Prognostic Role of High-Sensitivity Cardiac Troponin T in Patients With Nonischemic Dilated Cardiomyopathy

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Background: Cardiac troponin T (cTnT) is a useful biomarker in patients with chronic heart failure (CHF). However, its clinical use is limited by the low sensitivity of the conventional commercial assay system. Recently, a highly sensitive cTnT (hs-cTnT) assay has become commercially available.

Methods and Results: To compare the prognostic value of conventional cTnT and hs-cTnT in patients with nonischemic dilated cardiomyopathy (DCM), hemodynamic parameters and the serum levels of conventional cTnT, hs-cTnT and brain natriuretic peptide (BNP) were measured in 85 consecutive CHF patients with non-ischemic DCM and then these patients were followed for a mean of 4.1 years. During long-term follow up, there were 20 cardiac deaths. In 85 DCM patients, conventional cTnT was elevated (≥0.03 ng/ml) in 4 patients (5%) and hs-cTnT was elevated (≥0.01 ng/ml) in 46 patients (54%). In non-survivors (n=20), conventional cTnT was elevated (≥0.03 ng/ml) in 2 patients (2%) and hs-cTnT was elevated (≥0.01 ng/ml) in 17 patients (85%). In the stepwise multivariate analyses, a high plasma level of BNP (P=0.002), low left ventricular ejection fraction (<30%, P=0.012) and high hs-cTnT (≥0.01 ng/ml, P=0.006) were independent significant prognostic predictors, but conventional cTnT (≥0.03 ng/ml) was not.

Conclusions: The findings of the present study indicated that a high serum concentration of hs-cTnT is a useful prognostic predictor that is independent of LVEF or BNP in CHF patients with non-ischemic DCM, suggesting that an increased hs-cTnT concentration sensitively reflects ongoing myocardial damage. (Circ J 2011; 75: 656–661)

Key Words: Brain natriuretic peptide; Heart failure; High-sensitivity cardiac troponin T; Prognosis

The plasma level of brain natriuretic peptide (BNP), is a well-established biomarker of ventricular wall stress in patients with chronic heart failure (CHF).1-4 Cardiac troponins, such as cardiac troponin T (cTnT) and cTnI as markers of myocardial injury,5-6 are also important and useful in these patients.7-12 However, compared with BNP, the clinical use of the serum levels of cTnT has limitations because of the low sensitivity of the assay system.13 Indeed, as recommended in the recent guideline for biomarker evaluation, optimal precision (the coefficient of variation (CV) at the 99th percentile upper reference limit for assay should be defined as ≤10%) and reliable precision allows for more sensitive assays.14 Recently, a highly sensitive commercial assay of cTnT became available and in the present study we evaluated the prognostic value of cTnT using a conventional commercial assay, the high-sensitivity-cTnT (hs-cTnT) and BNP in CHF patients with nonischemic dilated cardiomyopathy (DCM).

Methods

Patients

The subjects were 85 consecutive symptomatic CHF patients (left ventricular ejection fraction (LVEF) <45%) with a non-ischemic DCM etiology diagnosed from 1999 to 2008.15,16 The diagnosis of DCM was based on patient history, physical examination, electrocardiography, chest radiology, echocardiography, left ventriculography coronary angiography and endomyocardial biopsy. Endomyocardial biopsies were obtained to rule out secondary cardiomyopathies caused by viral or other infectious myocarditis, sarcoidosis, amyloidosis or other metabolic heart disease. Patients with high creatinine level (≥2.0 mg/dl) were excluded. Informed consent was given by all patients before participation in the study, and the proto-
We measured serum concentrations of cTnT using a commercial kit (4th generation Elecsys Troponin T immunoassay; Roche Diagnostics, Switzerland). In this assay, the lower limit of detection is 0.001 ng/ml, the lowest concentration at which the CV is <10% was 0.03 ng/ml, and the intra- and interassay CVs were 3.5% (n=4) and 4.2% (n=4), respectively in a sample with a cTnT concentration of 0.01 ng/ml or higher. We also measured serum hs-cTnT using a commercial assay kit (Roche Diagnostics and Kyowa Medex (Japan)). In this assay, the lower limit of detection is 0.001 ng/ml, the lowest concentration at which the CV is <10% was 0.01 ng/ml, and the intra- and interassay CVs were 3.5% (n=4) and 4.2% (n=4), respectively in a sample with a cTnT concentration of 0.01 ng/ml. In the present study, a positive conventional cTnT test was defined as ≥0.03 ng/ml. We also measured serum hs-cTnT using a commercial assay kit (n=85) in which the lowest concentration at which the CV is <10% was 0.01 ng/ml and the intra- and interassay CVs were 3.5% (n=4) and 4.2% (n=4), respectively in a sample with a cTnT concentration of 0.01 ng/ml as previously reported.11 In the present study, a positive conventional cTnT test was defined as ≥0.03 ng/ml. We also measured serum hs-cTnT using a commercial assay kit19,20 (Roche Diagnostics and Kyowa Medex (Japan)). In this assay, the lower limit of detection is 0.001 ng/ml, the lowest concentration at which the CV is <10% was 0.01 ng/ml, and the intra- and interassay CVs were 3.5% (n=4) and 4.2% (n=4), respectively in a sample with a cTnT concentration of 0.01 ng/ml. In the present study, a positive hs-cTnT test was defined ≥0.01 ng/ml or higher.

