ARTYKUŁ ORYGINALNY / ORIGINAL ARTICLE

Postoperative serum troponin T concentration in patients undergoing aortic valve replacement does not predict early postoperative outcome

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Abstract

Background: The measurement of serum cardiac troponin T concentration (cTnT) after aortic valve replacement (AVR) provides the opportunity to assess the degree of myocardial damage and may have some prognostic value.

Aim: To determine whether elevated troponin level is related to patient outcome.

Methods: We investigated patient outcome and postoperative serum concentration of troponin T in 79 patients who underwent AVR. Serum levels of cTnT were measured within 24 h of AVR. We searched for the occurrence of subsequent adverse events i.e. requirement for intraaortic ballon pump (IABP) or inotropic support, prolonged Intensive Care Unit (ICU) stay, and in-hospital death.

Results: Serum concentration of cTnT after AVR increased significantly compared to the preoperative value. We found significant positive correlations between aortic cross-clamp time (r = 0.23, p = 0.04), cardiopulmonary bypass time (r = 0.4, p = 0.00029), duration of the surgery (r = 0.30, p = 0.008), and postoperative cTnT level. Three (4%) patients required IABP support, 37 (46%) patients required inotropic support, and 11 (14%) patients had a prolonged ICU stay (> 48 h). Thirty eight (48%) patients required either inotropic support or IABP insertion. At least one adverse event occurred in 44 (56%) patients. Median postoperative serum cTnT concentration was 0.31 ng/mL (interquartile range 0.23–0.60 ng/mL). We failed to find a statistically significant difference in postoperative cTnT level between patients with and without adverse events. According to multiple logistic regression analysis, the postoperative serum level of troponin T was not independently associated with adverse patient outcome. Diabetes mellitus, patient age and left ventricular ejection fraction below 50% were significant independent predictors of adverse events after AVR. The area under receiver operating curve (AUROC) for postoperative serum troponin T concentration as a determinant of various adverse outcomes was never significantly different from 0.50.

Conclusions: Serum cTnT concentration is frequently — if not universally — elevated after AVR. Serum level of troponin T measured on the first postoperative morning is a poor predictor of patient outcome after AVR and should not be relied on when planning postoperative care.

Key words: cardiac troponin T, aortic valve replacement, adverse events

Kardiol Pol 2013; 71, 12: 1237-1244

INTRODUCTION

Cardiac troponin I (cTnI) and troponin T (cTnT) are the most sensitive and specific biochemical markers of myocardial damage [1–3]. Elevation of cardiac troponin (cTn) is expected nearly universally after cardiac surgical procedures [4–7]. Release of cTn after cardiac surgery may be caused by mechanical, ischaemic or reperfusion injury of myocytes [8]. Elevation of serum cTn concentration is a prerequisite for the diagnosis

of myocardial infarction (MI). The Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction has recommended that a diagnosis of MI should be based on an increase of the cTn pattern in the appropriate clinical situation [9]. MI (Type 5) is defined as a 10-fold increase above the 99th percentile of upper reference limit (URL) of the cTn during the first 48 h following coronary artery bypass grafting (CABG) plus characteristic alterations in the electrocardiogra-

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phy, echography or angiography [8, 9]. The aforementioned threshold is higher than the previously endorsed value (a 5-fold increase above the 99th percentile of URL). Based on the data available in the literature, the new arbitrarily defined cutoff point seems to be more useful in clinical practice and significantly reduces the misclassification rate of false diagnosis of MI. Impaired outcome after CABG has been reported when postoperative concentration of cTn was elevated to the highest quartile of the measurements [4, 10, 11].

As noted above, Type 5 MI according to the new universal definition refers only to a patient after CABG, and not any other post cardiac surgical scenario, including aortic valve replacement (AVR). Patients submitted to AVR generally have a hypertrophic myocardium which makes myocardial protection during surgery more difficult; this may translate into higher release of cTn postoperatively.

