Congestive heart failure (CHF) is as a major public health issue in developed countries, and the cause of considerable morbidity and mortality among older adults. In the past 2 decades, the pharmacologic management of chronic CHF has undergone profound transformation, from the use of medications that immediately improved hemodynamic function and alleviated symptoms, to pharmaceuticals that prolong survival by blunting sympathetic nervous activity or the renin–angiotensin–aldosterone pathway, both of which participate in the progression of myocardial failure. The process of worsening chronic CHF is usually punctuated by several admissions to hospital for acute cardiac decompensation. However, the evidence of the safety and efficacy of medications administered during the decompensated phases is weaker than that supporting the use of drugs administered in the long term. Recent clinical trials in patients presenting with cardiac decompensation suggested that dobutamine and milrinone might increase morbidity and mortality. Guidelines for the treatment of acute heart failure (HF) recently issued by the European Society of Cardiology recommend that the use of these inotropic agents be limited to patients presenting with hypotension caused by low cardiac output. Moreover, an analysis of the Acute Decompensated Heart Failure National Registry (ADHERE) found that the in-hospital mortality of patients who had received intravenous nitroglycerin or nesiritide was lower than that of patients treated with dobutamine or milrinone. However, most of this evidence is derived from retrospective analyses and, when unspecified adjustment factors are present, comparing various patient groups is problematic.

We and other authors have recently suggested that the key contributors to the pathophysiology of acutely decompensated HF are congestion and myocardial injury, and that future therapies should focus on preserving the myocyte, as well as on improving hemodynamic function. If inotropic agents are injurious to the myocyte, the concentrations of biochemical markers of myocyte injury during treatment of acutely decompensated HF are expected to rise. We studied the serial measurements of brain natriuretic peptide (BNP) as a marker of myocardial load, and cardiac troponin (cTnI) as a marker of myocyte injury, in patients with acute cardiac decompensation in the absence of acute coronary syndrome, and discuss the significance of myocyte injury in this clinical setting.
were retained in the analysis are listed in Table 1. The characteristics of the 52 patients who were >18 years of age who were admitted to the intensive care unit of Hyogo Prefectural Amagasaki Hospital between June 2005 and November 2006 for management of decompensated HF without acute coronary event, were included in this study. A chest roentgenogram, screening blood samples and electrocardiogram were obtained upon admission to hospital. Stress scintigraphy or cardiac catheterization performed within 3 years was used to diagnose ischemic vs non-ischemic heart disease. The echocardiographic measurement of the left ventricular ejection fraction (LVEF) was done by 2 experts, who were unaware of the patients with serum cTnI concentrations >0.5 ng/ml was based on the observation of concentrations below 0.5 ng/ml in 100% of more than 500 consecutive patients presenting in New York Heart Association (NYHA) functional class I or II, (2) did not require treatment with intravenous diuretics, (3) had a history of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers (ARB), (4) suffered from vasodilators, inodilators or inotropes, (5) had a history of ischemic vs non-ischemic heart disease. The echocardiographic measurement of the left ventricular ejection fraction (LVEF) was done by 2 experts, who were unaware of the patients with serum cTnI concentrations >0.5 ng/ml was based on the observation of concentrations below 0.5 ng/ml in 100% of more than 500 consecutive patients presenting to our institution with non-ischemic heart disease (unpublished data). The characteristics of the 52 patients who were retained in the analysis are listed in Table 1.

### Study Population

All measurements of BNP, creatine kinase (CK)-MB, and cTnI were made by the PATHFAST rapid assay (Mitsubishi Kagaku Iatron Inc, Tokyo, Japan http://www.mitsubishichemical.com/HealthcareDiag/Products.html).

Because PATHFAST cannot measure BNP >2,000 ng/ml, those patients were excluded from our analysis.

### Statistical Analysis

Continuous variables were compared by factorial analysis of variance, and categorical variables were compared by chi-square analysis. Changes during follow-up were analyzed by 2-tailed Student’s paired t-test. Correlations between the patients’ baseline characteristics and category in the cTnI concentrations on day 1 were examined by logistic regression analysis. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. Actuarial analyses of freedom from rehospitalization for worsening CHF and deaths from CHF were performed by the Kaplan-Meier method, and compared by log-rank test. Hazard ratio was calculated by Cox-proportional-hazards analysis. Data are expressed as means±standard deviation. A p-value <0.05 was considered significant.