### Statistical Analysis

All results are expressed as the mean±SD. A Chi-square test was used to determine differences between groups. Univariate analyses were performed using Student’s t-test. Differences in the mean levels of BNP between 2 groups were tested by Mann-Whitney U test for unpaired values with 2-tailed P values of <0.05. Log BNP was used for correlations. Multivariable Cox proportional hazard analyses were performed as stepwise regressions with backward elimination. Kaplan-Meier analysis was performed on the cumulative rates of survival stratified into 2 groups based on cut-off values for conventional cTnT (0.03 ng/ml) and hs-cTnT (0.01 ng/ml). Kaplan-Meier analysis was also performed on the cumulative rates of survival stratified into 4 groups based on the cut-off value of the LVEF (30%) and the cut-off value of hs-cTnT (0.01 ng/ml) and the differences between survival curves were analyzed by log-rank test. The cut-off level of LVEF (30%) for predicting mortality was determined by receiver-operating characteristics (ROC) analysis. A value of P<0.05 was considered significant.

### Hemodynamic and Neurohumoral Variables in 85 Patients With Nonischemic Dilated Cardiomyopathy

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients (n=85)</th>
<th>Survivors (n=65)</th>
<th>Nonsurvivors (n=20)</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59.1±15</td>
<td>59.7±13.9</td>
<td>57±18</td>
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<tr>
<td>Sex (M/F)</td>
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<td>44/22</td>
<td>22/5</td>
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<tr>
<td>AF, n (%)</td>
<td>15 (18%)</td>
<td>14 (21%)</td>
<td>1 (5%)</td>
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NYHA class

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<tr>
<th>Class</th>
<th>Age (years)</th>
<th>HR (beats/min)</th>
<th>MBP (mmHg)</th>
<th>LVEDP (mmHg)</th>
<th>LVEF (%)</th>
<th>Cardiac index (L·min⁻¹·m⁻²)</th>
<th>eGFR (ml·min⁻¹·1.73m⁻²)</th>
<th>BNP (pg/ml)</th>
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<tr>
<td>I or II/III or IV</td>
<td>61/24</td>
<td>76.7±20</td>
<td>84.8±15.4</td>
<td>13.8±7.4</td>
<td>33.9±7.6</td>
<td>2.58±0.6</td>
<td>66.6±21</td>
<td>187 (67, 391)</td>
</tr>
<tr>
<td>III or IV</td>
<td>78±21</td>
<td>78±15</td>
<td>13±7.5</td>
<td>32.2±7.6</td>
<td>2.66±0.7</td>
<td>73±37</td>
<td>647 (298, 1,356)</td>
<td>1,015 (673, 1,689)</td>
</tr>
</tbody>
</table>

**Table 1. Hemodynamic and Neurohumoral Variables in 85 Patients With Nonischemic Dilated Cardiomyopathy**

NYHA, New York Heart Association; HR, heart rate; MBP, mean blood pressure; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; cTnT, cardiac troponin T; hs-cTnT, high-sensitivity cardiac troponin T; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.
Results

