Biomarkers for Evaluation of Postoperative Myocardial Necrosis in Vascular Surgery

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Myocardial necrosis is one of the leading causes of postoperative adverse events in vascular surgery. Early diagnosis of mild and moderate myocardial necrosis may allow a better understanding of its pathophysiological basis as it is often associated with predisposing events and may occur in patients with no or mild coronary arteries disease. The current study aims to evaluate the role of the cardiac troponin I (cTnI) biomarker in diagnosing mild and moderate postoperative cardiac events, its prognostic value and dynamics related to patient's evolution. The authors retrospectively analysed 102 patients undergoing open repair surgery for abdominal aortic aneurysm between January 2010 - October 2015 at the Cardiovascular Diseases Institute (Iasi, Romania). All patients were followed-up for minimum 6 months postoperatively and the status of all patients was known at the end of study. During the study period, 12 patients (11.76%) deceased, and age (OR 2.3), postoperative cTnI (OR 1.5) and haemoglobin (OR 0.7) proved to be independent mortality risk factors. In conclusion, the current study proves that cTnI has a prognostic value for short, mid and long term mortality following abdominal aorta surgery and low elevations of cTnI should be included in the definition of the postoperative cardiac morbidity.

Keywords: cardiac troponin I, creatine kinase muscle-brain, biomarker, myocardial necrosis

Myocardial necrosis is one of the most important factors responsible for postoperative morbidity and mortality in vascular surgery [1]. Constraints of the operative period destabilize the balance between myocardial oxygen supply and demand, exposing the operated patient to myocardial necrosis. In fact, this complication is a continuum of severity, since it covers a wide spectrum of lesions, ranging from a limited necrosis affecting few myocardial cells to extended myocardial infarction that may determine a cardiogenic shock [2].

Current medical, interventional and surgical treatments of coronary arteries disease (CAD) led to a clear reduction of the incidence of major postoperative cardiac events in non-cardiac surgery. Postoperative cardiac morbidity is represented today mainly by mild to moderate myocardial necrosis and mortality rate decreased in elective vascular surgery.

Early diagnosis of mild and moderate myocardial necrosis may allow a better understanding of the pathophysiological mechanisms involved as these cardiac events are most often associated with predisposing events and may occur in patients with no CAD or with non significant coronary artery stenosis.

Troponin is a complex of three regulatory proteins (C, I and T) that is integral to skeletal and cardiac muscle contraction. Cardiac troponin I (cTnI) is present in the myocardium as a single isoform with molecular weight 23876 Da and it consists of 209 amino acid residues. Most cTnI released into the blood stream is phosphorylated. Currently, cTnI is considered a reliable marker of myocardial injury, more sensitive and more specific than the *golden marker* of last decades – creatine kinase muscle-brain (CK-MB) [3, 4].

The aim of the current study is to evaluate the contribution of the biomarker cTnI to the diagnosis of mild and moderate postoperative cardiac events, its prognostic value and to study its dynamics related to patient's evolution.

Experimental part

Material and methods

The authors retrospectively analysed 102 patients undergoing open repair surgery for abdominal aortic aneurysm (bypass) between 1st January 2010-1st October 2015 at the Cardiovascular Diseases Institute from Iasi, Romania. Serum samples were collected 2, 24, 48 and 72 hours postoperatively and cTnI was determined using PATHFAST Emergency Marker® (LSI Medience Corporation). PATHFAST is a chemiluminescent immunoassay analyser with an assay range of 0.019 – 50 ng/mL for cTnI.

Preoperative evaluation included systematic biological determinations, ECG, echocardiography, coronarography, CT angiography of the abdominal aorta.

