Postoperative patterns and kinetics of cTnI, cTnT, CK-MB-activity and CK-activity after elective aortic valve replacement

Ulrich Tim Opfermann[a], Ali Ashgar Peivandi[a], Manfred Dahm[a], Hendrik Hilgenstock[a], Gerd Hafner[b], Anja Loos[c], Hellmut Oelert[a]

[a] Department of Cardiothoracic and Vascular Surgery, University Hospital of Mainz, Germany
[b] Institute of Clinical Chemistry, University of Mainz, Germany
[c] Institute of Medical Statistics and Documentation, University of Mainz, Germany

Summary

Objectives: The aim of this prospective study was to evaluate postoperative kinetics of four different biochemical ischaemic markers after elective aortic valve replacement (AVR). Additionally, pre-, peri- and postoperative data were analysed in order to identify factors with possible impact on the postoperative release of the selected enzymes.

Design: Forty patients (14 males, 26 females, aged 70 ± 11 years; EF = 54 ± 18% [mean ± SD]) undergoing elective AVR were prospectively included in this study. For all patients, serum concentrations of cTnI, cTnT, and serum activities of CK-MB and CK were measured preoperatively as well as 0, 6, 12, 24, 48 and 120 hours after removal of the aortic cross-clamp. Clinical data were assessed in all patients and correlated with postoperative enzyme patterns.

Results: There were no major complications. Preoperatively, all patients showed enzyme values in the normal range whereas the four ischaemic markers reached higher values postoperatively. cTnI reached its maximum values 24 hours (X_{Med} = 2.35 µg/L, 95%-CI [2.0, 3.3]) and cTnT 48 hours after the operation (X_{Med} = 0.239 µg/L, 95%-CI [0.174, 0.283]). Typical biphasic release kinetics could be demonstrated for cTnT. There was a high linear correlation between cTnI and cTnT at all sampling times. In contrast, a high linear correlation between cTnI, cTnT, and CK-MB-activity was only found 48 hours after aortic unclamping. cTnI nearly was in normal range 120 h postoperatively (X_{Med} = 0.5 µg/L, 95%-CI [0.2, 0.6]), whereas cTnT still remained pathologically elevated (X_{Med} = 0.223 µg/L, 95%-CI [0.137, 0.299]). No linear correlation was found between maximum values of the ischaemic markers postoperatively and age, gender, body surface area, ejection fraction, LV-hypertrophy, operating time, ECC time, time of cardiac arrest, lowest body temperature, perfusion pressure, cardioplegia volume, reperfusion time, postoperative septiformic circulatory instability, or ventilation time.

Conclusions: All four ischaemic markers showed individual peak characteristics and kinetics after uncomplicated AVR. In contrast to previous findings, aortic cross-clamping time had no detectable impact on postoperative peak patterns of any ischaemic marker.

Key words: aortic valve replacement, cardiac troponin I, cardiac troponin T

Introduction

Cardiac troponin I (cTnI) and troponin T (cTnT) have proven to be highly specific markers for cardiac myocyte damage [1–3]. They are part of the troponin complex and exist in three different isoforms, encoded by three different genes. Because of a N-terminal amino acid sequence of the cardiac troponins differing from skeletal fast and slow twitch isoforms [4], specific antibodies could be developed showing no cross-reactivity with skeletal troponin I [5]. However, there is evidence that cTnT is released in patients with renal failure needing haemodialysis, as well as in patients suffering from chronic myopathy or even acute muscular trauma such as in marathon running [6, 7]. cTnI does not seem to be expressed in diseased human skeletal muscle tissue [8].

The aim of this study was to evaluate specific time courses and patterns of cTnI, cTnT, CK-MB- and CK-activity in patients undergoing AVR. Additionally, pre- or perioperative variables with suspected influence on the postoperative kinetics of the four focused markers were analysed.

Methods

Patient selection

Fourty patients suffering from severe aortic valve stenosis/insufficiency scheduled for elective aortic valve replacement were consecutively included in the study. Patients who suffered from a myocardial infarction in the previous 8 weeks were excluded from the study, as well as patients with redo-cardiac operations, severe coronary artery disease, concomitant disease of other heart valves, or those patients requiring combined cardiac procedures. All patients preoperatively underwent control coronary angiography to ensure the absence of coronary artery disease. The patients were followed up for seven days after surgery.

