Independent Prognostic Value of Cardiac Troponin T in Patients With Confirmed Pulmonary Embolism

Evangelos Giannitsis, MD; Margit Müller-Bardorff, MD; Volkhard Kurowski, MD; Britta Weidtmann, MD; Uwe Wiegand, MD; Markus Kampmann, MD; Hugo A. Katus, MD

Background—Cardiac troponin T (cTnT) is a sensitive and specific marker, allowing the detection of even minor myocardial cell injury. In patients with severe pulmonary embolism (PE), myocardial ischemia may lead to progressive right ventricular dysfunction. It was therefore the purpose of this study to test the presence of cTnT and its prognostic implications in patients with confirmed PE.

Methods and Results—Fifty-six consecutive patients with confirmed PE were enrolled in this prospective study. PE was confirmed by pulmonary angiography, lung scan, or echocardiography and subsidiary analyses. Severity of PE was assessed by a clinical scoring system, and cTnT was measured within 12 hours after admission. cTnT was elevated (≥0.1 µg/L) in 18 (32%) patients with massive and moderate PE but not in patients with small PE. In-hospital death (odds ratio 29.6, 95% CI 3.3 to 265.3), prolonged hypotension and cardiogenic shock (odds ratio 11.4, 95% CI 2.1 to 63.4), and need for resuscitation (odds ratio 18.0, 95% CI 2.6 to 124.3) were more prevalent in patients with elevated cTnT. cTnT-positive patients more often needed inotropic support (odds ratio 37.6, 95% CI 5.8 to 245.6) and mechanical ventilation (odds ratio 78.8, 95% CI 9.5 to 653.2). After adjustment, cTnT remained an independent predictor of 30-day mortality (odds ratio 15.2, 95% CI 1.22 to 190.4).

Conclusions—cTnT may improve risk stratification in patients with PE and may aid in the identification of patients in whom a more aggressive therapy may be warranted. (Circulation. 2000;102:211-217.)

Key Words: embolism ■ pulmonary heart disease ■ coronary disease

Right ventricular (RV) dysfunction is a frequent consequence of severe pulmonary embolism (PE) and correlates with increased risk of death.1-5 Experimental and clinical evidence suggests that myocardial ischemia and even RV infarction may result from an acute rise in pulmonary artery pressures and may then cause RV failure and eventually death.6-9 Risk stratification is particularly important because more aggressive therapies such as thrombolitics and inotropic vasoactive drugs may improve outcome.1,4,9 Detection of severe myocardial ischemia leading to minor myocardial damage or acute myocardial infarction (AMI) may improve risk stratification.

Cardiac troponin T (cTnT) is a highly sensitive and specific marker of myocardial cell injury,10,11 and its role for risk stratification in acute coronary syndromes is well established.12-15 The aim of the present study was to determine the incidence of minor myocardial damage and AMI in patients with PE and to elucidate the prognostic value of cTnT in these patients.

Methods

Study Population

A cohort of 56 consecutive patients with confirmed diagnosis of acute PE were enrolled. Patients examined beyond 14 days after onset of symptoms were not included because potential benefits of more aggressive therapy, particularly thrombolytic therapy, have not been established in these patients.16 Diagnosis of PE was confirmed by pulmonary angiography or high probability ventilation-perfusion lung scan. A combination of abnormal echocardiography with clinical presentation (acute onset of dyspnea, tachypnea, chest pain, syncope, hypotension, or shock) in the absence of preexisting chronic pulmonary disease was regarded diagnostic as well. Diagnosis was further strengthened by objective evidence of deep-vein thrombosis, a positive plasma D-dimer–ELISA (≥500 µg/L), a blood gas analysis revealing otherwise unexplainable hypoxemia and hypocapnia, or an abnormal ECG (tachycardia, large S wave in lead I or Q wave in lead III, complete or incomplete right bundle-branch block, inverted T waves in right precordial chest leads).

The severity of PE was classified clinically into (1) massive, (2) moderate to large, and (3) small PE according to the grading system of Goldhaber.17 Patients were classified as having massive PE in the presence of persistent systemic hypotension or cardiogenic shock and signs of RV dysfunction. Moderate PE was defined as RV dysfunction in the presence of normal systemic arterial blood pressure, and small PE in the absence of both systemic arterial hypotension, and RV dysfunction.

