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Original Article

Cardiac troponin T as a predictor of cardiac death in patients with left ventricular dysfunction

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ABSTRACT

Background: Cardiac troponin T (cTnT) has been reported to be associated with cardiac mortality.

In the present study, we evaluated the role of routine assessment of cTnT as a predictor of future cardiac death in patients with left ventricular (LV) dysfunction.

Methods: Patients who were eligible for prophylactic implantable cardioverter defibrillator (ICD) were included from cardiac catheterization database. Inclusion criteria were patients with LV ejection fraction of $\leq$ 35% and with New York Heart Association (NYHA) $\geq$ class II. Exclusion criteria were patients with acute coronary syndrome, ICD for secondary prevention, NYHA class IV, and lack of data. The final study patients were divided into the following three groups in accordance with two quartile points of serum cTnT levels: low cTnT, intermediate cTnT, and high cTnT groups. The primary endpoint of this study was cardiac death.

Results: A total of 70 patients were included (mean age, 62 $\pm$ 13 years; male individuals, 56; ischemic, 36; and non-ischemic, 34). During the observation period of 2.2 years, cardiac death was observed in 17 patients (fatal arrhythmic event, 9; heart failure, 7; myocardial infarction, 1). In the Kaplan–Meier analysis, the high cTnT group showed the highest risk among all the groups ($p < 0.001$). Even in sub-analyses for ischemic and non-ischemic patients, the results were the same, and the high cTnT group showed the highest event rate ($p < 0.05$). In contrast, no cardiac death was observed in the low cTnT group.

Conclusion: The cTnT levels in a stable state were associated with cardiac death in patients with LV dysfunction, even in those with non-ischemic diseases.

1. Introduction

Patients with left ventricular (LV) dysfunction have been shown to be at risk of cardiac death [1,2]. Many mega-trials have demonstrated a significant reduction in the risk of sudden cardiac death with an implantable cardioverter defibrillator (ICD) among patients with LV dysfunction [LV ejection fraction (LVEF), < 35%] [3–6]. Therefore, the European and American guidelines recommend prophylactic use of ICDs as a class I indication in patients with symptomatic heart failure and low LVEF, even without preceding fatal arrhythmic events [1,2,7,8]. Japanese guidelines have recommended prophylactic ICD implantation in patients with LV dysfunction as a class I or IIa indication [7]. However, evidence for the benefit of prophylactic ICD is much stronger among patients with ischemic heart disease (IHD) than among those with non-IHD. Køber L et al. [9] reported that prophylactic ICD implantation was not associated with improvement of mortality with respect to death from any cause in patients with non-IHD heart failure. Therefore, practical risk stratification is important to make accurate decisions on the prophylactic use of ICD, especially in patients with LV dysfunction due to non-IHD. Elevation of serum cardiac troponin T (cTnT), a sensitive biomarker of myocardial injury, has been reported to be associated with poor long-term prognosis in patients with LV dysfunction in the absence of any obvious myocardial ischemia [10]. However, the usefulness of routine assessment of cTnT in patients with LV dysfunction in a stable state has not been evaluated. In the present study, we evaluated clinical

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outcomes of patients with LV dysfunction who were eligible for prophylactic ICD and assessed the role of cTnT measurement as a predictor of future cardiac events in such a population.

2. Material and methods

2.1. Study population

This single-institution retrospective observational study used patient data from the cardiac catheterization database of Kitasato University Hospital. We assessed 2500 patients who underwent cardiac catheterization between 2010 and 2013. The inclusion criteria were as follows: (1) age of $\geq$20 years (male or female gender), (2) cardiac catheterization performed between 2010 and 2013 in our institution, (3) LV dysfunction of $<$35%, (4) New York Heart Association (NYHA) $\geq$class II (because this study was designed to evaluate future cardiac events in patients with LV dysfunction and moderate symptomatic heart failure who were eligible for prophylactic ICDs), and (5) presence of written informed consent. The exclusion criteria were as follows: (1) acute coronary syndrome, (2) ICDs for secondary prevention, (3) NYHA class IV, and (4) lack of clinical data including cTnT. LVEF was examined with transthoracic echocardiography using the modified Simpson method (Aplio500, TOSHIBA, Tochigi, Japan). IHD was diagnosed according to the presence of $>$75% stenosis of at least one of the three major coronary arteries or a documented history of myocardial infarction. Other cardiac diseases were diagnosed according to the findings of cardiac catheterization, echocardiography, and/or myocardial biopsy. Clinical data, such as medical history, physical examination findings, electrocardiogram findings, and blood test results, were obtained in the stable state of each underlying heart disease. We defined stable state as a condition without any changes in symptoms or heart condition in each patient at least more than a month after or before being hospitalized. All of the laboratory data, including cTnT, were obtained from outpatients who visited for regular medical check-up.

