DIAGNOSTIC SIGNIFICANCE OF HIGHLY SENSITIVE TROPONINS IN CARDIAC SURGERY

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Background: *The level of troponins after cardiac surgery always exceeds the reference values, however, the interpretation of these changes is difficult.* ***Aim:*** *To determine the relationship between the high-sensitivity cardiac troponin I and troponin T levels and the risk of heart failure (HF) development within 24 hours after the heart surgery.* ***Methods:*** *A prospective, observational, single-center study included 70 patients undergoing elective heart surgery. The patients were retrospectively divided into two groups based on the development of HF in the first 12 hours after the surgery. The group without HF included 57 patients, the group with HF included 13 patients.* ***Results:*** *The levels of highly sensitive Troponin I (HsTI) in patients who underwent elective heart surgery without complications were 61 times higher than the upper limit of the normal values, in those with the development of HF they were 111 times higher than the upper limit of the normal values. The levels of highly sensitive Troponin T (HsTT) were 25.5 times and 51 times the upper limit of the normal values, respectively. The level of HsTI at the end of the surgery can be a predictor of the HF development, regardless of the use of cardiac bypass (threshold value =1483 ng/l), as well as a predictor of the need for inotropic support for 2 days or more, regardless of the operation type (threshold value = 1573 ng/l). There was a direct moderate correlation of the HsTI level at the end of the operation and 6 hours after the operation with cumulative hemohydrobalance for 24 hours, which was 60% higher in patients with HF than that in patients without complications.* ***Conclusion:*** *In uncomplicated patients, the level of highly sensitive troponins T and I in the postoperative period is 25–61 times higher than the upper limit of the normal values, and with the HF development it is 51–111 times higher. Highly sensitive troponins can be considered as predictors of the HF development and the duration of inotropic support. The increase in the level of troponins is influenced by the duration of cardiac bypass and the volume of infusion therapy in the perioperative period.*

Keywords: *highly sensitive Troponins I and T; postoperative prognosis; cardiac surgery; resuscitation and intensive care.*

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BACKGROUND

Determining the concentration of highly sensitive troponins (Tn-hs) is the current gold standard in diagnostics of myocardial infarction and non-ischemic myocardial injury. Tn-hs tests enable early detection of myocardial infarction, have high predictive value, and improve diagnostic accuracy in patients with suspected acute coronary syndrome. An increase in the Tn-hs level 1–3 times higher than the 99th percentile determines the probability of acute myocardial infarction in 50%–60% of cases. An increase in troponin levels greater than five times the upper limit of normal increases the probability of myocardial infarction to >90%. However, even in this case, to establish the final diagnosis, other data must be considered, such as new symptoms of myocardial ischemia, new changes in the ST segment, or appearance of the left His bundle branch block on the electrocardiography, appearance of a pathological *Q* wave, visual data on new zones of myocardial hypokinesia, and detection of a blood clot in the coronary artery during angiography or autopsy [1]. In addition, elevated levels of cardiac troponins can be considered

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independent risk factors of lethal outcomes from all causes in the general population and patients with stable coronary heart disease, heart failure, and atrial fibrillation, and patients who underwent myocardial revascularization for acute coronary syndrome [2, 3]. A 100% increase in TnT-hs levels was found to be an independent predictor of postoperative complications in abdominal surgery [4]. Troponin I has been described as a more specific marker of the risk of death from cardiovascular causes [5].

Coronary artery bypass grafting under cardiopulmonary bypass (CPB) is a traditional surgical treatment of coronary heart disease. Acute cardiovascular dysfunction occurs perioperatively in >20% of patients undergoing cardiac surgery, and 25% of patients undergoing elective coronary artery bypass grafting require inotropic support [6, 7]. One of the typical pathophysiological processes during CPB is the development of a systemic inflammatory response, endothelial damage, and hypoperfusion [8]. The level of troponins after cardiac surgery always exceeds the reference values; however, the interpretation of these changes is difficult. Until now, no single threshold level of troponins has been established in cardiac surgery. Currently, for diagnostics of type 5 myocardial infarction, the use of troponin value >10 times the upper limit of normal with a normal initial concentration of cardiac troponins (together with signs of new myocardial ischemia) in the first 48 h after coronary artery bypass grafting was proposed [9]. In some studies, in addition to new signs of ischemia, the threshold for diagnosing myocardial infarction is troponin levels 35 times higher than the upper limit of normal [10]. A troponin threshold of 70 times, increasing the upper reference limit, was described as an independent criterion for clinically significant perioperative myocardial injury. TnI-hs levels after cardiac surgery in patients with an increased 30-day mortality risk were significantly higher than the levels currently recommended for the definition of clinically important perioperative myocardial injury [11].

