Detectable Serum Cardiac Troponin T as a Marker of Poor Prognosis Among Patients With Chronic Precapillary Pulmonary Hypertension

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Background—Right ventricular failure is a leading cause of death in patients with chronic pulmonary hypertension (PH). We checked whether detection of cardiac troponin T (cTnT), a specific marker of myocyte injury, could be useful in prognostic stratification of those patients.

Methods and Results—Initial evaluation of 56 clinically stable patients (age 41±15 years) with pulmonary arterial (51 patients) or inoperable chronic thromboembolic (5 patients) PH (mean pulmonary arterial pressure 60±18 mm Hg) included cTnT test, allowing detection of its serum levels ≥0.01 ng/mL [cTnT(+)]. cTnT was detectable in 8 of 56 (14%) patients (mean±SD, 0.034±0.022; range, 0.010 to 0.077 ng/mL). Despite similar pulmonary hemodynamics, they had higher heart rate (92±15 versus 76±14 bpm, P=0.004), lower mixed venous oxygen saturation (50±10% versus 57±9%, P=0.04), and higher serum N-terminal pro-B–type natriuretic peptide (4528±3170 versus 2054±2168 pg/mL, P=0.03) and walked less during the 6-minute walk test (298±132 versus 396±101 m, P=0.02). Cumulative survival estimated by Kaplan-Meier curves was significantly worse at 24 months in cTnT(+) compared with cTnT(−) (29% versus 81%, respectively, log-rank test P=0.001). Multivariate analysis revealed cTnT status (hazard ratio, 4.89; 95% CI, 1.18 to 20.29; P=0.04), 6-minute walk test (hazard ratio, 0.93 for each 10 m; P=0.01), and pulmonary vascular resistance (hazard ratio, 1.13; P=0.01) as independent markers of mortality. All 3 cTnT(+) patients who survived the follow-up period converted to cTnT(−) during treatment.

Conclusions—Detectable cTnT is a so-far ignored independent marker of increased mortality risk in patients with chronic precapillary PH, supporting the role of progressive myocyte injury in the vicious circle leading to hemodynamic destabilization. (Circulation. 2003;108:844-848.)

Key Words: prognosis ■ hypertension, pulmonary ■ ventricles ■ ischemia ■ heart failure

Right ventricular (RV) failure resulting in low cardiac output is the main cause of death in patients with pulmonary arterial hypertension. It has been suggested that RV ischemic injury may be an important element of the final vicious circle leading to hemodynamic collapse.1 Severe pulmonary hypertension (PH) results in lower systemic blood pressure, both at rest and during exercise, and this may decrease coronary perfusion gradient.2 At the same time, increased RV intramural pressure may disturb the physiological pattern of RV myocardial perfusion, which no longer can be maintained throughout the heart cycle. In acute precapillary PH, such as attributable to an episode of pulmonary embolism, injury of myocytes evidenced by transient elevation of cardiac troponins was consistently reported and was related to increased in-hospital mortality.3–5 The objective of our study was to check whether circulating cardiac troponins can be detected and might have clinical significance also in patients with RV overload attributable to chronic precapillary PH.

Methods

The study population consisted of 56 consecutive patients with chronic PH who underwent complete diagnostic, hemodynamic, echocardiographic, and functional evaluation between June 1999 and November 2002 in a reference pulmonary vascular center.

Differential Diagnosis

This trial reports on baseline cardiac troponin T (cTnT) assessed in serum samples of patients ultimately diagnosed as having pulmonary arterial hypertension (PAH, n=51) or distal chronic thromboembolic pulmonary hypertension (CTEPH) not suitable for surgical treatment (n=5). The diagnosis required adherence to a local algorithm, including in all patients lung function tests and arterial blood gases, perfusion lung scintigraphy, spiral computed tomography with both contrast enhancement and high resolution assessment, transthoracic...
pulmonary hypertension was eventually diagnosed in 36 patients. Atrial septal defect with partial anomalous pulmonary venous drainage window with PH developing despite surgical closure, and atrial septal defect with partial anomalous pulmonary venous drainage, respectively, and portal hypertension in 1 patient. Primary pulmonary hypertension was eventually diagnosed in 36 patients.

**Troponin T**

Peripheral venous blood sampling for cTnT was performed after informed consent in fasting state on the morning of the day of the 6-minute walk test (6mWT). This was a part of a trial evaluating safety of exercise testing of patients with severe chronic PH, which was approved by a local ethical committee. Serum was centrifuged and stored frozen for later analysis of cTnT levels, which did not influence management. cTnT was assessed with highly sensitive third-generation quantitative test (electrochemiluminescence method ECLIA, Roche Diagnostics). Detection limit for cTnT was 0.01 ng/mL. According to the manufacturer, 99% of the healthy population has cTnT < 0.01 ng/mL, as assessed with this test. Thus, detectable concentrations of cTnT ≥ 0.01 ng/mL were considered abnormal.

