Cardiac Troponin I Is Associated With Impaired Hemodynamics, Progressive Left Ventricular Dysfunction, and Increased Mortality Rates in Advanced Heart Failure

Tamara B. Horwich, MD; Jignesh Patel, MD; W. Robb MacLellan, MD; Gregg C. Fonarow, MD

Background—Cardiac troponin I (cTnI), a sensitive and specific marker of myocardial cell injury, is useful in diagnosing and assessing prognosis in acute coronary syndromes. Small studies report that cTnI is elevated in severe heart failure (HF) and may predict adverse outcomes.

Methods and Results—The present study evaluated 238 patients with advanced HF referred for cardiac transplantation evaluation who had cTnI assay drawn at the time of initial presentation. Patients with acute myocardial infarction or myocarditis were excluded from analysis. cTnI was detectable (cTnI ≥0.04 ng/mL) in serum of 117 patients (49.1%). Patients with detectable cTnI levels had significantly higher B-type natriuretic peptide (BNP) levels (P<0.001) and more impaired hemodynamic profiles, including higher pulmonary wedge pressures (P=0.002) and lower cardiac indexes (P<0.0001). A significant correlation was found between detectable cTnI and progressive decline in ejection fraction over time. Furthermore, detectable cTnI was associated with increased mortality risk (RR, 2.05; 95% CI, 1.22 to 3.43). After adjustment for other factors associated with adverse prognosis including age, sex, ejection fraction, and coronary artery disease, cTnI remained a significant predictor of death. cTnI used in conjunction with BNP further improved prognostic value.

Conclusions—cTnI is associated with impaired hemodynamics, elevated BNP levels, and progressive left ventricular dysfunction in patients with HF. cTnI may be a novel, useful tool in identifying patients with HF who are at increased risk for progressive ventricular dysfunction and death. (Circulation. 2003;108:833-838.)

Key Words: hemodynamics ■ natriuretic peptides ■ mortality ■ heart failure ■ tests

Heart failure (HF) is a significant cause of morbidity and mortality, with a current US prevalence of 5 million and 5-year survival near 50%. As medical and surgical therapies advance, it becomes important to identify high-risk patients who may derive increased benefit from transplantation referral or other aggressive treatment. Although some patients have significant improvement in left ventricular function over time in response to HF medical therapy, other patients do not respond or have progressive left ventricular dysfunction. A reliable marker to predict which patients are likely to have improvement in left ventricular systolic function would be particularly helpful in managing HF.

Troponins are proteins involved in the regulation of cardiac and skeletal muscle contraction. The presence of cardiac troponins in the serum indicates myocardial injury or loss of cell membrane integrity. Several small studies have reported elevated cardiac troponin levels in patients with decompensated HF, in the absence of acute coronary syndromes, and furthermore have correlated troponin elevation with poor prognosis. Although the cardiac troponins, troponin I (cTnI) and troponin T, are well-established diagnostic and prognostic markers in acute coronary syndromes, the role of troponins in the evaluation and risk stratification of patients with HF is less certain. Our study aimed to confirm and further explore the prognostic implications of cTnI levels in HF.

Methods

Patient Population

The study population consisted of 251 consecutive patients referred to a single university medical center for heart transplantation evaluation between June 2000 and March 2002 who had cTnI samples obtained at the time of initial evaluation. All subjects were followed in a comprehensive HF treatment program. Medical record review was approved by the Medical Institutional Review Board of the University of California–Los Angeles. Patients clinically diagnosed with acute myocardial infarction, acute coronary syndrome, or myocarditis at time of initial evaluation were excluded from analysis (n=13). No patients were receiving chronic inotropic therapy. The final study population consisted of 238 subjects (68 women, 170 men).

Baseline Patient Data

cTnI was analyzed in all patients at time of initial referral, and B-type natriuretic peptide (BNP) was analyzed in 98 patients at the
Detectable levels of serum cTnI were significantly associated with ischemic in 50% of patients and idiopathic in 33%; other causes included alcohol or drug-related, peripartum, and hypertrophic cardiomyopathy. Table 1 outlines baseline clinical and laboratory variables of the entire cohort and of cTnI-detectable and cTnI-undetectable patient groups. Demographic variables, medical history, baseline LVEF, underlying cause of HF, and renal function were similar in patients with and without detectable levels of cTnI. BNP was significantly higher (738±422 versus 461±407 pg/mL), and albumin and HDL levels were significantly lower in patients with HF with detectable cTnI levels (± 0.04 ng/mL).