Cardiac TnT concentration has been shown to be a useful predictive feature after CABG. If serum concentration of cTnT on the first postoperative morning after AVR correlates with adverse events, cTnT testing after AVR may add important prognostic information about requirements for more intensive monitoring in patients after operation, due to a higher risk of postoperative complications. We decided to investigate the release of cTnT after AVR to determine whether elevated troponin level is related to patient outcome.

Patients

Eighty nine patients underwent isolated AVR in the calendar year 2010 in the 2nd Department of Cardiac Surgery, Medical University of Silesia in Katowice. Seven patients underwent transcatheter aortic valve implantation, one patient suffered from MI shortly before admission to the hospital, and two patients died early postoperatively before blood samples had beentaken for the analysis of cTnT. They were excluded from the study. Thus, a total of 79 patients served as the study group.

The preoperative baseline demographic and intraoperative data for all 79 patients is detailed in Table 1. Aortic stenosis, either alone (35 patients; 44%) or with aortic insufficiency (37 patients; 47%), was the most common indication for AVR. Other indications included aortic insufficiency in four (5%) patients, and endocarditis in three (4%) patients.

METHODS Study plan

We investigated early outcomes and postoperative serum concentration of cTnT in all patients who underwent a first time isolated AVR procedure at the 2nd Department of Cardiac Surgery, Medical University of Silesia in Katowice within one calendar year. Serum cTnT level was measured by highly specific electrochemiluminescence immunoassay (ECLIA, Roche) on the first postoperative morning after AVR. We searched for the occurrence of subsequent adverse events: a requirement for intraaortic ballon pump (IABP) or inotropic support, pro-

Table 1. Demographic data for all 79 patients included in the study

study					
Preoperative data					
Age [years]	65 ± 13				
Male gender	50 (63%)				
Body surface area [m²]	1.91 ± 0.51				
LVEF < 50% 20 (26%)					
Sinus rhythm 69 (87%)					
NYHA class III–IV 34 (43%)					
CCS class III–IV 6 (8%)					
Creatinine [mg/dL] 0.9 ± 0.2					
GFR [mL/min]	88 ± 26				
GFR > 90 mL/min	33 (42%)				
GFR 60-89 mL/min	34 (44%)				
GFR 30-59 mL/min	10 (13%)				
GFR 15–29 mL/min	0 (0%)				
GFR < 15 mL/min (or dialysis)	1 (1%)				
Perioperative data					
Type of implanted prosthesis:					
Biological	50 (63%)				
Mechanical	29 (37%)				
Type of cardioplegia:					
Warm	8 (10%)				
Cold	70 (89%)				
Warm and cold	1 (1%)				
Aortic cross-clamp time [min] 52 ± 17					
Cardiopulmonary bypass time [min]	69 ± 24				
Duration of surgery [min]	140 ± 37				

LVEF — left ventricular ejection fraction; NYHA — New York Heart Association; CCS — Canadian Cardiovascular Society; GFR — glomerular filtration rate

longed Intensive Care Unit (ICU) stay, and death. We defined the following endpoints: (1) low cardiac output necessitating inotropic support (administration of norepinephrine and at least one another vasopressor: epinephrine, dobutamine, dopamine) or requirement for IABP; (2) prolonged ICU stay (more than routine 48 h); (3) the occurrence of any aforementioned complication (requirement for IABP or inotropic support or prolonged ICU stay); and (4) death.

Statistical analysis

Categorical variables were summarised as frequencies and percentages, and continuous variables as median with 1st and 3rd quartile. The pre- and postoperative cTnT levels were compared using Wilcoxon signed rank test. The comparison of postoperative cTnT levels between patients with and without adverse outcome was performed by two-tailed Mann-Whitney rank sum test. Spearman's rank correlation coefficient was

