Persistently Increased Serum Concentrations of Cardiac Troponin T in Patients With Idiopathic Dilated Cardiomyopathy Are Predictive of Adverse Outcomes

Yukihito Sato, MD; Tasuku Yamada, MD; Ryoji Taniguchi, MD; Kozo Nagai, MD; Takeru Makiyama, MD; Hideshi Okada, MD; Kazuaki Kataoka, MD; Haruyasu Ito, MD; Akira Matsumori, MD; Shigetake Sasayama, MD; Yoshiki Takatsu, MD

Background—The measurement of serum concentrations of cardiac troponin T (TnT) is a simple, useful method to detect myocyte injury that may be repeated multiple times to follow patients without interobserver variability.

Methods and Results—Multiple measurements of TnT with a second-generation assay were performed in 60 patients with dilated cardiomyopathy confirmed by coronary angiography and endomyocardial biopsy between April 1996 and December 1999. Three evolutionary patterns of TnT concentrations were identified. Thirty-three patients had concentrations of TnT <0.02 ng/mL throughout the follow-up period (group 1). The remaining 27 patients had high initial serum concentrations of TnT (≥0.02 ng/mL). In 10 of these 27 patients, TnT decreased to <0.02 ng/mL during follow-up (group 2), whereas 17 had persistently high serum TnT concentrations despite being conventionally treated for chronic congestive heart failure (group 3). Although the initial echocardiographic left ventricular diastolic dimension (LVDd) and left ventricular ejection fraction (LVEF) were not significantly different among the 3 groups, follow-up echocardiography showed significantly decreased LVDd and increased LVEF in group 1 (each P<0.01) and group 2 (each P<0.05) compared with increased LVDd and decreased LVEF in group 3 (each P<0.05). The cardiac event-free rate was significantly lower in group 3 than in groups 1 and 2 (each P<0.001), and the survival rate was lower in group 3 than in group 1 (P<0.05).

Conclusions—Persistently increased TnT concentrations in dilated cardiomyopathy suggest ongoing subclinical myocyte degeneration associated with deterioration of the patients’ clinical status. (Circulation. 2001;103:369-374.)

Key Words: proteins ▪ cardiomyopathy ▪ heart failure

Idiopathic dilated cardiomyopathy (DCM) is a primary myocardial disease of unknown origin characterized by ventricular dilatation and depressed myocardial contractility. Although characteristics such as ventricular dimensions, left ventricular ejection fraction (LVEF), NYHA functional class, cardiopulmonary exercise performance, and hemodynamic measurements are helpful to estimate the risk of adverse cardiac events,1 the assessment of prognosis in individual patients with DCM remains difficult and would benefit from a more accurate marker of disease activity.

Troponins are proteins found in cardiac and skeletal muscle, and the troponin complex (subunits I, T, and C) on the actin filament regulates the force and velocity of muscle contraction. Troponin T anchors the troponin complex to tropomyosin. The serum concentration of cardiac troponin T (TnT) is a specific and highly sensitive marker of myocardial injury. The diagnostic and prognostic value of this marker has been established and extensively reported in acute coronary syndromes.2–4 However, its significance in DCM is not known. Microscopic abnormalities associated with DCM are roughly divided between myocytic degeneration and interstitial changes. We have recently reported that patients with idiopathic and secondary DCM whose prognosis is poor have abnormally high serum concentrations of TnT in the absence of an increase in serum creatine kinase (CK) concentrations and that, in this population, TnT is a prognostic marker.5,6 It is noteworthy that most patients with poor outcomes had persistently high TnT, even when heart failure was compensated for by conventional treatment and when they were free of dyspnea or roentgenographic and auscultatory signs of pulmonary congestion.6 Serial measurements of serum TnT concentrations seem to be a reliable immunopathological indicator of subclinical ongoing myocyte degeneration, and we hypothesized that, in patients with cardiomyopathy, treat-


The purpose of this retrospective study was to closely analyze the correlation between long-term changes in TnT concentrations and clinical symptoms in patients with DCM and to show the value of serial measurements and the ominous prognosis predicted by persistently increased TnT levels.