Anaesthetic protocol differed according to physician. Postoperative monitoring consisted in ECG (with ST segment analysis), blood pressure, arterial O_2 saturation, diuresis. Extubation was performed in the ICU and sedation using propofol in continuous perfusion was continued postoperatively. Analgesia was also initiated in the ICU using various drugs according to pain severity. Hypovolemia was corrected with crystalloid or colloid solutions. In case of hemodynamic instability, vasopressor amines (adrenalin, dobutamin) were administered. cTnI, blood count, blood ionogram, arterial gas, haemostasis parameters were determined and ECG and chest X-ray were performed at the arrival in the ICU.

All patients received heparin (in the absence of contraindications) immediately after surgery, and antiplatelet therapy was initiated in day 1. Beta-blockers,

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statins and anti-ischemic drugs were administered according to cardiologist's indication.

All patients were followed-up for at least 6 months postoperatively and the status of all patients (alive or deceased) was known at the end of study (April 2016).

Perioperative data, cTnI values and follow-up data were statistically analysed using univariate and multivariate statistical tests (IBM SPSS Statistics 23 for Mac).

Results and discussions

In the current study there were included 102 patients that undergone emergency or elective open repair surgery for abdominal aortic aneurysm. Patients deceased in the first 24 hours were not included in the study.

Study group characteristics are detailed in table 1. Most patients suffered from arterial hypertension and CAD. 19 patients (18.63%) already benefited from coronary revascularisation (surgical or interventional) prior to current intervention. Concerning the preoperative treatment, 39 patients (38.24%) received beta blockers, and 51 patients (50%) statins.

During the study period, 12 patients (11.76%) deceased, 1 (0.98%) in the first 3 days after surgery, 2 (1.96%) within 30 days, 3 within 3 months (2.94%), 2 between 3 and 6 months (1.96%), 1 between 6 months and 12 months (0.96%) and 3 (2.94%) beyond 12 months.

Pre, intra and postoperative parameters were compared between survivors and deceased patients (table 2).

Age, congestive cardiac failure, chronic kidney disease, aortic cross clamp time, volemic correction, blood loss, ICU haemoglobin level, creatinine level, and cTnI level were associated with mortality at univariate analysis. Deceased patients were older, had both cardiac and renal failure, a more difficult surgery (prolonged aortic cross clamp time, increased blood loss and volemic correction), and postoperative myocardial necrosis as indicated by cTnI levels.

Previous CAD was not associated with mortality thus indicating that cTnI could be an independent predictor not necessarily indicating complicated CAD.

Odds ratio were calculated for cTnI and day 1 cTnI increased 3 times mortality rate (OR 3.135, 95% CI 1.168 – 8.584), and day 2 cTnI 6 times (OR 6.019, 95% CI 3.129-18.534).

Variables found significant at the univariate analysis were used for multivariate logistic regression and finally only age (OR 2.3, 95% CI 1.7-3.9), day 2 cTnI (OR 1.5 95% CI 0.9-2.2) and day 0 haemoglobin (OR 0.7 95% CI 0.5 – 1.1) proved to be independent mortality risk factors.

Aortic surgery involves long operative times, increased blood loss, and is associated to sudden volemic changes, potential emboli, coagulation disorders, intense operative stress. All these factors are a favourable terrain for the occurrence of cardiovascular complications and most important myocardial necrosis.

Positivity of cTnI defines myocardial necrosis and, if associated to ischemia signs, indicates myocardial infarction [5]. There are cases with markedly elevated cTnI and myocardial necrosis but no myocardial infarction. Myocardial necrosis defined by biomarker elevations is a blurred nosographic entity set to change with the progress of biomarker sensibility and threshold level. No causal concept is not, or should not, be contained in the term since it is based on a biological assay. Postoperatively, the

Table 1
STUDY GROUP CHARACTERISTICS

	No (%)
Sex (M:F)	92:10 (90.2%:9.8%)
Mean age	65.8 ±10.7 years
Arterial hypertension	58 (66.67%)
Cardiac failure	15 (14.71%)
CAD	54 (52.94%)
Chronic kidney disease	19 (14.71%)
Diabetes mellitus	14 (13.73%)
Previous stroke	4 (3.92%)
Emergency surgery	15 (14.71%)
Elective surgery	87 (85.29%)
Previous coronary revascularisation	19 (18.63%)
Type of surgery:	
Aorto-aortic bypass	29 (28.43%)
Aortic Bifemoral Bypass	62 (60.78%)
Other	11 (10.78%)

