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Original article

The prognostic value of high sensitivity cardiac troponin T in patients with congenital heart disease

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ABSTRACT

Background: Cardiac troponin T (cTnT) is a specific marker of myocardial injury that is elevated in patients with coronary artery disease or heart failure; it has been investigated as a prognostic marker. A highly sensitive, commercially available assay has been developed to detect cardiac troponin T (hs-cTnT). This study aimed to evaluate the clinical implications and prognostic value of hs-cTnT in patients with congenital heart disease (CHD).

Methods: We evaluated 122 consecutive patients hospitalized at our institution because of heart failure or scheduled cardiac catheterization. We measured the serum concentration of hs-cTnT at the time of hospitalization, and we prospectively followed-up all patients for 3 years and monitored rates of cardiovascular events (e.g. cardiac death, readmission owing to worsening of heart failure or arrhythmia, and reintervention) as endpoints.

Results: We classified the patients according to their hs-cTnT level into non-detectable (ND group, hs-cTnT $<$0.003 ng/mL), detectable normal (DN group, 0.003 ng/mL $\leq$hs-cTnT $<$0.014 ng/mL), or elevated (EL group, 0.014 ng/mL $\leq$hs-cTnT) group; 20 of 122 (16.4%) patients were in the EL group, in which 17 cardiovascular events occurred during follow-up. In the multivariate Cox proportional hazard analyses, the EL group [$p = 0.024$, hazard ratio (HR) 2.7, 95% confidence interval (CI) 1.1–5.8] was an independent significant predictor of cardiovascular events. A Kaplan–Meier curve revealed a high incidence of cardiovascular events in the EL group (EL vs ND log rank $p < 0.0001$, HR 7.6, 95% CI 3.2–20.0, EL vs DN log rank $p < 0.0001$, HR 4.1, 95% CI 2.1–7.8).

Conclusions: Because the EL group is more likely to have an adverse outcome, elevated hs-cTnT level can be a prognostic marker in patients with CHD.

Introduction

Cardiac troponin is a structural protein that forms part of the cardiac myofilament complex, and it consists of three different subtypes including troponin T, I, and C. Among them, troponin T and I are myocardial-specific proteins and useful as specific markers of myocardial injury [1,2]. Recently, a highly sensitive commercial assay for cTnT (hs-cTnT) became available; this assay detects low troponin concentrations and improves precision at the lower limit of detection. The serum concentration of hs-cTnT has been shown to be increased in patients with chronic heart failure, and to correlate with disease severity and prognosis in patients with normal heart structure [3]. Measurement of cardiac troponin T with the hs-cTnT assay may provide strong prognostic information in patients with acute coronary syndrome, stable coronary artery disease, heart failure, and the general population [4].

Multiple prognostic biomarkers have been identified in the field of congenital heart disease (CHD) including angiotensin, endothelin, norepinephrine, aldosterone, neurohormonal factors (i.e. renin), inflammatory markers [i.e. high-sensitivity C-reactive protein, high sensitivity tumor necrosis factor (TNF), soluble TNF receptor type 1 and 2, interleukin-6], and brain natriuretic peptide (BNP) [5]. However, due to the small number of published reports, the data on prognostic biomarkers in CHD remain limited. In this study, we evaluated the clinical implications and prognostic value of hs-cTnT in patients with CHD.

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Materials and methods

Patient inclusion

This was a prospective, single center study consisting of 122 consecutive patients with CHD hospitalized at our institution due to heart failure (decompensated symptoms with cardiomegaly and/or lung congestion on chest radiography) or scheduled cardiac catheterization between June 2011 and March 2013. This study included children (3 patients < 15 years, and 16 patients aged 15–20 years).

The cardiac diagnoses of the 122 patients with CHD are described below. Fourteen patients had single-ventricle physiology (5 morphological left ventricle, and 9 morphological right ventricle). Twelve patients in this group underwent palliative surgery ($n = 1$, aorto-pulmonary shunt; $n = 1$, pulmonary artery banding; $n = 2$, Glenn procedures; and $n = 8$, Fontan procedures), one patient underwent reparative surgery (ventricular septation), and the remaining patients did not undergo surgery. Twenty patients had tetralogy of Fallot (TOF), of whom 17 underwent reparative surgery. Fourteen patients had transposition of the great arteries (TGA), of whom three underwent atrial baffle surgery ($n = 2$, Mustard procedures; and $n = 1$, Senning procedure), 1 underwent a conventional Rastelli procedure, 3 underwent a Fontan operation, and the remaining 7 patients underwent a double-switch or Jatene operation. We excluded intellectually disabled patients such as those with Down syndrome and 22 q11.2 deletion syndrome, patients with ischemic heart disease, abnormal coronary perfusion, and/or coronary stenosis, or with severe renal dysfunction defined as serum creatinine level >2.0 mg/dL.

The study was performed in accordance with the Declaration of Helsinki. The study protocol was approved by the Institutional Medical Ethics Committee (Approval Certificate Number 3583). Written informed consent and informed assent for minors were obtained from all subjects.