In addition to initial evaluation, 52 of 56 patients had at least 1 reassessment of cTnT during the follow-up period. In 31 patients, serum cTnT level was reassessed within 24 hours to check for the reproducibility of the results. In 43 of 56 patients, a total of 141 serum samples were evaluated for cTnT beyond the 2nd day but within the 2nd year of the follow-up. In 26 patients, results of at least 4 serial cTnT tests were available for analysis.

**Prognostic Evaluation**

All patients underwent baseline evaluation including assignment of WHO functional class and unencouraged 6mWT with self-evaluation of dyspnea using Borg dyspnea score. Serum for assessment of N-terminal pro-BNP (NT-proBNP) with electrochemiluminescence method (ECLIA, Roche) was secured. At right heart catheterization, mean pulmonary arterial, mean right atrial pressures, pulmonary artery occlusion pressure, and mixed venous oxygen saturation were assessed. Pulmonary vascular resistance and cardiac index were calculated based on thermodilution or Fick measurements of pulmonary flow, whichever was appropriate. Oxygen consumption was directly measured in all patients with Eisenmenger syndrome. Pulmonary vasoreactivity was assessed with inhaled nitric oxide administered as 20-ppm mixture over 5 minutes. In addition, echocardiographic studies were performed with patients in left lateral position using the methodology previously reported as useful for evaluation of patients with primary PH. The ratio of diastolic areas of both ventricles, RV systolic area change, and left ventricular eccentricity index were assessed.7 Doppler index of myocardial function was calculated.8 Right atrial area was measured.9 The amount of pericardial effusion, if present, was assessed using a previously described score.

**Treatment and Follow-Up**

Fifteen of 56 patients were taking chronic low-dose calcium channel blockers already at presentation. According to local management strategy, the patients who decreased mean pulmonary arterial pressure by ≥ 20% and pulmonary vascular resistance by ≥ 30% (n= 5 among 51 patients with PAH) received chronic oral treatment with calcium channel blockers in maximal tolerated doses. All patients received chronic anticoagulation, unless contraindicated. Patients with signs of fluid retention received diuretics. Ten patients were undergoing chronic digoxin treatment, and this treatment was maintained in the absence of side effects. Chronic oxygen therapy was introduced in a few patients with resting hypoxemia. Neither chronic intravenous epoprostenol therapy nor lung or heart and lung transplantation were available therapeutic options during the time of this study. However, most nonresponder in functional class III/IV attributable to PAH after initial evaluation received either oral (n= 21) or subcutaneous (n= 12) prostacyclin analogues or endothelin receptor blocker (n= 7). Patients in the CTEPH group were treated with conventional therapy and subcutaneous (n= 3) or inhalal (n= 1) prostacyclin analogues. Two patients underwent balloon atrial septostomy. Patients were followed for a mean of 17 ± 8.5 months (range, 0.5 to 24 months).

**Statistical Analysis**

Patients with cTnT(+) and cTnT(−) were compared with respect to clinical characteristics, functional reserve, hemodynamics, and outcome. Data are expressed as mean ± SD. For categorical variables, the differences between the groups were compared using Yates corrected χ² test. For continuous variables, Student’s t test or Wilcoxon test was used depending on the character of distribution. P < 0.05 was considered statistically significant. The proportion of patients surviving at each time point was estimated by the Kaplan-Meier method. Survival for the groups with and without detectable cTnT was compared using the log-rank test. Univariate and multivariate Cox proportional hazard analysis of selected variables was performed to identify factors independently related to mortality and providing best-fitted model related to outcome. Results are expressed as hazard ratios with 95% CIs. All analyses were performed using STATISTICA 5.5 (StatSoft) computer software.