Surgical procedure

The operative technique was similiar in all patients. AVR was accomplished via skin incision from the sternal notch to the xiphoid process followed by a complete median sternotomy. The ascending aorta and the right atrial appendage were cannulated for institution of ECC. Antegrade cardioplegia was achieved by administration of St. Thomas II-Cardioplegia in both coronary ostia. Additionaly, topical cooling of the heart was achieved by installation of ice water into the pericardial crave. All aortic valve prostheses were implanted in a supraannular position by using interrupted mattress sutures. Either a mechanical valve prosthesis (St. Jude Medical Inc, St. Paul, MN) or a Carpentier-Edwards PERIMOUNT pericardial valve (Baxter Healthcare Corp., Deerfield, IL) were implanted. After weaning from ECC and haemodynamic stabilisation, all patients were admitted to the ICU.

Duration of surgery, duration of ECC and aortic cross-clamp-time as well as type (mechanical/tissue valve) and size of aortic valve prosthesis were recorded.

Postoperative data collection

ECG

A 12-lead-ECG was recorded the day before surgery, postoperatively on arrival at the ICU, and on days 1, 2 and 5 after surgery. A new Q-wave was defined as the appearence of a Q-Wave ≥40 ms in at least two adjacent leads. Perioperative myocardial infarction was defined as either the appearence of a new Q-wave >40 ms in at least two adjacent leads, or an R-reduction >25% in at least two adjacent leads of the ECG.

Biochemical markers

Blood samples were drawn preoperatively, as well as 0, 6, 12, 24, 48, and 120 h after removal of the aortic cross-clamp.

CK-activity and *CK-MB-activity* were measured with the CK NAC from Boehringer Mannheim GmbH, Germany using the Hitachi 717 analyser (Boehringer Mannheim GmbH, Germany). *Cardiac troponin I (cTnI)* was measured using the Stratus Analyser II (Dade Diagnostica GmbH, Germany). As a reagent, a cTnI-fluorescence immunoassay (Dade Diagnostica GmbH, Germany) was used. *Cardiac troponin T (cTnT)* was measured using the ES 300 Analyser (Boehringer Mannheim GmbH, Germany). As a test reagent, we used the enzyme-immunoassay ELISA cTnT from Boehringer Mannheim GmbH, Germany.

Statistical analysis

All continuous variables are described in terms of summary statistics (n, median, first and third quartile [Q_1, Q_3], minimum and maximum). In the case of normality, mean and standard deviation are given instead of quartiles. The course of all enzyme activity is demonstrated by confidence intervals for median values at a local 95%-significance level (95%-CI). To account for non-normality, non-parametric statistical test procedures were used for all continuous variables. Spearman's rank correlation coefficient, including the corresponding test for independence, was calculated to describe and test associations between continuous variables. A p-value <0.05 was considered to be statistically significant. Statistical analysis was performed using SPSS® for Windows, Release 8.0.0 (SPSS Inc, Cary, NC, USA). Calculation of 95%-confidence intervals based on the median was done using SAS 6.12.® (SAS Institute, Cary, NC, USA).

Results

Preoperative data

Preoperatively, all 40 patients included in the study showed enzyme values of CK-activity, CK-MB-activity, cTnI, and cTnT within the normal range. Patient characteristics and frequency of risk factors and associated diseases are presented in table 1.

Operative data

There were no perioperative deaths. Thirteen Patients (32.5%) received a mechanical aortic valve (St. Jude Medical Inc, St. Paul, MN), and 27 patients (67.5%) received a Carpentier-Edwards PERIMOUNT pericardial valve (Baxter Healthcare Corp., Deerfield, IL). Perioperative data of all patients are presented in table 1.

Postoperative data

Postoperatively, the incidence of the loss of sinus rythm in the ECG was 7.5% (n = 3). There was no perioperative myocardial infarction marked by the occurence of new Q-waves, or significant R-reduction on the ECG. Three Patients (7.5%) developed a septiformic circulatory instability as marked by significantly higher doses of intravenous catecholamines (table 1).