Many aspects related to the prognostic value of Tn-hs are still debatable, especially in relation to the critical diagnostic threshold of Tn-hs for various patients and types of surgical intervention, such as perioperative myocardial injury in cardiac and noncardiac surgeries, CPB, and radiofrequency ablation procedures.

This study aimed to determine the relationship between the levels of highly sensitive cardiac troponin I and troponin T and the risk of cardiovascular failure within 24 h after heart surgery.

METHODS

Study design

A prospective observational single-center study was conducted.

Eligibility criteria

The *inclusion criteria* were patients of any sex and age >18 years old, admitted to the resuscitation and intensive care unit of the Federal Scientific and Clinical Center of the Federal Medical and Biological Agency of Russia, who underwent elective cardiac surgery.

The *exclusion criteria* were cases of emergency surgery and planned stay in the resuscitation and intensive care unit for <1 day.

Study conditions

The study was conducted at the Federal Scientific and Clinical Center of the Federal Medical and Biological Agency of Russia from October 6 to December 30, 2021.

Medical intervention

The patients (n=70) were distributed into two groups based on the development of cardiovascular insufficiency (CVI) in the first 12 h after surgery. CVI was determined by the need for catecholamine support after the main stage of the surgery and postoperative volume of dopamine >5 μg/kg per minute and/or norepinephrine >0.1 μg/kg per minute, and by a decrease in the left ventricular ejection fraction >10% of the preoperative level and/or new zones of hypokinesis according to echocardiography findings in the first 12 h after surgery.

The demographic indicators and presence of concomitant pathology were recorded. The clinical, laboratory, and instrumental data of patients admitted for elective surgical treatment for coronary heart disease or atrial fibrillation before surgery, at the end of surgery, at 6 h and 24 h after surgery, and at the time of hospital discharge were analyzed.

During the surgery and early postoperative period, the state of the cardiorespiratory system was followed up using B850 monitors (General Electric, USA). Electrocardiogram, invasive blood pressure, and blood oxygen saturation using a pulse oximeter were recorded. All patients underwent duplex examination of the lower-limb veins and a standard transthoracic echocardiographic examination using a Vivid 7 Pro Ultrasound Unit (General Electric).

Blood gas parameters, water–electrolyte state, and hemoglobin and hematocrit levels were asses-

sed by conventional laboratory methods using automatic gas analyzers Rapidlab (Bayer Health Care, Germany) and Stat Profile pHox Plus (Nova Biomedical, USA). Carbohydrate metabolism was assessed by the blood glucose level (glucose oxidase method). Clinical blood test was performed using an automatic RUBY hematology analyzer manufactured by Abbott Laboratories (USA). Plasma creatinine, total bilirubin, albumin, aspartate aminotransferase, alanine aminotransferase, and C-reactive protein concentrations were determined on an Architect 8000 Biochemical Analyzer (Abbott Laboratories).

Adipose metabolism was assessed based on the results of examination (development of subcutaneous fat, weight, and height) and body mass index. Diagnostics of the hemostasis system, including D-dimer parameters, was performed on an ACLTOP 300 CTS Automatic Coagulometric Analyzer (USA). Invasive and non-invasive artificial lung ventilation was performed using Engstrom CareStation (General Electric, USA) and Puritan Bennett 980 (Medtronic/Covidien, USA).