calculated to search for associations between the postoperative serum cTnT level and aortic cross-clamp time, cardiopulmonary bypass time and duration of surgery. We divided the patients into quartiles according to postoperative serum cTnT level and compared frequencies of adverse events between quartiles using contingency tables with χ^2 test with Yates correction for continuity. Receiver operating characteristics (ROC) analysis was used to assess the ability of postoperative serum cTnT level to predict the occurrence of various adverse events. Univariable analysis identified clinical and biochemical factors predictive of adverse events and was followed by a multiple logistic regression analysis utilising stepwise logistic regression to look for independent predictors of adverse events. Clinical characteristics such as age, gender, indications for valve replacement, glomerular filtration rate, stroke before AVR, diabetes mellitus before AVR, type of cardioplegia solution, cardiac arrhythmias, and left ventricular ejection fraction (LVEF) were entered into the model. These significant variables were then included in a multiple logistic regression model and removed using a backward stepwise process if their significance was not retained. Postoperative serum cTnT level (in quartiles) was always forced into the model to check if it was predictive of adverse outcome after adjustment for other above mentioned factors. A p value of 0.05 was considered statistically significant. The data was collected using Microsoft Access 2010, and statistical analysis was performed using Statistica (version 10), SPSS 14.0 and MedCalc statistical software.

RESULTS Serum troponin T level

Cardiac TnT concentration after AVR was significantly increased compared to TnT serum level before the AVR procedure (Fig. 1). Positive correlations were noticed be-

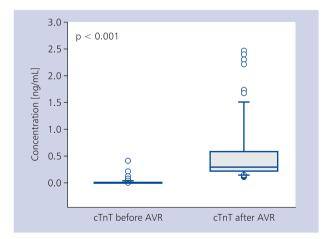


Figure 1. Serum cardiac troponin T (cTnT) concentrations before and after aortic valve replacement (AVR). Median with lower and upper quartiles are presented. Whiskers represent the 5th and the 95th percentile. Outliers are presented as dots. P from Wilcoxon signed rank test

Table 2. Frequency of adverse events

Requirement for IABP	3 (4%)
Inotropic support	37 (46%)
Requirement for IABP or inotropic support	38 (48%)
Prolonged ICU stay	11 (14%)
Requirement for IABP or inotropic support or prolonged ICU stay	44 (56%)

IABP — intraaortic balloon pump; ICU — intensive care unit

tween postoperative cTnT levels and aortic cross-clamp time (r = 0.23, p = 0.04), cardiopulmonary bypass time (r = 0.40, p = 0.0003), and the duration of surgery (r = 0.30, p = 0.008). Postoperative cTnT did not depend on cardioplegia used (median 0.29 ng/mL, 0.21–0.59 vs. 0.45 ng/mL, 0.25–0.64; p = 0.4 cold vs. warm, respectively), or on the initial valve pathology. Also, we failed to prove a correlation between postoperative cTnT and estimated glomerular filtration rate (r = -0.20, p = 0.08).

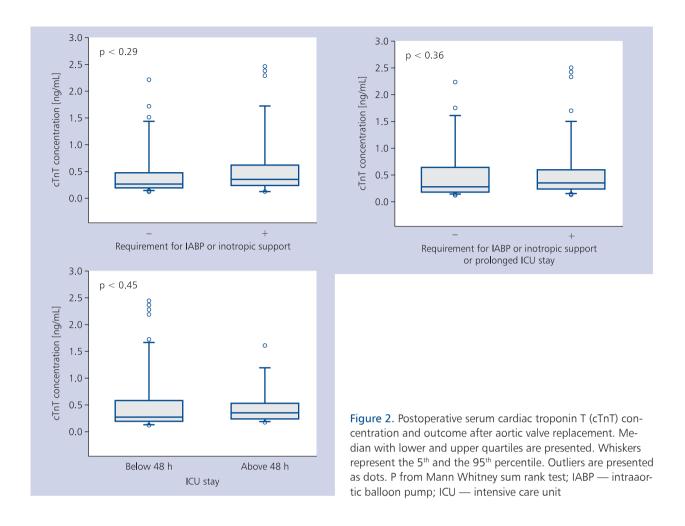
Adverse events

The frequency of postoperative adverse events is shown in Table 2. 56% of the patients had at least one of the adverse events. Serum cTnT concentration in patients with and without various adverse events is presented in Figure 2. We failed to find a statistically significant difference in postoperative cTnT level between patients with and without adverse events. However, among patients who had a complicated postoperative course, the median cTnT was slightly higher (0.35 [0.25–0.60] ng/mL vs. 0.27 [0.15–0.56] ng/mL; p=0.13). The frequency of adverse events in quartiles of serum cTnT concentration is presented in Figure 3. We failed to confirm an association between the frequency of adverse events and postoperative serum levels of cTnT.