Cardiac troponin I (cTnI)

Preoperatively, serum levels of cTnI were less than 0.1 µg/l in all patients. Postoperatively, cTnI increased significantly in all patients and reached its peak 24 h after removal of the aortic cross-clamp (X_{Med} = 2.35 µg/L, 95%-CI [2.0, 3.3]). Following 120 hours postoperatively, serum levels of cTnI decreased to nearly normal values (X_{Med} = 0.5 µg/L, 95%-CI [0.2, 0.6]). Figure 1 shows median postoperative concentration time courses and quartiles, 95%-confidence intervals based on the median are shown in table 1.

Preoperative data	
Age (years)	69.9 ± 10.8
Male/female (%)	14 (35%)/26 (65%)
Recent AMI (>8 weeks) (%)	3 (7.5%)
Left ventricular hypertrophy (%)	72.5
Left ventricular ejection fraction (%)	54.3 ± 17.7
Aortic valve stenosis/ regurtgitation/combined	11/2/27
Aortic valve area (cm²)	0.65 ± 0.18
Systolic pressure gradient (mm Hg)	75.9 ± 31.5
Intraoperative data	
Duration of surgery (min)	151 ± 32
Duration of ECC (min)	76 ± 16
Perfusion pressure (mm Hg)	65.2 ± 7.6
Cardioplegia volume (ml)	1800 ± 500 (1150–2900)*
Aortic cross-clamp-time (min)	51 ± 11
Reperfusion time (min)	24.3 ± 10.6
Size of aortic valve prosthesis (mm)	23.6 ± 2.1 (21–29)*
Mechanical/pericardial tissue valve	13 (32.5%)/27 (67.5%)
Postoperative data	
Mechanical ventilation time (min)	15.4 ± 8.7
Transient septiformic circulatory instability	4 (7.5%)

Cardiac troponin T (cTnT)

cTnT showed an early peak immediately after surgery, followed by a decrease, and reached its maximum value 48 hours after surgery (X_{Med} = 0.239 µg/L, 95%-CI [0.174, 0.283]). After 120 hours, cTnT-levels remained markedly elevated in all patients (X_{Med} = 0.223 µg/L, 95%-CI [0.137, 0.299]). Postoperative patterns, and 95%-confidence intervals based on the median are shown in figure 1 and table 2.

Creatine kinase-MB-activity

Serum levels of CK-MB-activity peaked immediately after surgery (X_{Med} = 41.45 U/L, 95%-CI [35.0, 44.8]). One hundred and twenty hours after aortic unclamping, serum levels had de-creased and were comparable to the preoperative values (X_{Med} = 10.15 U/L, 95%-CI [7.8, 11.5]. Figure 2 and table 2 demonstrate postoperative time courses and 95%-confidence limits based on the median.

CK-activity

CK-activity reached its maximum value 48 hours postoperatively (X_{Med} = 339.5 U/L).

Pre-, intra- and postoperative variables influencing postoperative enzyme peaks

None of the observed clinical data recorded in this study (gender, age, body surface area, left ventricular hypertrophy, ejection fraction) was found to have a statistically significant influence on postoperative peaks of the four ischemic markers. Furthermore, there was no significant correlation between intra- or postoperative data (duration of surgery, duration of ECC, perfusion pressure, cardioplegia volume, aortic cross-clamp-time, reperfusion time, need for inotropic support) and postoperative enzyme peaks.

Correlations between postoperative enzyme patterns and peak values

Postoperative values of cTnI and cTnT showed a high linear correlation at all sampling times (r_s = 0.859 postoperatively, 0.746 at 6 hours, 0.848 at 12 hours, 0.728 at 24 hours, 0.758 at 48 hours, and 0.662 at 120 hours, respectively) with a p-value <0.01. Between cTnI and CK-MB, a high linear correlation was only found postoperatively (r_s = 0.483, p <0.01) and 48 hours after removal of the aortic cross-clamp (r_s = 0.514, p <0.01).