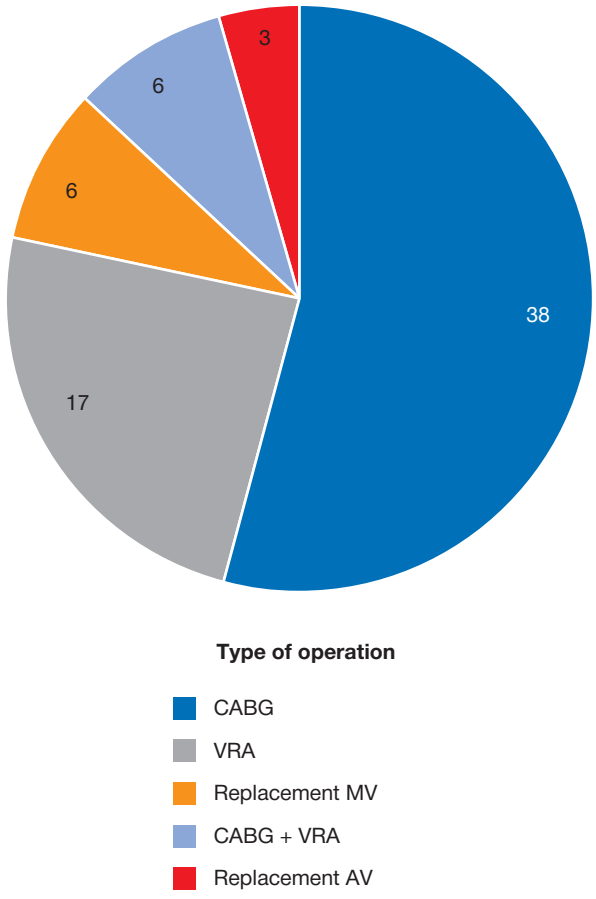

Fig. 1. Types of surgical interventions, *n*.
Note: CABG — coronary artery bypass grafting; VRA — videothoracoscopic radiofrequency ablation; MV — mitral valve; AV — aortic valve.

The TnI-hs levels were determined by the immunochemiluminescent method with the PATHFAST analyzer (Japan) using the PATHFAST hs-cTnI test systems (Japan). TnT-hs levels were measured by electrochemiluminescence on Cobas e411 Automated Immunochemical Analyzer (Roche Diagnostics, Switzerland) with a set of reagents troponin T hs-STAT Elecsys (Cobas e).

The perioperative hydrobalance, incidence of postoperative complications, duration of artificial lung ventilation, duration of hospitalization and stay in the resuscitation and intensive care unit, and mortality were assessed.

Ethical considerations

The study protocol was approved by the local ethics committee of the Federal Scientific and Clinical Center of the Federal Medical and Biological Agency of Russia (Minutes of Meeting No. 7b, dated 10/06/2021).

Statistical analysis

Data analysis was performed using the IBM SPSS Statistics for Windows version 28 (IBM Corp., Armonk, NY, USA). Quantitative data were presented as median (Me) and quartiles (25%; 75%), whereas categorical data were presented as absolute number (*n*) and proportion (%). The Mann–Whitney test was used to study differences in quantitative traits; for categorical attributes, χ^2 test with Yates correction and Fisher's exact test were used. Intragroup data comparisons were performed using the Wilcoxon *z*-test, and correlation analysis was performed using the Spearman test (rho). The discriminatory ability and significance of the predictive capabilities of risk factors for an adverse outcome and the sensitivity and specificity for each risk factor were assessed using the receiver operating characteristic analysis. When testing statistical hypotheses, the presence of statistical significance was established at $p < 0.05$.

RESULTS

Study participants

The study included 70 patients who underwent elective heart surgery, including 53 interventions with CPB use; in 17 cases, videothoracoscopic radiofrequency ablation was performed without CPB (Fig. 1). During the follow-up, the patients were distributed into groups according to the development of CVI in the first 12 h after surgery, where the non-CVI group included 57 patients the CVI group included 13 patients.

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When analyzing the preoperative state of the patients in both groups, no significant differences in age, sex, initial left ventricular ejection fraction, and range of comorbidity were found (Table 1). The risk of surgery was higher in the CVI group.

Primary results

In the analysis of the intraoperative characteristics of the patients in both groups, the CVI group had significantly longer CPB duration than the non-CVI group (Table 2). In patients who underwent video-assisted thoracoscopic radiofrequency ablation, CVI was not noted in the postoperative period.

A study of changes in troponins I and T in the CVI and non-CVI groups showed significantly higher levels of both troponins upon surgery completion and after 24 h in the CVI group (Fig. 2, Table 3).

Correlation analysis revealed a strong direct correlation between intraoperative TnI-hs and TnI-hs 6 h after surgery with the CPB duration (rho=0.531; p <0.001) and a moderate direct relationship with the duration of myocardial ischemia (rho=0.433; p=0.002).