Patients’ Characteristics

Table 1 summarizes the patients’ characteristics according to survival. During a median follow-up of 4.1 years, 20 patients died of cardiac-related causes. Of 85 CHF patients with nonischemic DCM, serum conventional cTnT concentrations were detected (≥0.01 ng/ml) in 31 (36%) and were elevated (≥0.03 ng/ml) in 4 (5%). In the same population, serum hs-cTnT concentrations were detected (≥0.001 ng/ml) in 76 patients (89%) and were elevated (≥0.01 ng/ml) in 46 (54%). Among 76 patients (hs-cTnT ≥0.001 ng/ml), serum hs-cTnT concentrations were significantly higher in nonsurvivors than in survivors (Figure 1). Kaplan-Meier curves for cardiac death according to cTnT and hs-cTnT levels are shown in Figure 2. Among 76 patients (hs-cTnT ≥0.001 ng/ml), serum log hs-cTnT concentrations significantly correlated with log BNP (r=0.497, P<0.0001) and did not correlate with LVEF (Figure 3). There was no significant correlation between eGFR and serum hs-cTnT (r=−0.146, P=0.204) in these patients.

Univariate and Multivariable Predictors of Mortality: Comparison of cTnT, hs-cTnT, BNP and Hemodynamic Parameters

Eight variables, including the biomarkers and hemodynamic variables, were analyzed using univariate and stepwise multivariable Cox proportional hazards regression analyses (Table 2). In the stepwise multivariate analyses, a high plasma level of BNP (P=0.002), low LVEF (<30%, P=0.012) and high hs-cTnT concentration (>0.01 ng/ml, P=0.0061) were independent significant prognostic predictors, but conventional cTnT (≥0.03 ng/ml) was not. The hazard ratio for mortality of patients with a low LVEF (<30%) and high hs-cTnT level (≥0.01 ng/ml) was 10.5 (95% confidence interval (CI) 1.35–81.6, P=0.024) compared with those with a low LVEF (<30%) and low hs-cTnT level (<0.01 ng/ml) (Figure 4). The hazard ratio for mortality of patients with a low LVEF (<30%) and high hs-cTnT level (≥0.01 ng/ml) was 18.8 (95%CI 2.42–146.8, P=0.005) compared with those with preserved LVEF (>30%) and a low hs-cTnT level (<0.01 ng/ml) (Figure 4).

Discussion

We have demonstrated for the first time the prognostic value of the hs-cTnT level in CHF patients with nonischemic DCM. We measured serum concentrations of conventional cTnT (4th generation Elecsys Troponin T immunoassay, Roche Diagnostics) and of hs-cTnT (Roche Diagnostics and Kyowa Medex) in the same 85 CHF patients with DCM. In these patients, conventional cTnT serum concentrations were elevated (≥0.03 ng/ml) in only 4 patients (5%), but hs-cTnT serum concentrations were elevated (≥0.01 ng/ml) in 46 patients (54%). Moreover, an elevated level of hs-cTnT (≥0.01 ng/ml), but not of conventional cTnT (>0.03 ng/ml), was an independent significant prognostic predictor, suggesting that the assay for hs-cTnT is more sensitive than the conventional commercial assay for cTnT and that a sensitive assay system for cTnT provides useful information on the prognosis of CHF. Latini et al reported the prognostic value of very low plasma...
Table 2. Univariate and Multivariate Predictors of Mortality of Patients With Nonischemic Dilated Cardiomyopathy

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th>Multivariate</th>
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<tbody>
<tr>
<td></td>
<td>Chi-square</td>
<td>P value</td>
</tr>
<tr>
<td>Age (years)</td>
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<td>0.800</td>
</tr>
<tr>
<td>NYHA class (III/IV=1, I/II=0)</td>
<td>3.461</td>
<td>0.0628</td>
</tr>
<tr>
<td>Cardiac index (L·min⁻¹·m⁻²)</td>
<td>3.318</td>
<td>0.0685</td>
</tr>
<tr>
<td>LVEDP (mmHg)</td>
<td>3.297</td>
<td>0.0694</td>
</tr>
<tr>
<td>LVEF&lt;30 (%)</td>
<td>5.025</td>
<td>0.141</td>
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<tr>
<td>BNP (pg/ml)</td>
<td>12.68</td>
<td>0.0004</td>
</tr>
<tr>
<td>cTnT ≥0.03 (ng/ml)</td>
<td>5.114</td>
<td>0.0237</td>
</tr>
<tr>
<td>hs-cTnT ≥0.01 (ng/ml)</td>
<td>9.895</td>
<td>0.0017</td>
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</table>

Abbreviations are listed in Table 1.