2.2. Grouping and data comparison

Patients were divided into the following three groups according to serum cTnT levels using the 1st and 3rd quartile points: low cTnT, intermediate cTnT, and high cTnT groups. Various clinical parameters and future cardiac events were compared among these three groups.

2.3. Evaluation of cardiac events

The primary outcome of this study was cardiac death. The causes of cardiac death were classified into fatal arrhythmic events, exacerbation of heart failure, and myocardial infarction. A fatal arrhythmic event was defined as the composite of sudden cardiac death or documentation of life-threatening arrhythmia.

2.4. Statistical analysis

The baseline characteristics were compared among the three groups using analysis of variance (ANOVA) with a Tukey-HSD post hoc test for continuous data and the Pearson's chi-square test for categorical data, respectively. Mortality levels in the three groups with different levels of serum troponin T were evaluated using Kaplan–Meier survival analysis and the log-rank test. Association between troponin T levels and mortality was also analyzed in each group using the multivariate Cox proportional hazard model, and the hazard ratios (HRs) and 95% confidence intervals (95% CIs) were determined. A p-value of $<$0.05 was considered statistically significant. All statistical analyses were performed using the JMP 11 (SAS Institute Inc., Cary, NC, USA) statistical software.

3. Results

3.1. Baseline characteristics

A total of 105 patients met the inclusion criteria. Of these patients, 35 met the exclusion criteria (6 had acute coronary syndrome, 10 received an ICD for secondary prevention, one had NYHA IV, and 18 did not have sufficient clinical data). Finally, the remaining 70 patients were selected as the follow-up population with LV dysfunction and moderate heart failure symptoms.

Table 1 shows the baseline characteristics of all patients and the three subgroups with different levels of serum cTnT. The low cTnT group ($\leq$0.006 ng/ml) included 16 patients, intermediate cTnT group (0.006–0.04 ng/ml) included 36 patients, and high cTnT group ($>$0.04 ng/ml) included 18 patients. In the overall population, the mean patient age was 62 years, and the male:female ratio was 56:34. IHD and non-IHD were the underlying heart diseases in 36 and 34 patients, respectively. Non-IHD included idiopathic dilated cardiomyopathy (n=28), cardiac sarcoidosis (n=4), valvular heart disease (n=1), and hypertrophic cardiomyopathy (n=1). There were no significant differences in serum cTnT levels in both ischemic and non-ischemic patients (p=0.3919, data not shown). In the high cTnT group, 16 of 18 patients had NYHA class III. The prevalence of diabetes and renal failure with dialysis history was higher in the high cTnT group than in the other groups. A defibrillation device was prophylactically implanted in 16 (22.8%) patients, and all of these devices were cardiac resynchronization therapy defibrillator (CRT-D) devices. There were no differences in the parameters of electrocardiography among the three groups. With regard to laboratory data, serum blood urea nitrogen, creatinine, and sodium levels were higher in the high cTnT group than in the other two groups; however, the brain natriuretic peptide level did not show any difference. With regard to baseline medications, the use of beta-blockers was lower in the high cTnT group than in the other two groups.

3.2. Long-term follow-up and prognosis

The follow-up period was 38.2 $\pm$ 20.5 months. Cardiac death was observed in 17 of 70 patients (21.4%; incidence rate, 6.8 per 100 person-years). Of the 17 patients, death was due to fatal arrhythmia in 9 (12.9%, SCD in 4, ventricular tachycardia (VT)/ventricular fivrillation (VF) post cardio pulmonary arrest in 5 patients), heart failure in 7 (10.0%), including two with CRT-D, and myocardial infarction in 1 (1.4%). In contrast, appropriate therapy for VT/VF was delivered in 2 of 16 patients with CRT-D implantation, in whom a sudden cardiac death was prevented owing to appropriate therapy with implanted devices.

Table 2 shows the incidence of cardiac death in the total population and the three groups stratified according to cTnT levels. The high cTnT group exhibited the highest incidence of cardiac death events ($p<0.001$). In this group, 13 of the 17 cardiac deaths were observed. The remaining 4 events were observed in the intermediate cTnT group, and all were caused by fatal arrhythmia. In contrast, cardiac death was not observed in the low cTnT group.

Fig. 1 shows Kaplan–Meier estimates in the three groups. Panel A exhibits the results of all patients. The event-free rate was lower in the high cTnT group than in the other two groups ($p<0.001$). Panels B and C show similar data for the IHD and non-IHD subgroups, respectively. Interestingly, in the IHD subgroup, cardiac death was observed only in the high cTnT group and not in the other two groups ($p<0.05$; Fig. 1B). In contrast, in the non-IHD