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Original article

High-sensitivity troponin T is a prognostic marker for patients with aortic stenosis after valve replacement surgery

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ABSTRACT

Background: Aortic stenosis (AS) is recognized as a cause of sudden cardiac death. Recently, the measurement of high-sensitivity troponin T (hs-TnT) has become possible. Several studies have clarified that hs-TnT is a marker to indicate mortality of cardiovascular diseases.
Objectives: To examine whether hs-TnT can be used as a prognostic marker to predict the operative outcome of AS.
Methods: We enrolled 60 patients with AS (mean age = 68.7 ± 9.6 years, male/female = 30/30). Cardiac catheterization and echocardiography were performed to evaluate the severity of AS. Aortic valve replacement surgery was performed in all patients. We defined major adverse cardiac events (MACE) as composite events of heart failure, fatal arrhythmia, and all causes of death.
Results: We followed up the patients for 922 ± 800 days. Mean left ventricular ejection fraction was 60.0 ± 1.8%. Mean aortic valve area was 0.61 ± 0.03 cm^2. MACE occurred in 11 patients (18%), including 5 sudden cardiac deaths. We divided the patients into three groups based on the percentile of the plasma levels of hs-TnT. Kaplan–Meier curve revealed a statistically significant difference in MACE rate among the groups (log-rank test, $\chi^2 = 13.0$, $p = 0.002$). We conducted a Cox proportional hazard analysis with a model including age, sex, estimated glomerular filtration rate, and hs-TnT tertile as explanatory variables to predict MACE. We found that hs-TnT tertile to be a significant factor to predict MACE (hazard ratio: 3.71, $p = 0.03$).
Conclusions: hs-TnT can be a prognostic marker for patients with AS after valve replacement surgery.

Introduction

Aortic stenosis (AS) is associated with a poor prognosis once symptoms ensue [1,2]. Commonly, a decision on aortic valve replacement for severe AS is based on symptoms such as angina, syncope, and heart failure. However, there is marked mismatch between the onset of symptoms and severity of valvular stenosis. It makes it difficult to decide optimal operative time and predict prognosis of AS patients. Therefore, the establishment of a simple and objective marker to predict the prognosis of this disorder is needed.

Aortic valve replacement (AVR) is the standard treatment for severe AS, alleviating symptoms and improving survival [3–5]. However, despite the recent development of AVR, critical cardiovascular events such as fatal arrhythmias and congestive heart failure (CHF) remain problematic. The prognosis of patients with AS who have undergone AVR has improved, but a number of major adverse cardiovascular events (MACE) especially cardiac sudden death occur even after AVR. Therefore, the detection and management of high-risk patients have potential importance.

Cardiac troponins are ideal biochemical markers for the detection of myocardial cell injury because of their high-sensitivity and specificity, especially as markers of acute coronary syndrome [6–10]. Minute elevations of cardiac troponin are reported to be related to cardiovascular risk factors, carotid artery plaque burden, and myocardial dysfunction [11]. Previously, undetectable cardiac troponin T concentrations have been documented to contain substantial diagnostic and prognostic information [12–14]. Recently, a new high-sensitivity cardiac troponin T (hs-TnT) assay that can detect low levels of circulating cardiac troponin T has emerged. The new method makes it possible to measure concentrations >10-fold lower than the lower limit of the traditional assay. The superior sensitivity of the new assay currently provides a method that can detect cardiac troponin T levels in most patients with stable [15] and subclinical cardiovascular disease [16].

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We hypothesized that preoperative plasma hs-TnT is related to cardiovascular events in patient with severe AS who have undergone AVR. In this study, we have measured plasma levels of hs-TnT and investigated their clinical significance in patients with AS.

Subjects and methods

Patients

Consecutive patients who underwent AVR for the treatment of severe AS in Jichi Medical University Hospital between July 2003 and October 2010 were included in this study. Before AVR, all patients were subjected to cardiac catheterization and echocardiography to estimate the left ventricular ejection fraction (LVEF), aortic valve area (AVA), and pressure gradient (PG) between the left ventricle and aorta. We confirmed whether they had coronary artery disease, aortic regurgitation, and mitral regurgitation by cardiac catheterization and echocardiography.

Prosthetic valves were implanted into the aortic valve according to the operators' decision. After the AVR, all patients were followed up regularly every 4–8 weeks. The primary endpoint was the occurrence of MACE defined as composite events of re-admission to the hospital for CHF, fatal arrhythmia, and all causes of death. Fatal arrhythmia included ventricular tachycardia, ventricular fibrillation, and complete atrioventricular block.

We excluded patients with coronary artery disease, acute coronary syndrome, severe aortic regurgitation, combined mitral valvular disease, acute renal failure, and inoperable patients. Coronary artery disease was defined as evidence of significant stenosis of the epicardial coronary artery on angiograms (over 75% stenosis in the artery and over 50% stenosis in left main trunk). LVEF was measured by a modified Simpson's method and left ventricular mass and relative wall thickness by standard formulas by echocardiography. High-sensitivity C-reactive protein (hs-CRP) was measured by latex nephelometry as described by Ledue et al. [17]. Other biochemical substances were determined by standard assays. Hypertension [18], dyslipidemia [19], and diabetes mellitus [20] were diagnosed according to the criteria described by guidelines for each disease. The Ethics Committee of Jichi Medical University approved the study protocol. All patients enrolled in this study provided informed consent.