Table 1

Characteristics of the patients before surgery

Parameter	Postoperative cardiovascular insufficiency		p
	Developed *n*=13	Undeveloped *n*=57	
Age, years	68 [62–71.5]	64 [58–68]	0.089
Male sex, *n* (%)	9 (69.23)	45 (78.95)	0.476
History of COVID-19, *n* (%)	2 (15.38)	14 (24.56)	0.718
Diabetes mellitus, *n* (%)	3 (23.08)	15 (26.32)	1.000
History of acute cerebrovascular insufficiency, *n* (%)	1 (7.69)	5 (8.77)	1.000
Chronic heart failure according to NYHA, *n* (%)	7 (53.85) Grade 2 in all cases	28 (49.12), including grade 1 in 1 case, grade 2 in 26 cases, and grade 3 in 1 case	0.759
Arterial hypertension, *n* (%)	12 (92.31)	50 (87.72)	0.639
Chronic kidney disease, *n* (%)	0	1	1.000
Ischemic heart disease before surgery, *n* (%)	11 (84.62)	41 (71.93)	0.345
Myocardial infarction more than 1 month before surgery, *n* (%)	3 (23.08)	18 (31.58)	0.741
Atrial fibrillation before surgery, *n* (%)	2 (15.38)	26 (45.61)	0.061
Left ventricular ejection fraction, %	59 [57–60]	58 [52–60]	0.467
EuroScore, score (%)	4.14 [3.76–4.73]	1.16 [1.1–1.3]	0.001

Note: NYHA (New York Heart Association) — Classification of chronic heart failure by clinical stages of the New York Association of Cardiologists; the scale EuroScore II (European System for Cardiac Operative Risk Evaluation) is designed to assess the risk of an unfavorable outcome of coronary bypass surgery. Here and in Table 2–5 the data are presented in the form of absolute values (percentages), medians (25th–75th percentiles). The value of "*p*" is calculated by the Mann–Whitney method.

Table 2

Intraoperative characteristics of the patients

Parameter	Postoperative cardiovascular insufficiency		p
	Developed *n*=13	Undeveloped *n*=57	
Surgery duration, hours	4 [3.6–5]	3.8 [3.2–4.6]	0.586
Cardiopulmonary bypass, min	106 [99–116]	94 [81–111]	**0.054**
Myocardial ischemia, min	65 [61–81]	59 [49–79]	0.121
Videothoracoscopic radiofrequency ablation without cardiopulmonary bypass, *n* (%)	0	17 (100)	-

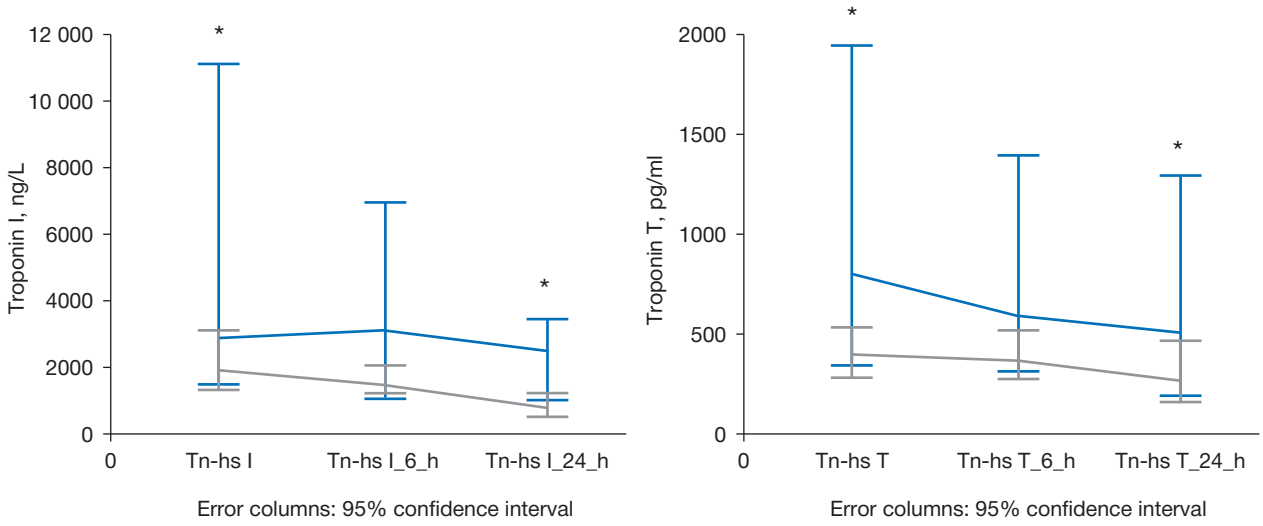

Fig. 2. Dynamics of troponins I and T in patients with/without heart failure after surgery. With heart failure blue line, without — grey line. Tn-hs — concentration of highly sensitive troponins.
Note: * p <0,05.