### Results

#### Increase in cTnI in the Treatment of Acute Cardiac Decompensation

The measurement of the biochemical markers made at baseline (n=52), and at means of 5.3 h (n=41), 25.2 h (day 1, n=48) and 7.1 days (day 7, n=40) after admission to the hospital were analyzed. The concentrations of BNP and CK-MB decreased and were both significantly lower on days 1 and 7 than at baseline (Table 2). In contrast, cTnI did not decrease significantly and, in 17 of the patients (35%), cTnI rose from 0.063±0.047 ng/ml at baseline to 0.167±0.181 ng/ml (p<0.05) on day 1 (Table 3). Patients with elevated cTnI concentrations on day 1 had (a) significantly lower baseline systolic (126.7±31.0 vs 153.3±32.0 mmHg) and diastolic (85.9±23.2 mmHg) blood pressures (p<0.01 for both comparisons), (b) significantly higher use of vasodilators (70% vs 29%, p<0.01), and (c) significantly lower use of vasodilators (41% vs 71%, p<0.05) than patients in whom cTnI had not increased between baseline and day 1. There were no significant differences at baseline between the 2 groups with respect to age, heart rate, serum creatinine concentration, blood hemoglobin content, LVEF, or administration of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers or Î±-blockers during the acute phase of cardiac decompensation (data not shown). There was no difference between the patients with ischemic vs non-ischemic heart disease in BNP, CK-MB and cTnI concentrations throughout the study, or in the percentage of patients with elevated cTnI.

### Measurement of Biochemical Markers

#### Table 1 Baseline Characteristics of the Study Population (n=52)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>71.9±12.2</td>
</tr>
<tr>
<td>Men, %</td>
<td>59</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>47±16</td>
</tr>
<tr>
<td>Blood pressure at admission, mmHg</td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>143±32</td>
</tr>
<tr>
<td>Diastolic</td>
<td>81±22</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>101±30</td>
</tr>
<tr>
<td>Underlying ischemic heart disease, n (%) of patients</td>
<td>14 (27)</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%) of patients</td>
<td>23 (44)</td>
</tr>
<tr>
<td>Creatinine, mg/dl</td>
<td>1.0±0.5</td>
</tr>
<tr>
<td>Hemoglobin, g/dl</td>
<td>12.6±2.4</td>
</tr>
<tr>
<td>Intravenous drugs during acute phase, n (%) of patients</td>
<td></td>
</tr>
<tr>
<td>Inotropes or inodulators</td>
<td>21 (40)</td>
</tr>
<tr>
<td>Vasodilators</td>
<td>33 (63)</td>
</tr>
<tr>
<td>Oral drugs during acute phase, n (%) of patients</td>
<td></td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitor or ARB</td>
<td>23 (44)</td>
</tr>
<tr>
<td>Î±-adrenergic blocker</td>
<td>18 (35)</td>
</tr>
</tbody>
</table>

Unless specified otherwise, values are means ± SD. ARB, angiotensin receptor blocker.

#### Table 2 Serial Measurements of Biochemical Markers in the Overall Patient Population

<table>
<thead>
<tr>
<th>Blood sampling time</th>
<th>All patients (n=52)</th>
<th>Baseline</th>
<th>5.3±1.6 h (n=41)</th>
<th>25.2±7.5 h (n=48)</th>
<th>7.1±1.6 days (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP (pg/ml)</td>
<td>902±529</td>
<td>819±417</td>
<td>529±495*</td>
<td>453±427*</td>
<td></td>
</tr>
<tr>
<td>CK-MB (ng/ml)</td>
<td>2.2±1.6</td>
<td>2.1±1.5</td>
<td>1.5±1.3*</td>
<td>1.2±1.6*</td>
<td></td>
</tr>
<tr>
<td>cTnI (ng/ml)</td>
<td>0.072±0.083</td>
<td>0.086±0.111</td>
<td>0.095±0.137</td>
<td>0.038±0.084</td>
<td></td>
</tr>
</tbody>
</table>

Values are means±SD. *p<0.0001 (all comparisons are vs baseline). See text for detailed explanation.
myocyte injury in acute heart failure

on day 1 (data not shown). Finally, at baseline, at 5 h and on day 7, the BNP, CK-MB, and cTnI concentrations were similar in patients with vs those without elevated cTnI on day 1. However, on day 1, the BNP (p<0.05), CK-MB (p<0.05), and cTnI (p<0.01) concentrations were significantly higher in patients with than in those without elevated cTnI on day 1 (Table 3).