A higher linear correlation was found between maximum postoperative values of cTnI and cTnT (r_s = 0.761, p <0.01) compared with maximum postoperative values of cTnT and CK-MB (r_s = 0.548, p <0.01). In contrast, there was no statistically significant correlation between maximum postoperative values of cTnI and CK-MB (r_s = 0.331, p = 0.037) and between cTnT and CK (r_s = 0.146, p = 0.369).

Figure 1

Postoperative median cTnI and cTnT serum concentration time courses. Vertical lines indicate 25%-quartile (Q1, inferior end of the line) and 75%-quartile (Q3, upper end of the line) of the median.
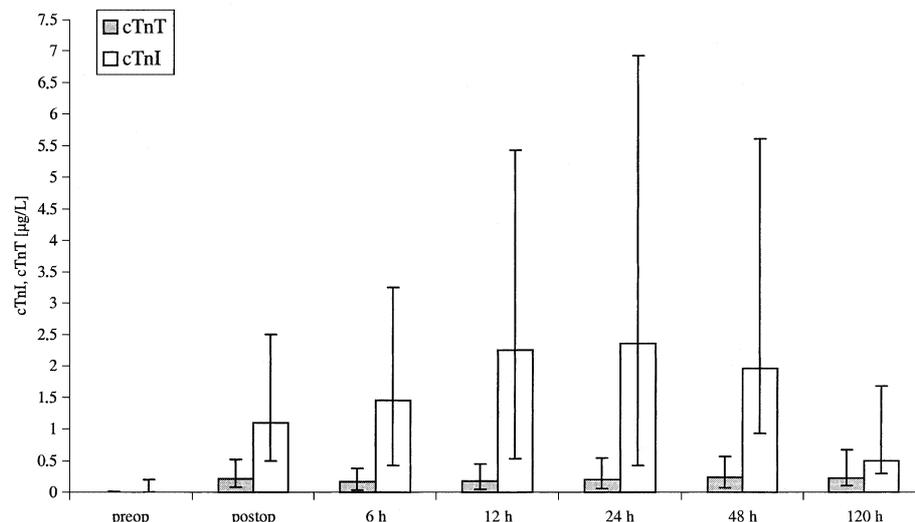
Table 2

95%-confidence limits based on the median for cTnI [µg/L], cTnT [µg/L], CK-MB-activity [U/L] and CK-activity [U/L].

	preop	postop	6 h	12 h	24 h	48 h	120 h
cTnI	0;0.1	0.7;1.2	1.2;1.7	1.8;2.6	2.0;3.3	1.1;2.4	0.2;0.6
cTnT	0;0	0.139;0.227	0.128;0.180	0.159;0.212	0.169;0.239	0.174;0.283	0.137;0.299
CK-MB	6.4;4.2	35.0;44.8	26.4;36.9	21.5;29.8	18.6;25.1	12.5;20.6	7.8;11.5
CK	43;65	144;191	174;230	192;275	237;391	180;371	46;81

Figure 2

Postoperative median time courses of CK-MB-activity and CK-activity. Vertical lines indicate 25%-quartile (Q1, inferior end of the line) and 75%-quartile (Q3, upper end of the line) of the median.
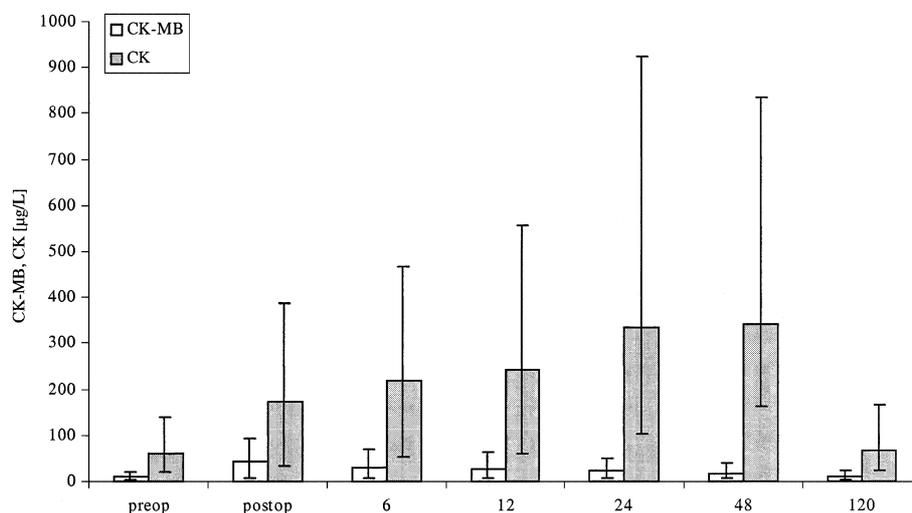
Discussion

