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

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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
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 cardiac 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 myofibrillar 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 1997. 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.

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.

### Methods

**Patient Population**

The study population consisted of 60 consecutive patients with DCM who fulfilled the definition of dilated cardiomyopathy (DCM) 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 \( \chi^2 \) 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 the 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.
NG/mL throughout study.

**Long-Term Follow-Up in 3 Patient Groups**

<table>
<thead>
<tr>
<th>Baseline TnT, ng/mL</th>
<th>Group 1 (n=33)</th>
<th>Group 2 (n=10)</th>
<th>Group 3 (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.02</td>
<td>0.08±0.11</td>
<td>0.09±0.11</td>
<td>0.02±0.46</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>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.

**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.

**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**

- **Oral drug**
  - Diuretics
    - n (%) 24 (75) 9 (90) 17 (100)
    - Duration, mo 26.1±13.6 28.0±14.3 27.8±16.1
  - ACE inhibitors
    - n (%) 14 (42) 5 (50) 8 (47)
    - Duration, mo 19.1±13.5 18.4±14.1 19.3±16.8
  - Anticoagulant
    - n (%) 11 (33) 6 (60) 6 (35)
    - Duration, mo 15.1±11.1 20.1±12.2 24.0±14.0

- **Intravenous drug**
  - Diuretics
    - n (%) 6 (18) 3 (30) 14 (82)*
    - Duration, d 5.6±3.5 4.6±1.5 39.0±49.5
  - Nitrates
    - n (%) 7 (21) 4 (40) 14 (82)*
    - Duration, d 4.4±2.5 5.0±1.4 16.5±15.4
  - Inotropes
    - n (%) 5 (15) 1 (10) 12 (70)*
    - Duration, d 5.2±3.7 6.0±0.0 27.2±31.2

*P<0.001 vs groups 1 and 2.

**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...
died suddenly in the absence of apparent cardiac decompensation. In group 2, 1 patient died suddenly with no previous signs of heart failure exacerbation, and no patient required rehospitalization for management of heart failure. In contrast, in group 3, 12 of 17 patients required rehospitalization for cardiac decompensation with pulmonary edema in 11 patients and sustained, hemodynamically unstable atrial fibrillation in 1 patient. Seven patients ultimately died of end-stage heart failure after 4 to 8 rehospitalizations for cardiac decompensation. No patient in group 3 died suddenly. The overall survival rate was significantly lower in group 3 than in group 1 (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. 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. 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. 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 antimony antibody imaging, that technique involves radioisotopes and cannot 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. 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
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 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 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.

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 this study, we were not able to identify which drug(s) effectively reduced TnT levels in this study. There were no significant differences in the use of oral medications among patient groups. However, because this may have been due to a small sample size, further large clinical drug trials with monitoring of TnT levels should be required. Persistently increased TnT concentrations may be a signal to proceed to the next treatment. When all conventional attempts have failed to decrease TnT, more aggressive steps, including cardiac transplantation, might be considered.

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

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