Predictors of Increase in cTnI During the Acute Phase

By single variable regression analysis, an elevated systolic blood pressure (SBP) >median (as a mitigating factor) (OR 0.22; 95% CI: 0.06–0.84; p=0.0265), use of inotropes or inodilators (OR 5.87; 95% CI: 1.60–21.53; p=0.0076), and vasodilators (OR 0.24; 95% CI: 0.07–0.86; p=0.0276), and an initially elevated cTnI (OR 5.04; 95% CI: 1.39–18.25; p=0.0137) were predictors of elevated cTnI on day 1 (Table 4). In contrast, the baseline serum concentration of BNP was not a predictor (data not shown). By multiple variable analysis, an elevated SBP (as a mitigating factor) (OR 0.12; 95% CI: 0.02–0.76; p=0.0248), and high baseline cTnI (OR 13.85; 95% CI: 1.96–97.54; p=0.0083) were significant predictors of an elevated cTnI on day 1.

Increase in cTnI and Prognosis

During follow-up (mean 143 days (13–540 days)), 6 patients in the elevated cTnI on day 1 group vs 4 patients in the not elevated cTnI on day 1 group were rehospitalized for management of worsening CHF. After rehospitalization, 2 deaths (1 CHF death, 1 sudden death) occurred in the elevated cTnI on day 1 group, in contrast to no deaths in the not elevated cTnI group. By Kaplan-Meier actuarial analysis, the rate of rehospitalization for worsening CHF and death from CHF was significantly higher (p<0.05) in patients with elevated cTnI on day 1 than in patients whose cTnI had not increased (Fig 1). Although BNP level on days 1 and 7 was a predictor of rehospitalization for worsening CHF and death from CHF (each p<0.05), initial concentrations of BNP and cTnI were not predictors. After adjustment for baseline age, LVEF and creatinine, the hazard ratio for rehospitalization for worsening CHF and death of an elevated cTnI on day 1 was 4.049 (95% CI: 1.081–15.159; p=0.0379).

Discussion

This study is the first to show a persistently increased cTnI measured by rapid assay in patients presenting with acutely decompensated HF in the absence of an acute coronary event. cTnI was elevated on day 1 in one-third of the patients. The most important observations of our study were (1) ongoing myocyte injury observed 1 day after initiation of treatment for decompensated HF predicted adverse long-term outcomes, and (2) the observation of (a) myocyte injury (detected by an elevated cTnI), or (b) a low SBP in patients presenting with decompensation of HF were strong predictors of persistent myocyte injury.

Biochemical Prognostic Markers of Myocyte Injury in HF

A sensitive and specific assay has become available,
which can measure the blood concentrations of cTn, the protein of the myocyte’s myofilaments. We and others have reported that, in patients with chronic CHF, the serum concentrations of both cTnT and cTnI are prognostically useful. It is noteworthy that persistently increased concentrations of cTnT or cTnI have been observed in patients with ongoing cardiac remodeling, which suggests that they are markers of ongoing myocyte injury during this process. BNP is a hormone released from ventricular myocytes, which has been used as a diagnostic, prognostic and therapeutic biochemical marker in patients with CHF. We and other investigators have recently reported that cTn and BNP are both independent prognostic biochemical markers, and that their combined measurement identifies the patients at highest risk.

In contrast, few studies have been conducted in patients presenting with acutely decompensated HF. The measurement of BNP in the emergency department has been found to be helpful in guiding the diagnosis in patients presenting with acute dyspnea, and its decrease during hospitalization has been associated with lower rates of death or readmission to the hospital within 30 days. cTnT has also been described as a prognostic factor in acutely uncompensated HF in the absence of an acute coronary event. In the multiple variable analysis of data collected in the ADHERE trial, cTnT and BNP were both independent prognostic indicators. Therefore, cTn is a biochemical marker that is applicable in chronic as well as in acutely decompensated HF.

One important issue in the management of acute cardiac decompensation has been access to rapid assays of biochemical markers, and this is, to the best of our knowledge, the first study in which biochemical markers of myocyte injury were measured serially by rapid assay.