**Methods**

**Patient Population**
The study population consisted of 60 consecutive patients with DCM examined in the Hyogo Prefectural Amagasaki Hospital between April 1996 and December 1999. Ten patients included in this study belonged to a population described in an earlier report. The study procedures were in accordance with the institutional guidelines of the Hyogo Prefectural Amagasaki Hospital. The demographic and baseline clinical characteristics of the study population are presented in Table 1. No patient had a history of myocardial infarction, infective myocarditis, metabolic disease, systemic illness, or heredofamilial disease. All patients underwent heart catheterization, coronary angiography, and endomyocardial biopsy. No significant coronary stenosis was found in any patient. At least 3 endomyocardial biopsy specimens were obtained from each patient, and 3 to 5 specimens per patient were stained with hematoxylin-eosin. Microscopic examination revealed myocyte hypertrophy, nuclear hypertrophy, myocyte degeneration with myofilibrillar attenuation, and/or interstitial and perivascular fibrosis in all patients. The final diagnosis of DCM was based on the definition of the World Health Organization/International Society and Federation of Cardiology Task Force. Myocarditis was excluded on the basis of the Dallas criteria.

Serum TnT was measured at baseline with a commercially available second-generation immunoassay kit (Roche Diagnostics). Stored samples were used for the period ranging from April 1996 to April 1999. CK enzyme was measured by standard laboratory methods. LVEF and left ventricular diastolic dimension (LVDd) were measured echocardiographically by 2 experts unaware of this study protocol and whose measurements were averaged.

**Clinical Follow-Up**
Patients were regularly followed up at intervals of 1 to 3 months by one of the study investigators. At each visit, patient functional status, use of medications, and significant clinical events were recorded. In addition, measurements of serum TnT, CK, and left ventricular function and dimensions were repeated by the same methods. Significant cardiac events were defined as death resulting from a cardiac cause or rehospitalization of the patient for management of cardiac decompensation with pulmonary edema or of a sustained, hemodynamically unstable tachyarrhythmia. Information pertinent to a patient’s mode of death occurring outside the hospital between follow-up visits was obtained from the family. In cases of death of a patient during follow-up, measurements made at the last follow-up visit before the patient’s death were recorded as final measurements. Correlations between TnT levels and pulmonary congestion on chest roentgenogram, serum CK concentrations, LVEF, LVDd, or cardiac event rate were tested.

**Statistical Analysis**
Comparisons between study variables were made with factorial ANOVA for continuous variables and chi-square analysis for categorical variables. Changes in parameters between points of the follow-up period were analyzed by 2-tailed Student’s paired t test. Cardiac event-free rates and survival curves were calculated by the Kaplan-Meier method. Data are expressed as mean±SD. A value of P<0.05 was considered significant.

**Results**

**Patterns of Serial Serum TnT Concentrations**
Over an average observation period of 15.9±10.5 months, 3 distinct evolutionary patterns of serum TnT levels were observed among the 60 patients. In 33 patients (55%), TnT concentrations remained <0.02 ng/mL throughout the observation period (group 1). The remaining 27 patients (45%) had high (≧0.02 ng/mL) initial serum concentrations of TnT. In 10 of these patients, TnT had decreased to <0.02 ng/mL at the end of the follow-up period (group 2), whereas in 17 patients, TnT levels remained abnormally high (group 3). No statistically significant age differences were found among the 3 groups (data not shown). TnT measurements at enrollment and at the end of study in groups 2 and 3 are presented in Figures 1 and 2. The changes in mean values of TnT at the beginning versus end of follow-up are shown in Table 2.