In cardiac surgery, aortic valve replacement is an accepted routine procedure carrying a mortality of 1.1% in low-risk patients [9]. However, perioperative myocardial infarction (PMI) following cardiac surgery remains a challenging problem. The incidence of PMI has been reported to range from 3 to 35%, depending on the type of procedure and the diagnostic criteria for PMI [10, 11]. It is still controversial which diagnostic marker is the most sensitive to prove cardiac cell damage. The ECG has been the first instrument to diagnose major myocardial cell damage. However, postoperative Q-waves have been often shown to be transient after cardiac operations and to appear in a variety of conditions not related with myocardial injury, e.g. unmasking of old infarct areas [12]. Biochemical markers such as creatine kinase or isoenzyme creatine kinase-MB are more sensitive to minor cardiac cell damage, but are also expressed in skeletal muscle tissue. Serum levels of CK and CK-MB can be elevated in individuals without evidence of cardiac muscle ischaemia or infarction [13].

Troponin I (cTnI) and troponin T (cTnT) are, together with troponin C (cTnC) part of the troponin complex which regulates the calcium-mediated actin-myosin interaction [14]. CTnI and cTnT exist in three different isoforms uniquely expressed by three different genes in fast-twitch, slow-twitch and cardiac muscle tissue.

Both cTnI and cTnT carry N-terminal amino-acid sequences differing from its skeletal isoforms. Whereas cTnI has 31 additional N-terminal amino acid residues and differs in about 40% from its skeletal isoforms, cTnT differs only by 6 to 11 amino acid residues as well as showing only 10-30% dissimilarity in its primary structure when compared with its skeletal isoforms [15, 16]. There is, however, evidence that cTnT is reexpressed in regenerating, chronically injured skeletal mucle tissue. Elevated serum levels of cTnT have been detected in patients with Duchenne's muscular dystrophy, rhabdomyolysis, polymyositis, or end-stage renal disease with need for permanent haemodialysis [17, 18]

All patients enrolled in the reported study preoperatively had values of CK, CK-MB, cTnI, and cTnT in the normal range. The peri- and postoperative course was uneventful except of three patients with septiformic circulatory instability in the early postoperative period. Each ischaemic marker showed individual time courses and peak values. CK-MB was the marker to reach its earliest maximum values one hour after cross-clamp removal, followed by cTnI after 24 hours, and cTnT and CK 48 hours postoperatively. Additionally, cTnT serum values peaked a second time 120 hours postoperatively; this has been associated with an uneventful postoperative course [14].

Serum values of cTnT and cTnI showed a high linear correlation at all sampling times despite their different release kinetics [19], whereas statis-

tically significant correlation between cTnI, cTnT and CK-MB could be found only at one time point.

In contrast to previous studies [20–22], no statistically significant correlation was found between any pre- or perioperative variable (especially ACC) and postoperative peak values of any of the four markers. All patients enrolled in this study preoperatively underwent coronary angiography that ensured the absence of coronary artery disease. Besides myocardial ischaemia due to aortic cross-clamping, iatrogenic mechanical injury brought to myocardium by cannulation and insertion of the valve conduit could most likely be responsible for additional release of even highly specific markers.

Etievent et al. [20] measured postoperative serum levels of cTnI in 20 patients with calcified aortic valve stenosis undergoing aortic valve replacement. A statistically significant correlation between postoperative peak levels of cTnI six hours after surgery and ACC was found ($r_s = 0.6$; $p < 0.01$). The duration of cardiac arrest was slightly shorter than it was in our study and a different enzyme assay was used. Katus et al. [21] investigated postoperative cTnT-levels in 56 patients undergoing CABG (n = 47) or non-coronary cardiac procedures (AVR: n = 6; MVR: n = 1; patch closure of ASD: n = 2). A statistically significant correlation was found between ACC-time and postoperative cTnT-maximum peak levels at Day 1 and 4. However, the heterogeneity of the investigated cardiac surgery group makes comparison with our results impossible.