Table 3

Dynamics of the troponins I and T levels with or without heart failure after surgery

Parameter	Postoperative cardiovascular insufficiency		*p*
	Developed *n*=13	Undeveloped *n*=57	
Highly sensitive troponin I, ng/L			
Surgery	2886 [1522–10395]	1592 [761.5–3235]	0.011
After 6 h	3060 [1114–6424]	1464 [1094–2514.5]	0.162
After 24 h	2506 [1032–3203]	800 [500–1444]	0.005
Highly sensitive troponin T, pg/mL			
Surgery	713.4 [322.5–1659]	356.5 [265.05–588.35]	0.020
After 6 h	544.9 [266.35–1152.6]	360.4 [272.75–537.55]	0.205
After 24 h	500.4 [186.48–1155.18]	252.55 [144.98–477.53]	0.052

Moreover, a moderate direct correlation was found between intraoperative TnT-hs and TnT-hs 6 h after surgery with the duration of CPB (rho=0.468; p <0.001) and the duration of myocardial ischemia (rho=0.373; p=0.008).

Compared with the non-CVI group, the CVI group had greater blood loss volume, higher frequency of blood transfusions, more frequent use of vasopressors and inotropes, and a significantly longer duration of inotropic therapy (Table 4). The left ventricular ejection fraction in the CVI group was significantly lower than with the standard course. In this group, a higher level of blood lactate and C-reactive protein was noted after surgery, and postoperative organ complications were recorded more frequently. The duration of hospitalization in the intensive care unit was significantly longer in the CVI group, whereas the duration of hospital stay was not significantly different from that in the non-CVI group.

The volume of infusion therapy during the surgery and stay in the intensive care unit and the cumulative hemohydrobalance for surgical day 1 (24 h from the start of the surgery) differed statistically significantly between the CVI and non-CVI groups (Table 5).

The TnI-hs levels at the end of the surgery and 6 h after the surgery correlated directly moderately with the infusion volume for 24 h (rho=0.328; p=0.021). Thus, the TnI-hs level at the end of the surgery can be a predictor of CVI development, regardless of CPB use. The area under the curve was 0.727 [0.581–0.874], p=0.011, with a cut-off point of 1483 ng/L, sensitivity of 85%, and specificity of 46%.

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Table 4

Char acteristics of the postoperative period

Parameter	Postoperative cardiovascular insufficiency		*p*
	Developed *n*=13	Undeveloped *n*=57	
Volume of blood loss through drains on day 1, mL	400 [312.5–587.5]	300 [150–400]	0.020
Hemotransfusion, *n* (%)	5 (38.5)	4 (7.0)	0.009
Vasopressors, ≥1 day, *n* (%)	5 (38.5)	5 (8.8)	0.009
Inotropic support, 1 day, *n* (%)	0	27 (47.4)	0.001
Inotropic support, ≥2 days, *n* (%)	13 (100)	12 (21)	0.001
Left ventricular ejection fraction, %	47 [46–48]	56 [53–58]	0.001
Lactate max, mmol/L	2.5 [2.025–5.125]	2.2 [1.6–2.85]	0.025
C-reactive protein after surgery, mg/L	93 [86–172]	72.05 [47–105.75]	0.045
Gastrointestinal tract dysfunction, *n* (%)	3 (23)	0	0.005
Acute renal failure, *n* (%)	3 (23)	1 (1.8)	0.019
Acute cerebrovascular insufficiency, *n* (%)	1 (7.7)	0	0.186
Atrial fibrillation, *n* (%)	5 (38.5)	4 (7)	0.009
Acute respiratory failure, *n* (%)	8 (61.5)	2 (3.5)	0.001
Duration of stay in the resuscitation and intensive care unit, days	3.5 [3–5.5]	1 [1–2]	0.03
Duration of hospital stay, days	14.2 [7–17.5]	13.4 [8–16.5]	0.409
Lethal outcome, *n* (%)	1 (7.7)	0	0.186