To look for the ability of postoperative serum cTnT concentration to predict adverse outcome, we constructed ROC curves for cTnT level and the probability of suffering postoperative haemodynamic instability (requirement for IABP or inotropic support), prolonged ICU stay, or any adverse outcome. In no case was the area under curve different from 0.5 (Fig. 4).

Predictors of complications: multiple logistic regression analysis

We decided to investigate if other factors disguised the impact of cTnT for patient outcome. After risk adjustment, postoperative serum level of cTnT was not independently associated with requirement for IABP insertion or inotropic support or prolonged ICU stay in the final model. Significant independent predictors of adverse events after AVR included diabetes mellitus, age and LVEF < 50% (Table 3). The most significant independent predictor of prolonged ICU stay was reduced



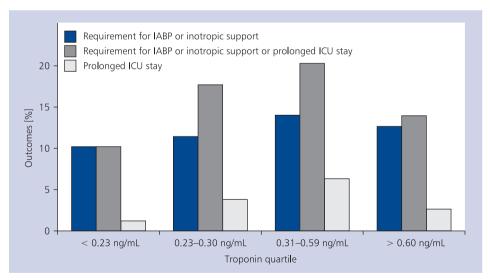


Figure 3. Association between serum troponin T level after aortic valve replacement and the frequency of adverse events; p=0.77 for requirement for intraaortic balloon pump (IABP) or inotropic support as per χ^2 test ($\chi^2=1.14$), p=0.45 for requirement for IABP or inotropic support or prolonged intensive care unit (ICU) stay as per χ^2 test ($\chi^2=2.66$), p=0.31 for prolonged ICU stay as per χ^2 test ($\chi^2=3.56$)

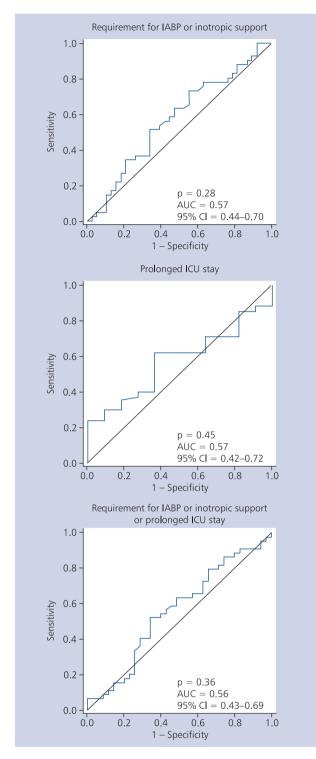


Figure 4. Area under receiver operating curve (AUC) for serum troponin T concentration for each adverse outcome; CI — confidence interval; IABP — intraaortic balloon pump; ICU — intensive care unit

LVEF (OR = 13.56, p < 0.001). The presence of diabetes mellitus significantly increased the risk of requiring inotropic support or IABP insertion (OR = 10.82, p = 0.03).

DISCUSSION

Several studies have shown that among the markers of myocardial necrosis, cTn level may be superior for risk prediction after cardiac surgery [10–13]. Postoperative cTnT level was above 0.23 ng/mL (> 16 times above 99th percentile of URL) in 75% of our study population (Fig. 3). In fact, in only six (8%) patients was the postoperative cTnT level lower than ten times the 99th percentile of URL (the cut-off value for Type 5 MI), even though there were no evident complications in many of them.

The results from our study are consistent with the findings from earlier studies, where higher ranges of cTnT, also among uncomplicated patients, have been noticed [7, 14–16]. Due to the fact that 95% of all the patients undergoing cardiac surgery have an elevated postoperative troponin level, clinical interpretation of postoperative troponin concentration is unclear and this remains a controversial but important issue [5–7, 12].