**cTnI and Cardiovascular Hemodynamics**

The initial hemodynamic profile was markedly impaired in the cTnI-detectable group compared with the cTnI-undetectable group (Table 2). After optimization of medical therapy, patients with detectable cTnI still had significantly higher pulmonary artery and pulmonary capillary wedge pressures and lower cardiac indexes.

**cTnI and Drug Regimens**

Although rates of β-blocker therapy at time of evaluation were similar between the two groups, ACE inhibitor or angiotensin receptor blocker therapy was more common in the group with undetectable cTnI levels. Conversely, amiodarone was more common in the group with detectable cTnI (Table 3).

**cTnI and Ischemic Versus Nonischemic HF**
cTnI was detectable in 48% of patients with ischemic and 52% of patients with nonischemic cause of HF. Patients with ischemic and nonischemic causes of HF were similar in terms of cTnI level and other laboratory values, NYHA class, LVEF, medications, and hemodynamics (Table 4).

**Progression of Left Ventricular Dysfunction: Correlation With cTnI Levels**

At the time of referral, mean LVEF was 0.25±0.09. In the 58 patients with 6-month follow-up echocardiography, mean LVEF increased to 0.29±0.11 (P=0.008). However, patients with detectable levels of cTnI were more likely to have progression of left ventricular systolic dysfunction (Table 5). In patients with detectable levels of cTnI, 44% had a decrease in LVEF on follow-up echocardiography, compared with only 18% of patients with undetectable cTnI levels (P<0.01).

**cTnI and Survival**

There were 29 deaths during the study period. Progressive HF death accounted for 14 (48%) of deaths, whereas 10 deaths were sudden and 5 were from other or unknown causes. At the end of the study period, 44 of the 238 patients had received heart transplantation (35 urgent, status IA; 9 nonurgent, status IB or II). Thus, 64 (26.9%) had end points counted as fatal (death or urgent transplantation).

Detectable levels of cTnI were significantly associated with death in this cohort of patients with advanced HF. cTnI level was significantly higher in patients who died or underwent urgent transplantation compared with those who sur-
vived (0.5±1.9 versus 0.1±0.5 ng/mL, P<0.01). On univariate analysis, detectable cTnI conferred a doubling of mortality risk (RR, 2.1; 95% CI, 1.3 to 3.5, P<0.0001). The survival curves of the 2 groups are shown in Figure 1.

There was no stepwise increase in risk as cTnI level increased above 0.04 ng/mL. Among patients with detectable cTnI levels, the 3 tertiles of troponin level (0.04 to 0.06, 0.07 to 0.21, and ≥0.22 ng/mL) had similar survival (48%, 52%, and 45% respectively; P=0.7). ROC analysis identified a cTnI level of 0.04 ng/mL as the optimal inflection point for risk of death (data not shown). Any detectable level of cTnI was associated with an increased risk of mortality.

The association between cTnI and increased mortality rate was preserved in subgroups of patients with and without CAD, men and women, and in a cohort excluding patients with transplantation (Figure 2). After adjustment for additional risk factors on multivariate analysis, cTnI remained a predictor of death (Table 6). Furthermore, in the group of patients with cTnI values >0.04 ng/mL, β-blocker therapy was associated with significantly lower mortality rates compared with patients not receiving β-blocker therapy (34% versus 74%, P<0.003).

cTnI used in conjunction with BNP further improved prognostic value; patients with detectable cTnI and BNP >485 pg/mL (optimal cutoff for this cohort based on ROC analysis) had a 12-fold increased risk of death compared with those with both undetectable cTnI and BNP <485 pg/mL (Figure 3).