Eikvar et al. [22] investigated serum levels of cTnT in 116 patients undergoing different cardiac procedures requiring extracorporeal circulation and cardiac arrest. A small group of ten underwent isolated uncomplicated AVR with no electrocardiographic evidence of PMI. Serum levels of cTnT peaked 24 hours after operation and correlated with duration of ACC, which is in contrast to the results of our study.

Alyanakian et al. [23] evaluated 24 patients undergoing either isolated or combined valvular procedures or CABG (n = 17). Based on electrocardiographic, echocardiographic, or clinical findings (prolonged postoperative inotropic support), patients were divided into three groups with no, slight or proved evidence of PMI, and postoperative serum levels of cTnI were evaluated. A trend towards higher enzyme values of cTnI was found in patients with proved evidence of perioperative myocardial ischemia. However, no correlation could be observed between duration of cardiac arrest and postoperative peak levels of cTnI in the subset of 24 patients undergoing isolated AVR or consecutive AVR/MVR.

In conclusion, a specific release characteristics for each marker could be demonstrated for patients undergoing AVR with an uncomplicated peri- and postoperative course. CK-MB-activity had its peak directly after operation, followed by cTnI, cTnT, and CK-activity. CTnT showed a typical biphasic release pattern and remained pathologically elevated five days after operation. None of the perioperative variables had statistically significant impact on postoperative serum levels of the ischemic markers. Further studies will be needed to clearly identify perioperative risk factors for ischemic myocyte damage in patients undergoing AVR.

Limitations of the study

The major goal of the study was to describe postoperative patterns and kinetics of cTnI, cTnT, and the non-cardiospecific markers CK-MB and CK in a larger group of elective patients receiving aortic valve replacement. Because of the uncomplicated intra- and postoperative course of nearly all patients, it was possible to demonstrate the patterns of cTnI and cTnT as they might appear in the patient without major perioperative myocardial infarction. On the other hand, it was not possible to distinguish between patients with and without minor myocardial damage. The reason for this is the low sensitivity of the ECG for minor myocardial damage and the lack of invasive diagnostic methods such as myocardium scintigraphy, which may have made a differentiation between these patients possible. Finally, small interindividual differences in perioperative data made the identification of perioperative risk factors impossible.

Correspondence:
Ulrich Tim Opfermann
Department of Cardiothoracic and Vascular Surgery
University Hospital of Mainz
Langenbeckstrasse 1
D-55131 Mainz
e-mail: uli.opfermann@web.de

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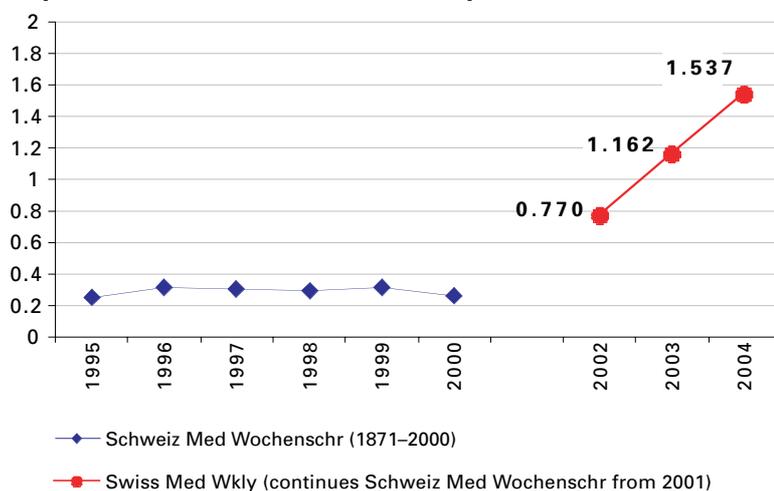- No page charges and attractive colour offprints at no extra cost

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