Data collection

At the time of hospitalization, we collected blood samples and measured cardiac biomarkers, including serum hs-cTnT and BNP, renal functional parameters [blood urea nitrogen (BUN), creatinine (Cre), and estimated glomerular filtration rate (eGFR)], and evaluated echocardiography systolic functional parameters [fractional shortening (FS) of the systemic ventricle]. Patient characteristics including age, sex, congenital cardiac diagnosis, prior interventions, and New York Heart Association (NYHA) functional class were recorded. We followed-up all 122 patients for 3 years from the date of hospitalization. The primary outcome of this study was cardiovascular event (cardiac death, readmission owing to worsening heart failure or arrhythmia, and reintervention) during follow-up period.

Laboratory testing

We measured serum hs-cTnT using a commercial assay kit (SRL, Tokyo, Japan). In this assay, the lower limit of detection is 0.003 ng/mL, the 99th percentile cut-off point is 0.014 ng/mL, and the coefficient of variation is 10% at 0.013 ng/mL. We categorized all patients into three groups based on the serum concentration of hs-cTnT [non-detectable (ND), hs-cTnT <0.003 ng/mL; detectable normal (DN), 0.003 ≤hs-cTnT <0.014 ng/mL; elevated (EL), 0.014 ng/mL ≤hs-cTnT].

Statistical analysis

All continuous variables are presented as mean ± standard deviation (SD), or median and interquartile range (IQR) according to normal or non-normal distribution. Categorical variables are presented as frequencies and percentages. Statistical differences between groups were compared using the Chi-square test for categorical variables, and Student's t test or Wilcoxon and Kruskal–Wallis tests were used for continuous variables (given the deviation from the assumptions of normality of the underlying distribution). Correlations between hs-cTnT and BNP were evaluated using Spearman's p coefficient. A Kaplan–Meier analysis was performed on the cumulative rates of cardiovascular events, which were stratified into 3 groups based on hs-cTnT values (ND vs DN vs EL); the differences between survival curves were analyzed with a log rank test. Univariate and multivariate analyses were carried out using a Cox proportional hazards model to ascertain which variables were independently associated with the cardiovascular event. All statistical analyses were carried out with the JMP software, version 12.2 (SAS Institute, Cary, NC, USA). A p-value <0.05 was considered statistically significant.

Results

Baseline characteristics

The baseline characteristics of the study population are shown in Table 1. The median age was 32 (IQR 25.43) years and 51.6% of the patients were men. The majority of patients were in NYHA functional class I (40%) and II (46%); no patients were in class IV. Mean serum Cre level was 0.79 ± 0.26 mg/dL. hs-cTnT was above the detection limit of 0.003 ng/mL in 88 patients (72.1%), and 20 patients (16.4%) out of the entire study population were in the EL group (0.014 ≤hs-cTnT). The proportion of patients in the EL group tended to increase with advancing NYHA functional class (Table 1). The serum concentration of hs-cTnT was significantly correlated with BNP (Fig. 1).

The comparison of clinical characteristics between the three groups of patients in relation to the serum concentration of hs-cTnT (EL, DN, and ND) is shown in Table 2. EL patients were older, had a higher ratio of men, and higher levels of BNP, BUN, and Cre; and lower eGFR (Table 2).

The anatomical classification of cardiac anomalies into five groups and comparison of the level of hs-cTnT between groups is displayed in Fig. 2. Single right ventricle (SRV) anomaly was most common among patients in the EL group. In the TGA and corrected TGA groups, one patient each was in the EL group. One patient in the EL group underwent the Mustard procedure for TGA, and one underwent the conventional Rastelli procedure for corrected TGA. The results of the comparison of patients who underwent a Fontan procedure with those who did not in terms of proportion of EL patients are summarized in Fig. 3. The proportion of EL patients who underwent the Fontan procedure was lower than the proportion of DN and ND patients who underwent the Fontan procedure.

During the follow-up period, 49 cardiovascular events ($n = 6$, cardiac death; $n = 23$, readmission owing to heart failure; $n = 7$, arrhythmia; and $n = 13$, reintervention) were observed. A summary of the results of univariate and multivariate analyses using Cox proportional hazards regression model and the predictors of cardiovascular events using six variables, including biomarkers and hemodynamic variables (age, BNP, Cre, FS, NYHA class III, EL group) is given in Table 3. In the multivariate Cox proportional hazard regression analysis including BNP, Cre, FS, and EL group, only EL group [hazard ratio (HR) 2.7, 95% confidence interval (CI) 1.1–5.8, $p = 0.024$] was an independent predictor of a cardiovascular event. Kaplan–Meier curves for cardiovascular event according to the serum concentration of hs-cTnT are shown in Fig. 4 (comparison of three groups: ND vs DN vs EL). A Kaplan–Meier curve revealed a high incidence of cardiovascular events in the EL

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