR = 1.27; 95% CI: 1.07 to 1.49; $P = 0.005$) [89]. Another RCT included 360 patients in the low target blood pressure (BP) group and 341 participants in the high target BP group. The results showed no significant difference in the incidence of POCD between the groups (*RR* = 1.26; 95% CI: 0.76–2.08; $P = 0.37$) [90]. Three RCTs including 731 patients compared the maintenance of low systolic blood pressure (SBP) (< 80 mm Hg) and high SBP (> 80 mm Hg) during coronary artery bypass grafting. POCD developed in 6.4% of all cases. Maintaining low SBP did not reduce the incidence of POCD (95% CI: 0.277–3.688; $Z = 0.018$; $P = 0.986$). Shorter cardiopulmonary bypass time reduced the incidence of POCD regardless of target BP (95% CI: –0.949 or –0.089; $P = 0.017$) [91, 92].

Cerebral saturation monitoring, along with maintaining optimal cerebral perfusion, may also help reduce the incidence of cognitive decline. A randomized trial of 192 elderly patients in the main group and 138 in the control group after abdominal surgery showed that cerebral saturation monitoring contributed to a significant ($P = 0.020$) reduction in the incidence of early POCD [93, 94].

Obesity and its comorbidities are becoming an increasingly pressing public health issue. Often, these patients undergo surgery under general anesthesia and are thought to be at high risk for developing HMF disorders. The available studies have not convincingly confirmed this hypothesis. A meta-analysis of 1432 patients over 60 years of age with a body mass index > 30 kg/m² versus ⩽30 kg/m² showed a non-significantly higher risk of POCD (OR = 1.27; 95% CI: 0.95 to 1.70; $P = 0.10$) [95]. In 17 studies with 2725 patients (mean age 67 years), there was no association between hypercholesterolemia and the risk of POCD (OR = 0.93; 95% CI: 0.80–1.08; P = 0.34). Preoperative statin use was associated with a reduced risk of POCD in eight studies (RR = 0.81; 95% CI: 0.67–0.98; P = 0.03), but data on duration of treatment were lacking [96].

Conclusion

Postoperative cognitive dysfunction is currently an urgent clinical and social challenge. Its prevention and treatment are complicated by the multiple adverse perioperative factors that underlie its development. Neurotoxic effects of general anesthetics, systemic inflammatory response with subsequent neuroinflammation after surgical stress and trauma, impaired autoregulation of cerebral blood flow due to intraoperative hypotension, abnormal blood-brain barrier permeability as a result of reperfusion injury after major cardiac surgery and vascular interventions, disorders of metal metabolism in the brain, oxygen deficiency in the brain, and imbalance of peripheral nervous system mediators play a role in the development of disorders of higher mental functions.

The solution of this problem, which is crucial for the quality of life of surgical patients, lies in further improvement of anesthesiological support of surgical interventions, implementation of advanced monitoring methods in anesthesiological practice and thorough study of POCD pathogenesis, which will allow to determine the spectrum of effective drugs for adequate correction of postoperative disorders of higher mental functions.

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Additional audio and video files, after pre-publication preparation, will be published together with your accepted paper on the website of the General Reanimatology journal **www.reanimatology.com.**

The use of graphic, audio, and video formats to accompany the paper expands the audience, increases interest in the material presented, contributes to a better understanding of the results, and consequently increases their visibility.

We wish you success in your scientific and practical activities and further productive cooperation!

Editorial team,
General Reanimatology Journal

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