It is extremely important to differentiate situations when cTn is prognostic for follow-up from situations when elevated concentration of cTnT is transient. The release of cTn occurs first from the early appearing sarcoplasmatic pool and subsequently from the structural pool. Release from the latter is the reason for sustained elevations observed clinically and this is an indication of the irreversible breakdown of sarcomeric proteins. It can be used to argue that transient elevations of cTn can occur without cardiomyocyte death [17]. This argument has been confirmed by Abramov et al. [18], who confirmed that postoperative cTnT increase is associated with enhanced cell permeability rather than permanent cellular damage. Opfermann et al. [19] analysed kinetics of cTnT release after AVR. Cardiac TnT showed an early peak immediately after surgery, followed by a decrease, and reached its maximum value 48 h after surgery.

Therefore, a single measurement of cTnT concentration on the postoperative morning after AVR may be considered a limitation of our study. Perhaps, a late-occurring peak of cTnT release from sarcomeric pool would correlate better with the patient outcome. Obviously, serial measurements of cTn could of more value in predicting adverse events. However this needs time, and is therefore less suitable for planning postoperative care. Meanwhile we searched for a simple clinical tool to guide the therapy. This is a case after CABG, where early postoperative cTnT levels have been shown to correlate with outcome and can help to make appropriate treatment decisions at an early stage. This was confirmed by Soraas et al. [20]. In their study, cTnT concentration at 7 h was a predictor of all-cause mortality after CABG in a patient population.

Many investigators have tried to establish a cut-off point of cTnT concentration that could be a significant predictor of adverse events after CABG [4, 12, 19, 21]. Nesher et al. [4] established a cTnT value of $0.8\,\mu\text{g/L}$ as such a point, where the cTnT level has the most predictive power for major adverse cardiac events. Lehrke et al. [21] found TnT levels higher

Table 3. Predictors of adverse outcomes in multiple logistic regression analysis

	Р	Odds ratio	95% CI OR				
Requirement for IABP or inotropic support							
DM	0.03	10.82	1.28	91.68			
Troponin T	0.34	1.50	0.66	3.41			
Prolonged ICU stay							
LVEF < 50%	0.00	13.56	2.51	73.17			
Troponin T	0.70	0.75	0.17	3.28			
Requirement for IABP or inotropic support or prolonged ICU stay							
LVEF < 50%	0.05	3.72	1.03	13.49			
Age	0.03	1.54	1.05	2.27			
Troponin T	0.77	1.15	0.46	2.83			

95% CI OR — 95% confidence interval for odds ratio interpretation; DM — diabetes mellitus; IABP — intraaortic balloon pump; ICU — intensive care unit; LVEF — left ventricular ejection fraction

than a threshold of $0.6 \mu g/L$ to be a significant predictor of death. Median postoperative value of cTnT in our study was 0.31 (0.23–0.60) ng/mL. This is well below the threshold predictive for complications in previous studies [4, 12, 21]. Perhaps for that reason we didn't find any association between the cTnT measured on the first postoperative morning after AVR, and adverse events. On the other hand, a comparison with the other studies and trials to establish a definite cut-off value is difficult. Many previous analyses included a mixture of cardiac procedures, including valve replacement/repair and CABG or explored patients who had an acute MI within 30 days before the operation; such patients were excluded from our study cohort [4, 7, 12, 21, 22].

Interestingly, cTnT concentration evaluated in our study on the first day after AVR correlated with aortic cross-clamp time, cardiopulmonary bypass time and the duration of surgery, although the correlation coefficients were low. These results are consistent with some previous studies [22, 23].

It is well-established that cTnT concentration is strongly predictive of adverse events after CABG [4, 10, 11]. In contrast, we confirmed that the cTnT measurement adds no independent prognostic information after AVR. Because two patients died early postoperatively before blood samples had been taken for the analysis of cTnT, an absence of deaths remains the essential limitation of our study. Thus, we based our conclusions on relatively 'soft' endpoints. Study on a large group of patients might bring different conclusions.