**Putative Causes of Myocyte Injury From the Perspective of Clinical Status**

In the presence of CHF, the sympathetic nervous, renin–angiotensin, and cytokine systems are activated. In concentrations measured in the failing heart, norepinephrine causes necrosis of the myocytes; Renin might cause myocyte injury via the renin–angiotensin system, because angiotensin II causes necrosis of both cytosol and adult ventricular myocytes. Likewise, TNF-α, an inflammatory cytokine, causes myocyte apoptosis. Finally, stretch because of myocardial overload can induce myocyte necrosis and apoptosis. Therefore, in chronic CHF, stretch, ongoing ischemia, and neurohumoral changes are putative causes of myocyte injury. In recent clinical studies, we and others found that patients suffering from CHF who had elevated cTnT concentrations also had significantly higher concentrations of circulating norepinephrine, renin, and C-reactive protein, than patients with lower cTnT.

**Putative Causes of Myocyte Injury From the Perspective of Drugs Used in the Management of Acute Cardiac Decompensation**

Some pharmaceuticals used in the treatment of acute cardiac decompensation promote apoptosis and loss of myocytes, in particular the positive inotropes that increase intracellular calcium. Treatment with catecholamines or inodilators for hours or days can increase hospital mortality and worsen the long-term prognosis. Therefore, it is recommended that inotropes be administered only when a hemodynamic improvement and lowering of myocardial load, which outweighs the direct detrimental effects of the drug, is expected. Our single variable analysis, which identified the use of inotropes or inodilators as an exacerbating factor, and the use of vasodilators as a mitigating factor of myocyte injury, supports these clinical observations. However, by multiple variable analysis, a low SBP and increased serum cTnT concentration at the time of presentation with decompensated HF were independent predictors of increased cTnT concentrations on day 1. Recently, Goreghiaie et al reported that SBP upon admission to the hospital was a strong predictor in patients hospitalized with acute HF. Although our observations support theirs, the individual pathophysiologic factors that cause myocyte injury in the clinical setting remain unknown.

**Management of Patients With Persistently Increased cTnT in Chronic and Acute HF**

Our current hypothesis is that persistently increased serum cTn concentrations during chronic CHF identify patients likely to have multiple admissions to hospital for management of acute cardiac decompensation, worsening their prognosis in the long term by causing further myocyte injury, as observed in this study. At this time, however, drugs that can lower the concentrations of cTn have not been identified. Prospective studies of interventions to lower cTn in both the chronic and acute phases of CHF are warranted.

**Study Limitations**

This preliminary study, conducted at a single medical institution, included a relatively small patient population and a large clinical trial is required to confirm the findings obtained from this study. Other considerations might have influenced its results. First, it is estimated that 60–70% of patients presenting with acutely decompensated HF suffer from coronary artery disease. Furthermore, the response to treatment with phosphodiesterase inhibitors is different in patients with ischemic vs non-ischemic heart disease. However, because we wanted to study myocyte injury occurring in the absence of acute ischemia, we excluded patients with disease manifestations consistent with acute coronary events, as well as those patients with baseline cTnI >0.5ng/ml. Second, we used olprinone, as well as milrinone, as the phosphodiesterase inhibitor. In contrast to dobutamine and milrinone, which have known adverse effects, olprinone has mild inotropic and prominent vasodilatory properties (data not shown). Third, because PATHFAST cannot measure serum BNP concentrations >2,000pg/ml, gravely ill patients were excluded from this study. However, at the present time, PATHFAST is the only available rapid assay that can measure both BNP and cTn. Fourth, BNP on days 1 and 7 had predictive power, which confirmed previous BNP data on a powerful predictor of prognosis in chronic HF. However, BNP at admission had no predictive power. This may reflect that marked BNP elevation occurs with acute aggravation, even in patients with relatively preserved left ventricular function whose prognosis is better at the chronic stage. Fifth, the endpoints used in most large clinical trials are mortality and morbidity. Several mechanisms, besides myocyte injury, might explain the adverse effects of inotropes on mortality, including arrhythmias and increased oxygen consumption. Our study, however, was limited to a correlation between biochemical markers of myocyte injury and rates of readmission to hospital for management of worsening CHF and death.
from CHF.

Acknowledgments
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References