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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.

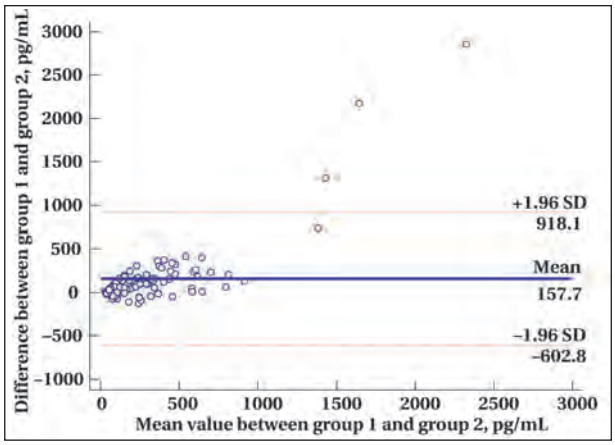

Fig 1. Bland-Altman plot for assessment of comparability of the test results of the series 1 and 2.

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

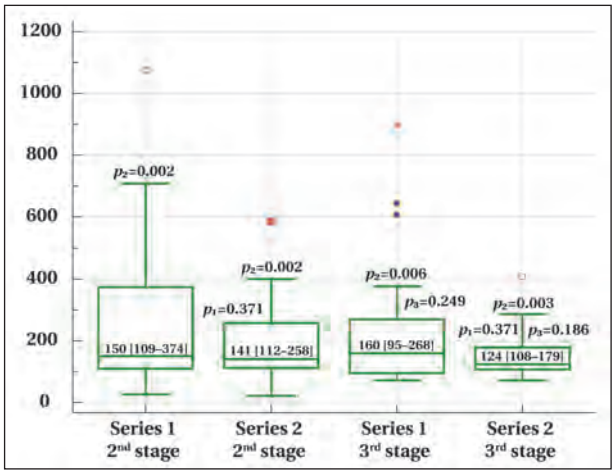

Fig. 2. Changes in the NT-proBNP level in the series 1 and 2 in relation to the stage 1 level taken as 100%.

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.

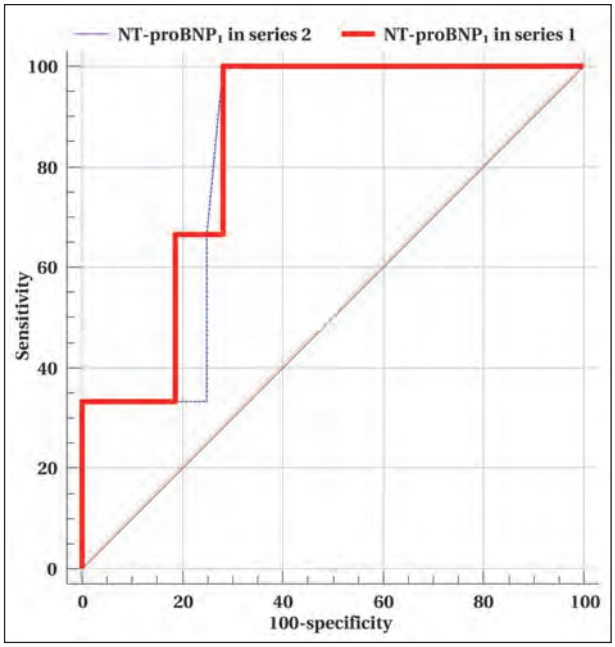

Fig. 3. ROC curves showing the discriminating power of NT-proBNP$_1$ for perioperative cardiovascular complications.

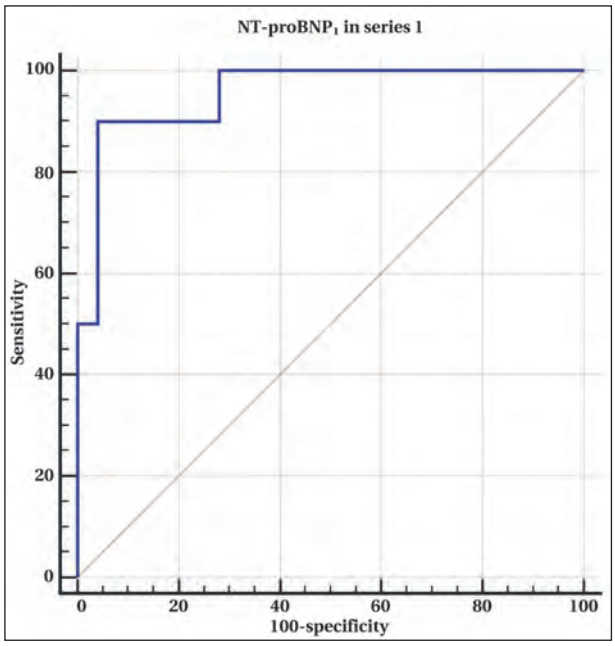

Fig. 4. ROC curve showing the discriminating power of series 1 NT-proBNP$_1$ vs series 2 NT-proBNP$_1$ values >350 pg/mL.

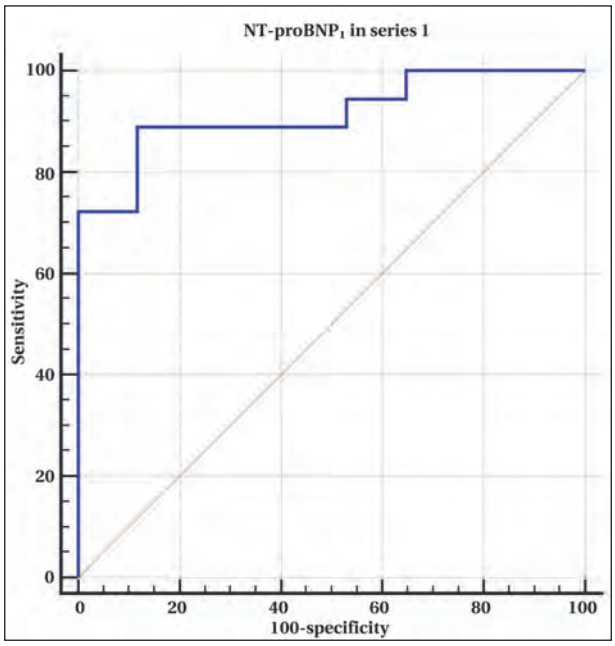

Fig. 5. ROC curve showing the discriminating power of series 1 NT-proBNP$_1$ vs series 2 NT-proBNP$_1$ values >125 pg/mL.

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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