Table 5

The volume of infusion therapy and cumulative hydrobalance on the first 24 hours

Parameter	Postoperative cardiovascular insufficiency		*p*
	Developed *n*=13	Undeveloped *n*=57	
Infusion in the operating room, mL	3200 [2565–3750]	2000 [1900–3675]	**0.034**
Infusion in the resuscitation and intensive care unit, mL	1950 [1125–2475]	1500 [1000–1900]	**0.050**
Hemohydrobalance for 24 h, mL	5765 [4720–6290]	3600 [3425–4605]	**0.006**

The TnI-hs level 24 h after the surgery may be a predictor of CVI during surgeries with CPB. The area under the curve was 0.735 [0.566–0.905], p=0.018, and the cut-off point was 825 ng/L, with sensitivity of 92% and specificity of 50%.

The TnI-hs level at the end of the surgery may be a predictor of the need for inotropic support for 2 days or more, regardless of CPB use during the surgery. The area under the curve was 0.785 [0.662–0.907], p=0.001, and the cut-off point was 1573 ng/L, with sensitivity of 88% and specificity of 55% (Fig. 3).

The TnI-hs level 6 h after surgery had an area under the curve of 0.713 [0.578–0.848], p=0.009, and the cut-off point was 1252 ng/L, with sensitivity of 82% and specificity of 43%.

The TnT-hs level 24 h after the surgery predicts the development of CVI during surgeries with CPB. The area under the curve was 0.698 [0.525–0.870], p=0.051, and the cut-off point was 178 pg/ml, with sensitivity of 92% and specificity of 41%.

DISCUSSION

The informational value of significant increases in Tn-hs levels after cardiac surgery for diagnostics of type 5 myocardial infarction still requires discussion. The fact that the myocardium is damaged during the main stage of the surgery is beyond doubt and is confirmed by a significant increase in Tn-hs levels. However, as clinical practice shows, the increase in troponin levels above the upper limit of normal for

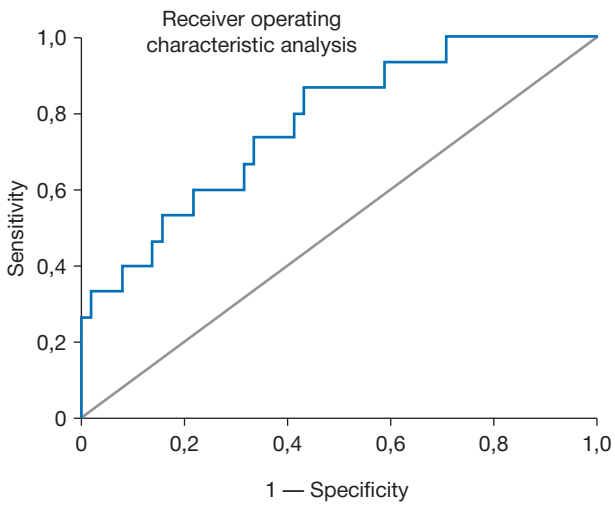

Fig. 3. Prediction of inotropic support for 2 days or longer according to the level of high-sensitivity Troponin I at the end of the surgery, regardless of its type.

noncardiosurgical case indicates severe myocardial damage, and it may not be accompanied by any signs of CVI in cardiac surgical cases [12]. Currently, for diagnostics of type 4 myocardial infarction, the troponin level is >5 times higher than the upper limit of normal, and for type 5 myocardial infarction, it is 10 times higher at a normal initial concentration of cardiac troponins [9]. Different authors offer their versions of "harmless" levels of troponin elevation after cardiac surgery and those levels at which it is worth taking diagnostic and treatment measures. In this study, we conducted a comparative assessment of troponin concentration with and without CVI. The TnI-hs levels in patients who underwent elective heart surgery without complications were 61 times higher than the upper limit of normal, whereas with CVI development, these were 111 times higher than the upper limit of normal, and the TnT-hs levels were 25.5 and 51 times higher, respectively.

Devereaux et al. [11] revealed a threshold of troponin I in coronary artery bypass grafting or aortic valve replacement on day 1 after surgery at 5670 ng/L (95% CI 1045–8260), i.e., 218 times the upper limit. On day 1 after other cardiac surgeries, the troponin I threshold reached 12.981 ng/L (95% CI 2673–16.591), i.e., increasing the upper limit by 499 times.