Table 2
PERIOPERATIVE PARAMETERS COMPARISON

	Survivors	Deceased	p
Sex M:F	80:10 (88.89%:11.11%)	12:0 (100%:0%)	n.s.
Age	65.4 ± 11.2 years	75.8 ± 6.3 years	0.0015
Emergency surgery	12 (13.33%)	3 (25%)	n.s.
Arterial hypertension	51 (56.67%)	7 (58.33%)	n.s.
Cardiac failure	11 (12.22%)	4 (33.33%)	0.0003
CAD	47 (52.22%)	7 (58.33%)	n.s.
Chronic kidney disease	15 (16.67%)	4 (33.33%)	0.006
Diabetes mellitus	12 (13.33%)	2 (16.67%)	n.s.
Aortic cross clamp time	64 ± 21.3 minutes	79 ± 33.4 minutes	0.0021
Volemic correction	4215 ± 1765 mL	5102 ± 1918 mL	0.027
Blood loss	1420 ± 1500 mL	2117 ± 1632 mL	0.035
Haemoglobin day 0	11 ± 1.5 g/dL	9.8 ± 1.2 g/dL	0.001
Haemoglobin day 1	12.1 ± 1.5 g/dL	10.9 ± 1.3 g/dL	0.012
Haemoglobin day 2	11.8 ±1.7 g/dL	11 ± 1.2 g/dL	0.017
Creatinine day 0	12.7 ± 6.6 mg/L	13.5 ± 3.2 mg/L	n.s.
Creatinine day 1	13.2 ± 8 mg/L	16.8 ± 6.5 mg/L	0.013
Creatinine day 2	13.9 ± 10.2 mg/L	19.6 ± 11.5 mg/L	0.027
cTnI day 0	3 patients (3.33%)	2 patients (16.67%)	0.0017
cTnI day 1	11 patients (12.22%)	4 patients (33.33%)	0.0003
cTnI day 2	10 patients (11.11%)	6 patients (50%)	0.0001

majority of cTnI elevation cases are associated with limited necrosis not always reflecting lesions of the coronary arteries but rather an imbalance between myocardial oxygen supply and demand [6].

Introduction of highly sensitive cardiac biomarkers extends this nosographic entity to minor lesions whose treatment has yet to be determined. Nevertheless, the medical reasoning is ultimately little changed since the onset of myocardial necrosis in the perioperative setting can only be an indicator of compensatory mechanisms failure.

The modern pathophysiological understanding of postoperative myocardial necrosis relies on a non-exclusive combination of one or more mechanisms leading to cell death [5, 7-9]:

- oronary arteries thrombosis complicating a pre-existent atherosclerotic plaque is the classical mechanism leading to myocardial infarction with ST segment elevation;

- coronary arteries stenosis characterized by progressive mechanical obstruction of native coronary arteries or intravascular stents;

- endothelial dysfunction involving both an inflammatory and a spastic component. Inflammation leads to atherosclerotic plaque instability thus inducing a hypercoagulability state and diminishing local nitric oxide (NO) production responsible for the spastic component. In this case, therapeutic agents addressing endothelial dysfunction (statins) are efficient;

- imbalance between myocardial oxygen supply and demand, although most often entangled in previous mechanisms, it can act apart and explain isolated myocardial necrosis. Postoperatively, this is the most important predisposing factor. Tachycardia caused by insufficient analgesia, surgical stress, hypothermia, and preoperative interruption of beta-blockers increases myocardial oxygen demand; arterial hypotension, anaemia, microvascular lesions, coronary spasm or thrombosis decrease myocardial oxygen supply. The relationship between haemoglobin levels and myocardial necrosis is largely dependent on the presence of coronary lesions and/or endothelial dysfunction, but also on the pre-operative haemoglobin level.