**Serum TnT and Symptoms of Chronic Heart Failure**
The average duration of disease before enrollment in this study was 13.1±14.4, 11.7±14.1, and 39.3±38.5 months in groups 1 through 3, respectively. Average periods of hospitalization before enrollment were 12.2±26.6, 11.5±9.9, and 44.5±48.5 days. These periods were significantly longer in group 3 than in groups 1 and 2 (P<0.01). Symptoms of heart failure, dyspnea, and palpitation were observed in 28 patients (84%) in group 1, 9 (90%) in group 2, and 16 (94%) in group 3 at study entry. Pulmonary congestion was apparent on chest roentgenogram in 7 of 33 patients (21%) in group 1, 3 of 10 patients (30%) in group 2, and 9 of 17 patients (53%) in group 3.
Serum TnT and Long-Term Drug Regimens

The oral drug regimens administered to the 3 groups of patients during the observation period were comparable (Table 3). The intravenous infusions used during follow-up for manifestations of cardiac decompensation, including dyspnea, palpitation, and/or pulmonary congestion on chest roentgenogram, are also listed in Table 3. The percentage of intravenous infusions of diuretics, nitrates, or inotropes was significantly higher in group 3 than in groups 1 and 2 (P<0.001).

CK Enzyme Measurements

The mean values of baseline CK enzyme at study entry were 109.5±69.1, 130.9±48.5, and 92.2±64.2 IU/L in groups 1 through 3, respectively. Mean CK values were 120.1±64.1, 127.1±59.4, and 91.7±56.0 IU/L at mean follow-ups of 18.1±10.4, 15.4±8.7, and 16.2±12.7 months. These mean CK values, which remained stable over time, were statistically comparable among the 3 groups of patients.

TABLE 2. Measurements of TnT Levels at Baseline and During Long-Term Follow-Up in 3 Patient Groups

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline TnT, ng/mL</td>
<td>&lt;0.02</td>
<td>0.08±0.11</td>
<td>0.09±0.11</td>
</tr>
<tr>
<td></td>
<td>(0.02–0.39)</td>
<td>(0.02–0.46)</td>
<td></td>
</tr>
<tr>
<td>Follow-up TnT, ng/mL</td>
<td>&lt;0.02</td>
<td>&lt;0.02</td>
<td>0.09±0.08</td>
</tr>
<tr>
<td></td>
<td>(0.03–0.31)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up duration, mo</td>
<td>15.7±9.7</td>
<td>16.6±9.3</td>
<td>15.8±13.0</td>
</tr>
</tbody>
</table>

Follow-up duration indicates interval between baseline and follow-up TnT. In group 1 patients, TnT concentrations remained <0.02 ng/mL throughout the observation period. In group 2 patients, TnT decreased to <0.02 ng/mL at the end of the follow-up period, whereas in group 3, serum TnT levels remained abnormally high. Numbers in parentheses indicate minimum and maximum values.

TnT and Follow-Up Echocardiographic Findings

Initial and follow-up echocardiographic findings are presented in Table 4. Initial LVDd and LVEF were comparable among the 3 patient groups. Follow-up echocardiography was obtained in 29 patients from group 1, 10 from group 2, and 16 from group 3. In groups 1 and 2, LVDd decreased significantly (P<0.01 and P<0.05, respectively) and LVEF increased (P<0.01 and P<0.05) compared with the initial echocardiographic measurements. In contrast, in group 3, LVDd increased from 58.0±9.0 to 60.8±9.4 mm (P<0.05), and LVEF decreased from 36.7±11.4 to 30.8±7.7 (P<0.05). There was no correlation between changes in TnT and changes in LVDd or LVEF (data not shown).