**Discussion**

cTnI is a cardiac-specific structural protein that is part of the troponin-tropomyosin complex, although a small pool of cTnI exists in the cytosol. Low-level elevation of serum cTnI elevation has been documented in a number of cardiovascular diseases, including HF. Although elevation of serum cTnI is a well-validated marker of necrotic myocyte injury during

<table>
<thead>
<tr>
<th>LABORATORY</th>
<th>Total Cohort</th>
<th>CtnI &lt;0.04 ng/mL</th>
<th>CtnI ≥0.04 ng/mL</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP, pg/mL</td>
<td>581±436</td>
<td>461±407</td>
<td>738±422</td>
<td>0.001</td>
</tr>
<tr>
<td>Sodium, mmol/L</td>
<td>135±5</td>
<td>136±4</td>
<td>134±5</td>
<td>0.060</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.4±1.2</td>
<td>1.3±0.9</td>
<td>1.5±1.4</td>
<td>0.196</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>3.6±0.6</td>
<td>3.7±0.6</td>
<td>3.4±0.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>164±61</td>
<td>172±66</td>
<td>155±54</td>
<td>0.069</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>37±14</td>
<td>40±14</td>
<td>34±14</td>
<td>0.009</td>
</tr>
</tbody>
</table>

LVEDD indicates left ventricular end-diastolic diameter; LVEDDI, left ventricular end-diastolic index (LVEDD/body surface area).

**Table 1. Baseline and Optimal Hemodynamics in Patients With Detectable and Undetectable cTnI**

**Table 2. Baseline Characteristics of the Cohort: Detectable Versus Undetectable cTnI**

**Table 3. Baseline and Optimal Hemodynamics in Patients With Detectable and Undetectable cTnI**

**Table 4. Baseline and Optimal Hemodynamics in Patients With Detectable and Undetectable cTnI**

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SBP indicates systolic blood pressure; MPA, mean pulmonary artery pressure; RA, right atrial pressure; PCW, pulmonary capillary wedge pressure; and CI, cardiac index.
myocardial infarction, the pathophysiology behind serum cTnI elevation in HF probably is distinct from that seen during myocardial infarction. The lower elevations of serum cTnI in chronic HF, including those identified in the present study, could signify the presence of limited, irreversible myocyte injury and cell death, or alternatively could represent leakage of the cytosolic pool of cTnI during reversible injury as a result of loss of cell membrane integrity.10 Progressive myocyte loss through necrotic and apoptotic cell death is increasingly recognized as a prominent pathophysiological mechanism in the evolution of cardiac dysfunction in HF,11-14 The mechanisms believed to be responsible for ongoing myocyte injury and/or cell death in HF include activation of adrenergic, renin-angiotensin-aldosterone, or endothelin signaling pathways, calcium-handling abnormalities, inflammatory cytokines, nitric oxide, oxidative stress, and mechanical stress.11

In our study, release of cTnI into the serum was strongly correlated with elevation of cardiac filling pressures and BNP. In vitro experiments with cardiac muscle cells have identified a link between myocardial wall stretch and myocyte functional injury and cell death,15 and increased troponin proteolysis has been identified in volume-overloaded rat hearts.16 At the cellular level, multiple intracellular signaling cascades are activated in the heart in response to changes in mechanical loading. Of note, these include mitogen-activated protein kinases (MAPKs), including p44/p2 extracellularly regulated kinases, c-Jun N-terminal kinase (JNK1/2), and p38 kinase, all of which have been shown to be involved in the regulation of myocyte apoptosis.17 These signaling pathways are upregulated in the ventricles of patients with ischemic and dilated cardiomyopathy.17

Several reports propose a relation between cTnI and death in clinical scenarios other than HF in which ventricular wall stress increases, such as massive pulmonary embolism, acute medical illness requiring intensive care, and infusion of cardiotoxic chemotherapy.18-21 The association between increased wall stress and myocyte death may be explained by multiple mechanisms. Increased wall stress may directly activate intracellular signaling cascades. It has also been hypothesized that increased myocardial wall stress leads to decreased subendocardial perfusion, even in the absence of CAD, resulting in a decline in systolic function.20–23

Additional factors, including activation of the renin-angiotensin system, sympathetic nervous system, and inflammatory cytokine system, have been implicated in provoking myocyte injury and cell death in HF.24 A study of patients with acute cardiogenic pulmonary edema found a correlation