In spite of this small group of patients, we were able to prove that some well known factors including age, diabetes mellitus or low LVEF affect the outcome. Meanwhile, post-operative cTnT concentration remained unrelated to outcome even after adjusting for other predictors, with ROC analysis confirming no predictive value. Therefore, bearing all these limitations in mind, we believe that even if some correlation of postoperative cTnT with the outcome existed and could be

shown in a larger study, it would be weak enough to preclude use of a single measurement of cTnT, the morning after AVR, to guide postoperative therapy.

CONCLUSIONS

Serum cTnT concentration is frequently — if not universally — elevated after AVR. We have shown that the serum level of cTnT measured on the first postoperative morning is a poor predictor of patient outcome after AVR and thus should not be relied on when planning postoperative care.

Conflict of interest: none declared

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Pooperacyjne stężenie troponiny T u pacjentów poddawanych wymianie zastawki aortalnej nie ma wartości prognostycznej dla wczesnego przebiegu pooperacyjnego

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Streszczenie

Wstęp: Pomiar stężenia sercowej troponiny T (TnT) w surowicy po wymianie zastawki aortalnej (AVR) umożliwia ocenę stopnia uszkodzenia mięśnia sercowego.

Cel: Celem badania było określenie, czy podniesione stężenie troponiny T ma związek z przebiegiem pooperacyjnym.

Metody: Badano przebieg pooperacyjny i stężenie TnT u 79 pacjentów, którzy zostali poddani AVR. Stężenie TnT mierzono w czasie 24 h od AVR. Oceniano wystąpienie następujących zdarzeń niepożądanych: zastosowanie kontrpulsacji wewnątrzaortalnej (IABP) albo wsparcia inotropowego, wydłużony pobyt na Oddziale Intensywnej Opieki Pooperacyjnej i zgon.

Wyniki: Stężenie TnT po AVR wzrosło znacząco w porównaniu z wartościami sprzed operacji. Stwierdzono występowanie pozytywnych korelacji istotnych statystycznie między: czasem zaklemowania aorty (r = 0,23; p = 0,04), czasem krążenia pozaustrojowego (r = 0,4; p = 0,00029), czasem trwania zabiegu operacyjnego (r = 0.30; p = 0,008) a pooperacyjnym stężeniem TnT. Trzech (4%) pacjentów wymagało wsparcia przy użyciu IABP, 37 (46%) chorych wymagało wsparcia inotropowego, a w przypadku 11 (14%) osób wydłużył się pobyt na Oddziale Intensywnej Opieki Pooperacyjnej (> 48 h). Wsparcia inotropowego lub zastosowania IABP wymagało 38 (48%) pacjentów. Co najmniej jedno zdarzenie niepożądane wystąpiło u 44 (56%) osób. Mediana wartości pooperacyjnego stężenia TnT wynosiła 0,31 ng/ml (zakres międzykwartylowy 0,23–0,60 ng/ml). Nie zaobserwowano różnicy istotnej statystycznie w pooperacyjnych wartościach stężenia TnT między pacjentami, u których stwierdzono i u których nie stwierdzono występowania zdarzeń niepożądanych. Analiza metodą wieloczynnikowej regresji logistycznej wykazała, że pooperacyjne stężenie TnT nie jest niezależnie związane z występowaniem zdarzeń niepożądanych u pacjentów. Cukrzyca, wiek i frakcja wyrzutowa lewej komory < 50% były znaczącymi niezależnymi predyktorami zdarzeń niepożądanych po AVR. Pole pod krzywą ROC (reciever operating characteristic) dla pooperacyjnego stężenia TnT jako wyznacznik zdarzeń niepożądanych nie było nigdy znacząco różne od 0,5.

Wnioski: Stężenie TnT w surowicy jest często — jeśli nie uniwersalnie — podniesione po AVR. Stężenie TnT mierzone pierwszego dnia po zabiegu jest słabym predyktorem przebiegu pooperacyjnego po AVR i nie powinno być wykorzystywane do planowania opieki pooperacyjnej w tej grupie pacjentów.

Słowa kluczowe: sercowa troponina T, wymiana zastawki aortalnej, zdarzenia niepożądane

Kardiol Pol 2013; 71, 12: 1237-1244