TnT and Prognosis

The actuarial cardiac event-free rate in the 3 groups of patients is shown in Figure 3. The event-free rate in group 3 was significantly lower than in groups 1 and 2 (each P<0.001). In group 1, a single patient developed decompensated heart failure requiring rehospitalization, and 2 patients...
Table 4. Measurements of LVDd and LVEF at Baseline and During Long-Term Follow-Up in 3 Patient Groups

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=29)</th>
<th>Group 2 (n=10)</th>
<th>Group 3 (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVDd, mm</td>
<td>60.9±7.3</td>
<td>58.5±5.6</td>
<td>58.0±9.0</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>37.0±8.9</td>
<td>45.3±13.5*</td>
<td>36.7±11.4†</td>
</tr>
<tr>
<td>Follow-up duration, mo</td>
<td>20.0±11.0</td>
<td>17.4±10.0</td>
<td>20.8±11.2</td>
</tr>
</tbody>
</table>

Follow-up duration indicates interval between baseline and follow-up echocardiography. Although the initial echocardiographic LVDd and LVEF were not significantly different among the 3 groups, follow-up echocardiography showed significantly decreased LVDd and increased LVEF in group 1 (each \( P<0.01 \)) and group 2 (each \( P<0.05 \)). In contrast, LVDd increased and LVEF decreased in group 3 (each \( P<0.05 \)).

Discussion

TNT Assay

The first generation of cardiac TNT assay was flawed by spuriously increased values in patients with severe skeletal muscle or renal diseases.\(^{11,12} \) Several explanations, such as cross-reactivity of the cardiac TNT assay with skeletal muscle troponin T or TNT expressed by skeletal muscles during regenerative processes, especially in patients with neuromuscular and renal diseases, have been proposed. The second generation of TNT assay, used in this study, has been found to be a sensitive and specific marker of myocyte injury even in presence of these diseases.\(^{13,14} \) Mean creatinine levels at study entry were 0.76±0.19, 0.94±0.45, and 1.20±0.52 mg/dL in groups 1 through 3, respectively, and no correlation was found between values of TNT and creatinine concentrations (data not shown). The differences in creatinine levels among the 3 groups of patients may be explained by variable degrees of renal ischemia secondary to low cardiac output.

The release and clearance mechanisms of TNT have not been fully elucidated. TNT is a structural protein, and it attaches the troponin-tropomyosin complex to the thin filament of actin, although a small free pool of TNT exists in the cytosol.\(^{15-17} \) Transient leakage of the cytosolic pool may occur as a result of loss of cell membrane integrity during reversible injury, and prolonged leakage may be due to degeneration of myofilaments in irreversibly injured cells.

TNT in DCM Patients

In this study, DCM patients with persistently elevated TNT had echocardiographic findings consistent with disease progression and adverse long-term outcomes. TNT in DCM seems to indicate subclinical myocyte degeneration. Although we had previously suspected ongoing myocyte degeneration in patients with DCM by indium-111 antimyosin antibody imaging,\(^{18} \) that technique involves radioisotopes and cannot to be used serially to follow up patients over the long term. TNT is easy to measure, does not need complicated laboratory methods, and can be used multiple times to follow up patients without interobserver variability. Although initial TNT concentrations were increased in groups 2 and 3, there were no significant differences in initial CK values among the 3 patient groups. Furthermore, CK values did not change significantly during the follow-up period. TNT was therefore a more sensitive marker of myocyte degeneration.

The detection limit of the second-generation assay is 0.0123 ng/mL.\(^{19} \) In our preliminary study, TNT levels in control samples obtained from 45 age-matched asymptomatic subjects (60.1±13.3 years of age) whose echocardiographic, chest roentgenographic, and ECG findings were normal were consistently <0.02 ng/mL (data not shown). Therefore, we chose 0.02 ng/mL as the upper normal limit for this population of patients with DCM, a relatively low value compared with that of patients with ischemic heart disease.

The mechanisms of myocyte degeneration in DCM are not fully understood. Programmed myocyte death, apoptosis and necrosis, interstitial changes in and signaling pathways of adrenergic stimulation, calcium handling abnormalities, the
renin-angiotensin system, endothelin, inflammatory cytokines, nitric oxide, oxidative stress, and mechanical stress have all been invoked. A possible correlation between these factors and TnT concentrations warrants further study. Furthermore, subclinical microvascular spasm may cause ischemia-induced release of TnT, although our patients did not have angiographically visible significant coronary stenoses, episodes of angina pectoris, or ECG findings consistent with myocardial ischemia.