TABLE 3. Medication Regimens According to cTnI

<table>
<thead>
<tr>
<th>Medication</th>
<th>CtnI &lt;0.04 ng/mL</th>
<th>CtnI ≥0.04 ng/mL</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Blocker, % (n)</td>
<td>71 (82)</td>
<td>70 (71)</td>
<td>0.853</td>
</tr>
<tr>
<td>ACEI or ARB, % (n)</td>
<td>94 (108)</td>
<td>83 (87)</td>
<td>0.011</td>
</tr>
<tr>
<td>Aldosterone antagonist, % (n)</td>
<td>50 (55)</td>
<td>37 (38)</td>
<td>0.071</td>
</tr>
<tr>
<td>Antiarrhythmic, % (n)</td>
<td>22 (24)</td>
<td>43 (44)</td>
<td>0.001</td>
</tr>
<tr>
<td>Amiodarone, % (n)</td>
<td>18 (20)</td>
<td>39 (40)</td>
<td>0.001</td>
</tr>
<tr>
<td>Sotalol, % (n)</td>
<td>4 (4)</td>
<td>3 (3)</td>
<td>0.777</td>
</tr>
<tr>
<td>Type I antiarrhythmics, % (n)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>0.298</td>
</tr>
<tr>
<td>Statin, % (n)</td>
<td>48 (55)</td>
<td>51 (49)</td>
<td>0.676</td>
</tr>
</tbody>
</table>

ACEI indicates ACE inhibitor; ARB, angiotensin receptor blocker.

TABLE 4. Patient Characteristics in Ischemic and Nonischemic Cardiomyopathy

<table>
<thead>
<tr>
<th></th>
<th>Ischemic CMY (n=99)</th>
<th>Nonischemic CMY (n=100)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>58±10</td>
<td>46±13</td>
<td>0.0001</td>
</tr>
<tr>
<td>Women, % (n)</td>
<td>18 (18)</td>
<td>35 (35)</td>
<td>0.007</td>
</tr>
<tr>
<td>NYHA class IV, % (n)</td>
<td>54 (30)</td>
<td>53 (31)</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF</td>
<td>26±8</td>
<td>26±10</td>
<td>NS</td>
</tr>
<tr>
<td>History of hypertension, % (n)</td>
<td>45 (34)</td>
<td>29 (23)</td>
<td>0.03</td>
</tr>
<tr>
<td>History of diabetes, % (n)</td>
<td>36 (29)</td>
<td>22 (18)</td>
<td>0.05</td>
</tr>
<tr>
<td>Laboratory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cTnI, ng/mL</td>
<td>0.22±1.4</td>
<td>0.29±0.9</td>
<td>NS</td>
</tr>
<tr>
<td>Detectable Tnl, % (n)</td>
<td>48 (46)</td>
<td>52 (49)</td>
<td>NS</td>
</tr>
<tr>
<td>BNP, pg/mL</td>
<td>631±397</td>
<td>434±468</td>
<td>NS</td>
</tr>
<tr>
<td>Sodium, mmol/L</td>
<td>136±3</td>
<td>135±6</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.5±1.1</td>
<td>1.3±1.0</td>
<td>NS</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blocker, % (n)</td>
<td>75 (69)</td>
<td>64 (58)</td>
<td>NS</td>
</tr>
<tr>
<td>ACEI or ARB, % (n)</td>
<td>90 (83)</td>
<td>88 (82)</td>
<td>NS</td>
</tr>
<tr>
<td>Spironolactone, % (n)</td>
<td>40 (36)</td>
<td>46 (41)</td>
<td>NS</td>
</tr>
<tr>
<td>Hemodynamics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>99±15</td>
<td>101±15</td>
<td>NS</td>
</tr>
<tr>
<td>PCW, mm Hg</td>
<td>14±5</td>
<td>15±4</td>
<td>NS</td>
</tr>
<tr>
<td>CI, L/min per m²</td>
<td>2.5±0.5</td>
<td>2.5±0.5</td>
<td>NS</td>
</tr>
</tbody>
</table>

CtnI indicates cardiomyopathy. Other abbreviations as in Tables 1, 2, and 3.