Postoperative myocardial necrosis is the result of one or more of these mechanisms themselves widely favoured by hemodynamic stress (blood pressure variations, arterial hypotension), arrhythmias (tachycardia) and metabolic factors (anemia, hypoxia) that may occur in the postoperative period.

According to the pathological mechanism responsible, the kinetics of cTnI elevation will be different. A prospective study performed on 1100 patients undergoing aortic surgery [10] identified 3 myocardial necrosis profiles. First profile (14% of cases) corresponds to an early myocardial necrosis in the first 6-48 h postoperatively. Speed of installation and high cTnI values can be explained by an acute thrombosis most often on a pre-existing stenosis [11, 12]. Second profile (21% of cases) is represented by late myocardial necrosis with moderately elevated cTnI values (0.2-1 ng/mL). In the third profile (64% of cases) elevation of cTnI spreads on 4 days postoperatively [10]. The release of cTnI fits in the continuum of myocardial injury and is explained by ischemia episodes. In our study cTnI levels were predictors of mortality independent of known CAD.

Other factors responsible for mortality at multivariate analysis were age and decreased haemoglobin levels. At unvariate analysis, volemic correction, blood loss, and chronic kidney disease registered significantly different values between the 2 groups, survivors and deceased and can lead to a haemoglobin level reduction through several mechanisms. Haemoglobin level if the final endpoint of these mechanisms than can alter myocardial perfusion and trigger necrosis.

cTnI is a very sensitive (100%) and specific (99%) biomarker for detecting minor myocardial cell destruction [13]. In postoperative setting, cTnI level was proved as an indicator of decreased survival on short, medium and long term [4, 7, 8, 14]. Landesberg et al. assessed the life expectancy of patients with CAD at 6 months and 2 years after general surgery, depending on the value of postoperative cTnI, and have shown that the life expectancy is impaired when postoperative cTnI exceeds the detection threshold [4]. Kim et al. [5] performed a study on 226 cases undergoing difficult vascular surgery and showed that patients with significant augmentation of cTnI levels (> 1.5 ng/mL) in the first 3 postoperative days have a 6 times higher mortality risk at 6 months.

Similar results showing the association between cTnI levels, length of ICU stay and mortality rates are found after aortic surgery [2] and in patients without known CAD hospitalized in intensive care unit (ICU) after major surgery [14-16].

From these studies, two opposing interpretations for elevated cTnI are identified: 1) postoperative myocardial cell destruction directly responsible for a decrease in patient's myocardial capital, which itself leads to long-term mortality, 2) the elevation of postoperative cTnI is a marker of pre-existing CAD the more severe the predisposing factors are minor.

In perioperative circumstances, occurrence of myocardial necrosis is a reflection of failure of coronary flow regulatory mechanisms induced by perioperative events. Diagnostic criteria for myocardial infarction being rarely accomplished in these special conditions, the apparent specificity of cTnI is inaccurate for the diagnosis of myocardial infarction. However, postoperative myocardial necrosis is most often a proof of chronic coronary insufficiency.

Myocardial necrosis is never insignificant postoperatively. Independently of any concept of false positive results, occurrence of myocardial necrosis imposes an etiological investigation, which even though it rarely leads to emergency angioplasty, allows adjustment of therapeutic management in order to maintain a balance between myocardial oxygen supply and demand and/or diagnosis of other diseases within a specific treatment (pulmonary embolism, myocarditis, severe cardiac failure, septic choc, acute renal failure, stroke). Early diagnosis of myocardial necrosis can avoid the onset of a late myocardial infarction secondary to prolonged ischemia.

Conclusions

The integration of the low elevations of cardio-specific biomarkers in the definition of the postoperative cardiac morbidity seems justified as long as they are associated with postoperative mortality. The current study proves that cTnI has a prognostic value for short, mid and long term mortality following abdominal aorta surgery.

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