Identification of Patients With Persistently Increased TnT Whose Prognosis Is Poor

Large clinical trials have established the effectiveness of digoxin, ACE inhibitors, and β-adrenergic blockers on the quality of life and/or survival of patients with chronic congestive heart failure. However, a subset of patients remains at high risk and requires aggressive management. On the basis of our preliminary work indicating a poor prognosis in patients with persistently elevated TnT levels, efforts were made to educate patients and families, particularly with respect to the importance of dietary salt and water restrictions, and TnT levels were closely monitored in this study. Nevertheless, the factors involved in the progression from chronic stable heart failure to acute decompensation in some of our patients with high serum concentrations of TnT remain unclear. Their serum TnT concentrations remained increased even in the absence of overt cardiac decompensation and pulmonary congestion and despite optimal treatment of heart failure. These findings suggest that, in some patients with DCM, subclinical myocyte degeneration continues despite therapy during the compensated stage of heart failure, ultimately resulting in acute decompensation.

A value of >0.1 ng/mL TnT is used for the diagnosis of ischemic heart disease. In group 2, 2 patients who remained free of cardiac events during the observation period had initial TnT values >0.1 ng/mL, which fell below 0.02 ng/mL at the end of the study (Figure 1). However, these 2 patients had no long-term echocardiographic improvement (data not shown), whereas on average group 2 patients had a statistically significant decrease in LVDd and increase in LVEF. Furthermore, 3 patients with TnT concentrations consistently >0.1 ng/mL and 2 patients whose TnT rose to >0.1 ng/mL during the follow-up period in group 3 had unfavorable outcomes (Figure 2). Three patients died of end-stage heart failure, and 2 patients developed cardiac decompensation and were dependent on intravenous infusions of inotropic agents at the end of the study. A single patient, whose TnT decreased from 0.46 to 0.11 ng/mL in group 3, had a favorable outcome (Figure 2). TnT concentrations >0.1 ng/mL seem to indicate the presence of considerable amounts of myocyte injury.

What Is the Optimal Therapy for DCM?

The short-term goals of therapy in patients with chronic heart failure consist of relieving symptoms of congestion and increasing tissue perfusion. Longer-term objectives include improvement or maintenance of quality of life and prolongation of survival. Recently, Setsuta et al have reported a decrease in TnT levels after medical therapy in patients with chronic heart failure caused by DCM and ischemic heart disease. However, in this study, some patients in group 1 who had favorable outcomes had TnT levels <0.02 ng/mL despite the presence of pulmonary congestion on the initial chest roentgenogram. Suboptimal management of chronic heart failure seems to lead to cardiac decompensation, even in the absence of elevated TnT levels. In addition, some patients in group 3 whose outcomes were poor had persistently elevated TnT, including during periods of cardiac compensation. TnT does not seem to be a marker of hemodynamic decompensation; rather, it appears to be a manifestation of the underlying pathophysiological process.

In conclusion, serial cardiac TnT measurements may be helpful in the management of patients with DCM. The recognition of persistently elevated TnT concentrations is important because it identifies patients with adverse prognoses. It would be also worthwhile to study patients with coronary disease and cardiac remodeling after myocardial infarction. Such studies would promote the acceptance of TnT as a monitoring tool in patients with chronic heart failure.

References

Persistently Increased Serum Concentrations of Cardiac Troponin T in Patients With Idiopathic Dilated Cardiomyopathy Are Predictive of Adverse Outcomes
Yukihito Sato, Tasuku Yamada, Ryoji Taniguchi, Kozo Nagai, Takeru Makiyama, Hideshi Okada, Kazuaki Kataoka, Haruyasu Ito, Akira Matsumori, Shigetake Sasayama and Yoshiki Takatsu

*Circulation*. 2001;103:369-374
doi: 10.1161/01.CIR.103.3.369

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/103/3/369

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Circulation* is online at:
http://circ.ahajournals.org//subscriptions/