Threshold values for the prognosis of CVI after heart surgery (with/without CPB) is perhaps the level of TnI-hs of 1483 ng/L at the end of surgery and the TnT-hs level of 178 pg/mL 24 h after surgery with CPB. Elevated TnI-hs level predicts the need for catecholamine support and the probability of a complicated postoperative period earlier than TnT-hs. TnT-hs measurements added information about serious adverse events in all cardiac surgical cases to the EuroSCORE II scale, e.g., postoperative TnT-hs >500 pg/mL was a predictor of lethal outcomes only in combination with an elevated preoperative level of >14 pg/mL [13].

In the present study, we revealed the predictive ability of TnI-hs at the end of surgery and 6 and 24 h after surgery in determining the risk of CVI development and the need for inotropic support for 2 days or more. Similar results were obtained by Ammirati and Dobrev [3] in patients with suspected acute coronary syndrome, namely, an increase in TnI-hs was associated with cardiovascular complications, whereas TnT-hs was associated with the risk of death not associated with cardiovascular diseases. Based on the available data, TnT-hs is highly sensitive to acute coronary syndrome, and its specificity is low, whereas some noncardiac causes also increased the concentration of TnT-hs, which leads to overdiagnosis and possibly overtreatment [3]. In an earlier study, creatine phosphokinase MB (CPK-MB) showed better prognostic value than troponins I and T in low-risk patients undergoing elective heart surgery [14]. Gualandro et al. [12] reported TnI-hs as an independent predictor of 30-day mortality and annual mortality from all causes.

In the present study, in addition to trying to determine the "signal" level of troponin in cardiac surgery, we identified factors associated with an increase in troponin level and CVI development postoperatively, namely, CPB duration and perioperative infusion volume. Given the relationship between the rise in troponin levels and CPB duration, but not the period of myocardial ischemia, the systemic inflammatory response may influence the level of troponins. A factor in the increase in troponins was a significant positive perioperative hemohydrobalance. Many studies have reported the risk of large volumes of infusion therapy, especially in patients with capillary leak syndrome, which is always present to some extent during surgeries with CPB [15–19]. The mechanism of the damaging effect of volumetric loading is associated primarily with the development of hemodilution and multiorgan interstitial edema. We have revealed a direct moderate correlation of TnI-hs at the end of the surgery and 6 h after it with the cumulative hemohydrobalance for 24 h, which was 60% higher in the CVI group than in the group without complications.

Further studies are required to identify the possible causes of a multiple increase in troponins after cardiac

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surgery, and multicenter analytical studies are warranted to determine the diagnostic significance of Tn-hs in cardiac surgery.

Study limitation

This study has some limitations. It was non-randomized, conducted in one center, on a small sample of patients. The patients were admitted for elective surgery and had no severe concomitant pathology. No comparison was performed with other markers of myocardial injury such as CPK-MB, brain natriuretic peptide, and genome-expressed growth factor 2. The influence of the confounding effect (main error of the correlation analysis) on the results is also possible due to the retrospective nature of the distribution of patients into groups.

CONCLUSION

An increase in the levels of both TnT-hs and TnI-hs 25–60 times the upper limit of the norm and 51–111 times the upper limit of the norm in the case of CVI is typical for cardiac surgery with a standard clinical course. The interpretation of the clinical and diagnostic significance of such a pronounced increase in these markers is still difficult, as is the unification of a “safe” level of troponins after heart surgery.

Tn-Hs can be considered predictors of CVI development and duration of inotropic support. The increase in troponin concentration is affected by CPB duration and infusion therapy volume in the perioperative period, which may be pathophysiologically associated with a systemic inflammatory response and interstitial organ edema. Further study of Tn-hs within major controlled randomized trials involving patients undergoing cardiac surgery is necessary.

ADDITIONAL INFORMATION

Author contribution. *I.M. Yanovskaya* — collection of the clinical data; *I.A. Mandel* — methodological support, statistical processing, literature analysis, manuscript writing; *T.V. Klypa* — manuscript proofreading, general management of the treatment; *N.A. Kolyshkina* — laboratory diagnostics; *I.S. Marey* — collection of the clinical data; *A.S. Zotov* — collection of the clinical data; *V.P. Baklaushev* — manuscript proofreading. The authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

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Competing interests. The authors declare that they have no competing interests.

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