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Figure 3. (A) Correlation between plasma log brain natriuretic peptide and serum log high-sensitivity cardiac troponin T (hs-cTnT) in patients with nonischemic dilated cardiomyopathy. (B) Comparison of left ventricular ejection fraction (LVEF) and serum log hs-cTnT in patients with nonischemic dilated cardiomyopathy.

Figure 4. Kaplan-Meier survival curves according to the combination of cut-off values for left ventricular ejection fraction (EF) (30%) and high-sensitivity cardiac troponin T (hs-cTnT: 0.01 ng/ml) in patients with nonischemic dilated cardiomyopathy.
concentrations of hs-cTnT measured by a precommercial assay in patients with stable CHF mainly caused by coronary artery disease (CAD). In the present study, we have, for the first time, demonstrated the prognostic value of measuring the hs-cTnT level by a commercial assay in patients with nonischemic DCM. Taking the findings of Latini et al together with our data, the hs-cTnT assay may be useful for predicting both the severity and the prognosis in patients with CHF with or without CAD.

In the present study, a low LVEF (<30%) and a high serum level of hs-cTnT (≥0.01 ng/ml) were independent significant prognostic predictors, and the hazard ratio for mortality of patients with a low LVEF (<30%) and high hs-cTnT level (≥0.01 ng/ml) was 10.5 (95% CI 1.35–81.6, P = 0.024) compared with those with a low LVEF (<30%) and low hs-cTnT level (<0.01 ng/ml) (Figure 4), suggesting that both a low LVEF and high hs-cTnT level provide important information about myocardial injury in CHF patients with nonischemic DCM. We recently reported the prognostic role of the hs-cTnT level in patients with systolic dysfunction mainly caused by CAD, and Sabatine et al. reported that an ultra-sensitive assay of cTnI (Singulex, Inc, Berkeley, CA, USA) was more useful for detecting myocardial injury during transient stress test-induced myocardial ischemia than the commercial hs-cTnI assay (Siemens Medical Solution Diagnostics) used in our previous study. Therefore, the greater the sensitivity of the assay system for both cTnI and cTnT, the more useful it will be for predicting myocardial injury and/or mortality in patients with CHF. Further large studies are needed to assess this issue, using more sensitive assays of cTnT and cTnI.

The plasma BNP level is a biomarker of hemodynamic abnormality such as an increase in left ventricular end-diastolic pressure or left ventricular wall stress in CHF patients. In our previous study, not only a high NT-proBNP level but also a high level of hs-cTnT was an independent and useful prognostic predictor in patients with CHF mainly caused by CAD. In the present study, not only a high BNP level but also a high hs-cTnT level was an independent and useful prognostic predictor in patients with nonischemic DCM. Further large studies are needed to directly compare the prognostic value of hs-cTnT, hs-cTnI and cardiac natriuretic peptides such as BNP and NT-proBNP in patients with nonischemic DCM, especially the repetitive measurements of these biomarkers.

Study Limitations

The small number of patients and deaths are limitations in this study. However, this is the first study to compare the prognostic value of cTnT using a conventional commercial assay and hs-cTnT using the current generation of sensitive commercial assay, as well as comparing the prognostic value of BNP, a marker of ventricular wall stress, in the same population. At entry to the study, most patients were stable in NYHA functional class I or II and although mechanical therapy, such as cardiac resynchronization therapy with defibrillator (CRT-D), has been available since 2006 in Japan, no patients received CRT-D. However, after intention to treatment analysis, 4 patients received CRT-D, but died because of progression of CHF during follow-up. The effect of CRT-D on the serum levels of hs-cTnT and BNP may help to evaluate responders to CRT-D, but further studies are needed.

In conclusion, the present study showed that a high plasma concentration of hs-cTnT is an independent and useful prognostic predictor in CHF patients with nonischemic DCM, independent of BNP, suggesting that increased hs-cTnT concentrations sensitively reflect ongoing myocardial damage.

References


Acknowledgments

We thank Ms Ayane Murasaki for her excellent technical assistance. We also express thanks to Mr Daniel Mrozek for assistance in preparing the manuscript.

References