**Results**

cTnT could be detected at initial evaluation in serum of 8 of 56 (14%) patients with a mean level of 0.034 ± 0.022 and range of 0.010 to 0.077 ng/mL. It was detected in 7 of 51 (14%) patients with PAH and 1 of 5 (20%) patients with CTEPH. Compared with cTnT(−) patients, those with detectable cTnT had similar pulmonary hemodynamics but higher heart rate (92 ± 15 versus 76 ± 14 bpm, P = 0.004), lower mixed venous oxygen saturation (50 ± 10% versus 57 ± 9%, P = 0.04), and higher serum NT-proBNP (4528 ± 3170 versus 2054 ± 2168, P = 0.03) and covered less distance during 6mWT (298 ± 132 versus 396 ± 101 m, P = 0.02) (Table 1). No statistically significant difference was found between cTnT(+) and cTnT(−) groups in the prevalence of patients initially receiving digoxin (37% versus 15%) and low-dose calcium channel blockers (25% versus 27%). Survival trends were significantly different between cTnT(+) and cTnT(−) patients (Figure). During follow-up, 5 of 8 (63%) patients died in the cTnT(+) and 7 of 48 (15%) patients in the cTnT(−) group (P = 0.01). Cumulative survival estimated by Kaplan-Meier curves was significantly worse at 24 months in cTnT(+) compared with cTnT(−) (29% versus 81%, respectively, log-rank test P = 0.001). This was also true when survival analysis was limited to 36 patients with PPH (56% versus 87%, log-rank test P = 0.04).

Additionally, in 2 of 7 cTnT(−) patients who died, this was not attributable to progressive RV failure but to massive pulmonary hemorrhage and abrupt discontinuation of chronic prostanoid treatment, respectively. Univariate analysis identified several factors related to mortality, including heart rate, WHO functional class, cardiac index, pulmonary vascular resistance, distance covered during 6mWT, ratio of RV and left ventricular diastolic areas, and cTnT status (Table 2).
Neither diagnosis nor the type of treatment ultimately received had significant effect on survival in the studied group. However, all 5 true responders were cTnT(−) and survived the follow-up period. One of 4 cTnT(−) Eisenmenger patients died, but this was attributable to abrupt discontinuation of therapy, as has already been mentioned. According to a stepwise multivariate analysis, the best model predicting survival consisted of result of 6mWT, cTnT status, and pulmonary vascular resistance (Table 3).

### Repeated cTnT Assessment

In clinically stable patients with PH, cTnT levels were reproducible. When rechecked after 24 hours, both tests were negative in 27 patients, whereas in 3 patients both tests were positive and revealed almost identical cTnT levels (0.049 and 0.046, 0.032 and 0.034, and 0.019 and 0.017 ng/mL, respectively) In 1 patient, TnT was negative on first evaluation and borderline (0.010 ng/mL) after 24 hours. This patient clinically improved as a result of combined treatment with bosentan, beraprost, and atrial septostomy and remained cTnT(−) at days 338 and 656 of follow-up.

Among 8 initially cTnT(+) patients, 7 had at least 1 reassessment of cTnT status. In 3 patients, cTnT remained increased whereas in 1 it was no longer present on day 210 of beraprost treatment but reappeared at day 337. All 4 of those patients died. In contrast, 3 patients in whom repeated tests revealed disappearance of initially elevated cTnT (0.029, 0.015, and 0.021 ng/mL, respectively) survived. They were treated with continuous subcutaneous treprostinil infusion, oral bosentan, and septostomy on top of combined prostanoid treatment (beraprost and treprostinil), respectively.

Among initially cTnT(−) patients, 3 became cTnT(+) during the first and an additional 2 during the second year of follow-up. Two of the 5 patients died. In both cases, cTnT was detected during the first year of follow-up.
cTnT as a Marker of Risk in Chronic Precapillary PH

**Discussion**

Precise prognostic stratification of patients with severe pulmonary arterial hypertension is of paramount importance. Criteria allowing for optimal timing of therapeutic procedures and especially of listing for lung transplantation is still a matter of controversy. Mortality on the waiting list remains a significant problem. However, because of suboptimal long-term results, listing for lung transplantation should be always fully justified. Most of the identified prognostic markers in primary pulmonary hypertension are related to RV function and cardiac output. These include various indices of exercise tolerance as well as mean right atrial pressure and cardiac index. Also, echocardiographic markers of adverse prognosis, such as right atrial area and pericardial effusion, both reflect elevated filling pressures of the right heart. Recently, elevated B-type natriuretic peptide, a biochemical marker of ventricular overload, was reported as an independent prognostic factor in patients with PPH. Our results indicate that cTnT, a biochemical marker of myocyte damage, can be detected in serum of 14% of patients with chronic precapillary PH and is a strong independent marker of mortality together with pulmonary vascular resistance and distance covered during 6mWT.

cTnT and cTnI are among key prognostic markers in acute coronary syndromes. However, elevated or detectable cTnT has been also reported in chronic left ventricular failure. Although it cannot be directly proved, it is likely that in our patients cTnT leaked from RV myocytes. Both RV function and peripheral tissue perfusion seem more disturbed in our cTnT(+) patients, as indicated by higher NT-proBNP level and lower mixed oxygen saturation, respectively.