Measurement of plasma high-sensitivity troponin T levels

Peripheral blood was taken from the patients before cardiac catheterization. Anti-coagulated samples were then centrifuged immediately at $1000 \times g$ (4 °C, 15 min) and stored at −80 °C until the assay. The concentration of hs-TnT in plasma was determined using electrochemiluminescence immunoassay kits according to the manufacturer's instructions (Roche Diagnostics GmbH, Mannheim, Germany). The test has an analytic range of 0.003–10 ng/mL, and the 99th percentile cutoff point has been reported as ≥0.014 ng/mL in healthy individuals [21].

Statistical analysis

All values are expressed as the mean ± SEM unless otherwise indicated. The significance of differences between the three groups was determined by a one-way analysis of variance for the parametric analysis and the Kruskal–Wallis test for the non-parametric analysis. The change in hemodynamic data before and after the operation was analyzed using Student's paired t test. Categorical variables were expressed as percentages and analyzed using the χ-square test or Fisher's exact test. Kaplan–Meier survival curve and Cox proportional hazard model analyses were conducted with computer software (SPSS version 16.0, Chicago, IL, USA). Values of $p < 0.05$ were considered significant.

Results

Basic characteristics of study subjects

We studied 60 patients (aged 68.7 ± 9.6 years), of whom 30 (50%) were male. The number of patients with chest pain, syncope, and heart failure was 28 (46.7%), 11 (18.3%), and 23 (38.3%), respectively. Table 1 shows the baseline characteristics of the subjects. The mean plasma hs-TnT level was higher than that in normal individuals (≥0.014 ng/mL).

In cardiac catheterization, the average catheter-derived peak-to-peak PG through the aortic valve, left ventricular end-diastolic volume index (LVEDVI), and left ventricular end-systolic volume index (LVESVI) were 77.4 ± 4.0 mmHg, 98.0 ± 5.3 mL/m^2, and 41.4 ± 4.0 mL/m^2, respectively. The left ventricular end-diastolic pressure and pulmonary capillary wedge pressure were 22.2 ± 1.04 mmHg and 11.9 ± 0.78 mmHg, respectively. Cardiac index was 3.09 ± 0.09 L/min/m^2. The comparison of echocardiographic findings (pre-operation and before discharge) revealed that the peak PG, mean systolic PG, and left ventricular mass index decreased significantly (from 96.2 ± 3.0 mmHg to 32.4 ± 1.4 mmHg, $p < 0.001$, from 58.8 ± 2.3 mmHg to 18.5 ± 1.1 mmHg, $p < 0.001$, and from 177.9 ± 8.3 g/m^2 to 160.5 ± 9.6 g/m^2, $p < 0.05$, respectively) with AVR. The left ventricular end-diastolic diameter reduced significantly (from 47.6 ± 0.99 mm to 43.5 ± 0.80 mm, $p < 0.001$), while interventricular septal thickness (IVST) and posterior wall thickness (PWT) did not change significantly (IVST: from 14.2 ± 0.34 mm to 14.1 ± 0.28 mm, $p = 0.79$; PWT: from 13.6 ± 0.28 mm to 13.3 ± 0.24 mm, $p = 0.28$). AVA increased significantly (from 0.61 ± 0.03 cm^2 to 1.13 ± 0.06 cm^2, $p < 0.001$) after the operation. LVEF did not change significantly (from 60.0 ± 1.8% to 62.3 ± 1.6%, $p = 0.18$).

In operative findings, bicuspid aortic valves were found in 34 patients (56.7%) and atherosclerotic changes in the remaining 26 patients (43.3%). Twenty-six (43.3%) patients received a mechanical prosthetic and 34 patients, a bioprosthetic valve replacement according to the operator's decision. Six (10%) patients underwent

Table 1
Baseline characteristics of the subjects.

Age (mean ± SD, years)	68.7 ± 9.6
Male patients (%)	30 (50)
Body mass index (kg/m^2)	23.2 ± 0.5
Hypertension (%)	40 (66.7)
Dyslipidemia (%)	18 (30.0)
Diabetes mellitus (%)	17 (28.3)
Smoking (%)	9 (15.0)
The peak-to-peak PG (mmHg)	77.4 ± 4.0
LVEDVI (mL/m^2)	98.0 ± 5.3
LVESVI (mL/m^2)	41.4 ± 4.0
LVEF (%)	60.0 ± 1.8
Aortic valve area (cm^2)	0.61 ± 0.03
The maximum PG (mmHg)	96.2 ± 3.0
The mean PG (mmHg)	58.8 ± 2.3
LVMI (g/m^2)	177.9 ± 8.3
hs-CRP (ng/mL)	2216 ± 686
eGFR (mL/min/1.73 m^2)	67.6 ± 3.1
hs-TnT (ng/mL)	0.110 ± 0.088

SD, standard deviation; PG, pressure gradient through aortic valve; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; hs-CRP, high-sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate; hs-TnT, high-sensitivity troponin T. The peak-to-peak PG, LVEDVI, and LVESVI were measured by cardiac catheterization. LVEF, aortic valve area, the maximum PG, the mean PG, and LVMI were measured by echocardiography.