TABLE 5. Change in Left Ventricular Ejection Fraction According to Baseline Cardiac Troponin I Level

<table>
<thead>
<tr>
<th></th>
<th>cTnI &lt;0.04 ng/mL</th>
<th>cTnI ≥0.04 ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline LVEF, % (n=33)</td>
<td>26±10</td>
<td>24±8</td>
</tr>
<tr>
<td>Follow-up LVEF, % (n=25)</td>
<td>32±11</td>
<td>25±11</td>
</tr>
<tr>
<td>Decrease in LVEF at follow-up, % (n=25)</td>
<td>18</td>
<td>44†</td>
</tr>
<tr>
<td>Follow-up duration, mo (n=25)</td>
<td>5±3</td>
<td>6±3</td>
</tr>
</tbody>
</table>

*P<0.001, follow-up vs baseline LVEF. †P<0.05 compared with those with cTnI <0.04 ng/mL.

Figure 1. Cumulative survival of patients with detectable and undetectable cTnI levels.
advanced disease who were referred for transplantation evaluation. We did not collect information on race and ethnicity. cTnl levels were assessed at a single point in time. Neither neurohormones nor cytokines were measured in our patients, and BNP was available in only a subset of patients. We performed only a limited multivariate analysis, and since cTnl is associated with multiple predictors of HF death, we cannot claim that the prognostic value of cTnl is independent of all other predictors of death. Because this study was retrospective, we could not perform additional testing to determine the nature of the relation between cTnl, progressive ventricular dysfunction, and survival in HF.

Conclusions
In this cohort of patients with advanced HF, detection of serum cTnl was associated with impaired hemodynamics, elevated BNP levels, and progressive left ventricular dysfunction. cTnl was a significant predictor of increased mortality rates in patients with ischemic and nonischemic HF. Patients with detectable cTnl and elevated BNP were at particularly high risk of death or need for urgent transplantation, whereas patients without detectable cTnl and lower BNP levels had a substantially lower risk of adverse outcome. cTnl may be a novel, useful tool in identifying patients with HF who are at increased risk of progressive ventricular dysfunction and death, who probably will benefit from aggressive treatment strategies.

References

Figure 2. Risk of death associated with detectable levels of cTnl (≥0.04 ng/mL) for total cohort compared with subgroups of men and women, those with and without CAD, and excluding patients who underwent elective or urgent transplantation.

Figure 3. Mortality rates stratified by cTnl and BNP: cTnl−, cTnl <0.04 ng/mL; cTnl+, cTnl ≥0.04 ng/mL; BNP−, BNP <485 pg/mL; BNP+, BNP ≥485 pg/mL.

between serum cTnl levels and markers of sympathetic nervous system activation.25 In our cohort of patients with advanced HF, elevation of cTnl was associated with significantly decreased albumin and HDL, findings associated with systemic cytokine activation and catabolic state.26

Troponins and Risk Stratification
cTnl elevation in this cohort of patients with advanced HF signaled a significant, independent risk of death. Our findings are consistent with previous smaller studies. Sato et al3 studied 60 patients with dilated cardiomyopathy and found that cTnlT was increased in 27 patients. Persistently elevated levels were associated with decline in LVEF and higher mortality rates.3 In another study, elevated cTnl was found in 10 of 34 patients (29%) hospitalized with HF and was a predictor of death at 3 months.2 A study of 98 patients hospitalized with class III and IV HF found that a cTnlT level >0.033 µg/L on admission was associated with an increased risk of cardiac death.27

In our cohort, the prognostic power of cTnl appeared to be additive to other predictors of death in HF. The combination of elevated cTnl and elevated BNP identified patients with HF with a markedly increased risk of death (12-fold increase); this multimarker approach to risk stratification is similar to recent observations in patients with acute coronary syndromes in which cTnl, BNP, and C-reactive protein provided additive prognostic information.28 Patients with abnormalities of both cTnl and BNP biomarkers may derive particular benefit from more aggressive treatment strategies such as heart transplantation or HF device therapy. Prospective studies of cTnl and BNP as predictors of therapeutic response to HF drug and device therapies are warranted.

Limitations
We acknowledge potential limitations of our study. Our study examines a selected population of patients with HF with advanced disease who were referred for transplantation evaluation. We did not collect information on race and ethnicity. cTnl levels were assessed at a single point in time. Neither neurohormones nor cytokines were measured in our patients, and BNP was available in only a subset of patients. We performed only a limited multivariate analysis, and since cTnl is associated with multiple predictors of HF death, we cannot claim that the prognostic value of cTnl is independent of all other predictors of death. Because this study was retrospective, we could not perform additional testing to determine the nature of the relation between cTnl, progressive ventricular dysfunction, and survival in HF.

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