**TABLE 3. Multivariate Cox Proportional Hazard Analysis**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
<th>Cumulative $\chi^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Six-minute walk distance, per 10 m</td>
<td>0.93</td>
<td>0.87–0.98</td>
<td>0.01</td>
<td>10.6</td>
</tr>
<tr>
<td>Detectable cTnT</td>
<td>4.89</td>
<td>1.18–20.29</td>
<td>0.03</td>
<td>14.4</td>
</tr>
<tr>
<td>PVR, Wood units</td>
<td>1.13</td>
<td>1.03–1.23</td>
<td>0.01</td>
<td>20.5 ($P=0.0001$)</td>
</tr>
</tbody>
</table>

PVR indicates pulmonary vascular resistance.

Pulmonary hypertension puts RV myocardium in a difficult metabolic situation, with lower systemic pressure and higher intramural RV pressure resulting in reduced coronary perfusion gradient. Higher heart rate in our cTnT(+) patients suggests hypotension-mediated compensatory increased adrenergic drive additionally increasing oxygen demand of RV myocardium. Similar mechanisms leading to RV ischemia seem to operate in acute pulmonary embolism, where elevated cardiac troponins were reported to identify a subgroup at high risk of adverse outcome.

Recently, Guler et al reported troponin I to be normal in exacerbated cor pulmonale attributable to chronic obstructive
pulmonary disease, contrasting with increased troponin I levels in decompensated left ventricular failure. Indeed, the serum levels of cTnT found among our PAH and CTEPH patients were below the threshold of point of care tests (>0.1 ng/mL) used in acute coronary syndromes in clinical practice. Nevertheless, we found cTnT even within this range to be a strong and independent prognostic factor. There is an ongoing debate as to whether cardiac troponins detected with current high-sensitive assays indicate myocyte death. Recently, alternative explanation has been brought forward suggesting primary intracellular degradation of troponin caused by excessive intracellular Ca^{2+} concentration in the failing myocardium. Troponin breakdown products leaking outside the myocyte would react with specific cTnT antibodies of presently used assays.22 According to this theory, serum troponin could be a marker of intracellular degradation of contractile proteins and not necessarily of necrosis of the myocytes. Whichever the mechanism, elevated cardiac troponin is increasingly reported as a marker of poor prognosis also outside acute coronary syndromes.4,19,23

It would be premature to formally recommend a place for cTnT assessment in clinical management of patients with PAH and CTEPH. However, detectable cTnT seems to convey an important message, indicating acceleration of the vicious circle of RV failure precipitating systemic hemodynamic collapse and death. Importantly, cTnT status of a patient may change with time because of either the natural history of the disease or applied treatment. Therefore, it seems likely that monitoring serum cTnT could assist in management decisions in patients with PH.

**Limitation of the Trial**

The study population was not entirely homogeneous, because it included patients representing various classes of PAH as well as a small group with nonoperable CTEPH. One might expect CTEPH patients, usually older and more likely to have concomitant coronary atherosclerosis, to suffer myocardial damage and release cTnT more easily when faced with severely altered pulmonary hemodynamics than patients with PAH.24 However, otherwise, CTEPH and PAH share similar mechanisms leading to RV ischemia in the setting of severe RV pressure overload. We noticed neither clear differences in the prevalence nor in the prognostic implication of detectable serum cTnT between those 2 groups.

Although patients in our trial were treated in several different ways, this did not significantly affect their outcome, whereas cTnT retained its prognostic significance. This may be attributable either to the small therapeutic subgroups or indicate that patients with cTnT(+) require therapy that was not available (intravenous prostanooids or lung transplantation) or was rarely used (atrial septostomy) in our study population. Only some of the previously identified prognostic markers were found significant in our study population (functional class, 6minWT, cardiac index, and pulmonary vascular resistance), whereas others were not (right atrial and pulmonary arterial pressures and mixed venous oxygen saturation). This could be attributable to the relatively small study group.

In summary, detectable cTnT is a so-far ignored independent marker of increased mortality risk in patients with chronic severe pulmonary arterial or thromboembolic hypertension, supporting the role of progressive RV myocyte injury in the vicious circle leading to hemodynamic destabilization. Identification of effective methods protecting RV myocytes against cTnT leakage and impact of such protection on outcome of patients with precapillary PH represents an interesting direction for future research.

**References**

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_Circulation._ 2003;108:844-848; originally published online August 4, 2003; doi: 10.1161/01.CIR.0000084544.54513.E2

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

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