RV function was assessed by transthoracic echocardiography. Diagnosis of RV dysfunction was made in the presence of any of the following: (1) abnormal motion of the interventricular septum, (2) dilation of the right ventricle (diastolic diameter ≥30 mm), (3)
hypokinesis of the RV, or (4) tricuspid valve regurgitation (jet velocity >2.5 m/s). Data were collected on (1) clinical symptoms and signs on admission, (2) presence of underlying diseases or predisposing factors for PE, (3) history of coronary artery disease (CAD), (3) findings of diagnostic procedures including blood gas analysis, ECG, echocardiography, pulmonary angiography, right and left heart cardiac catheterization, and coronary angiography, ventilation-perfusion scans. Laboratory tests included measurements of D-dimers (ELISA, Asserachrom, upper limit of normal 400 µg/L), cTnT, creatine kinase (CK) (upper limit of normal 80 IU/L for men and 70 IU/L for women), and MB-isoenzyme activities (upper limit of normal 9 IU/L).

Blood samples for cTnT were obtained on admission. Patients with a negative test received a second measurement within 12 hours of presentation by means of a qualitative immunological assay (TropT, Roche Diagnostics) or a quantitative ELISA (ES 300

### TABLE 1. Diagnostic Workup

<table>
<thead>
<tr>
<th>Pathological Analysis, n (%)</th>
<th>Pulmonary Angiography (n=18)</th>
<th>Lung Scan (n=22)</th>
<th>Either Pulmonary Angiography or Lung Scan (n=40)</th>
<th>Neither Pulmonary Angiography or Lung Scan (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary angiography</td>
<td>18 (100)</td>
<td>2 (9)</td>
<td>18 (45)</td>
<td>...</td>
</tr>
<tr>
<td>Ventilation/perfusion scan</td>
<td>2 (11)</td>
<td>22 (100)</td>
<td>22 (55)</td>
<td>...</td>
</tr>
<tr>
<td>Compression leg ultrasound</td>
<td>7 (38.9)</td>
<td>9 (40.9)</td>
<td>15 (37.5)</td>
<td>7 (43.8)</td>
</tr>
<tr>
<td>Transthoracic/transesophageal echocardiography</td>
<td>10 (55.5)</td>
<td>14 (63.6)</td>
<td>16 (40)</td>
<td>16 (100)</td>
</tr>
<tr>
<td>Swan-Gantz catheter</td>
<td>9 (50)</td>
<td>2 (9)</td>
<td>10 (25)</td>
<td>4 (25)</td>
</tr>
<tr>
<td>D-Dimer ≥500 ng/L (ELISA)</td>
<td>7 (38.9)</td>
<td>8 (36.4)</td>
<td>15 (37.5)</td>
<td>6 (37.5)</td>
</tr>
<tr>
<td>Abnormal ECG</td>
<td>15 (83.3)</td>
<td>15 (68.2)</td>
<td>31 (77.5)</td>
<td>10 (62.5)</td>
</tr>
<tr>
<td>Blood gas analysis</td>
<td>12 (66.7)</td>
<td>15 (68.2)</td>
<td>26 (65)</td>
<td>13 (81.3)</td>
</tr>
</tbody>
</table>

Values are given as absolute numbers with relative frequencies in parentheses.

### TABLE 2. Baseline Clinical Characteristics of 56 Study Group Patients According to Levels of Troponin T

<table>
<thead>
<tr>
<th>All Patients</th>
<th>≥0.1 ng/mL (n=18)</th>
<th>&lt;0.1 ng/mL (n=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>68.7 ± 1.6</td>
<td>71.6 ± 2.9</td>
</tr>
<tr>
<td>Men</td>
<td>28 (50)</td>
<td>10 (56)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.9 ± 0.7</td>
<td>28.9 ± 1.3</td>
</tr>
<tr>
<td>Clinical signs/symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syncope</td>
<td>12 (21)</td>
<td>6 (33)</td>
</tr>
<tr>
<td>Dyspnea/tachypnea</td>
<td>51 (91)</td>
<td>16 (89)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>38 (68)</td>
<td>10 (56)</td>
</tr>
<tr>
<td>History of cardiovascular disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous CABG</td>
<td>3 (5)</td>
<td>...</td>
</tr>
<tr>
<td>Previous PTCA</td>
<td>4 (7)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>11 (20)</td>
<td>3 (17)</td>
</tr>
<tr>
<td>Cardiovascular risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>13 (23)</td>
<td>3 (17)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>22 (39)</td>
<td>7 (39)</td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>40 (71)</td>
<td>12 (67)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>8 (14)</td>
<td>3 (17)</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>3 (5)</td>
<td>...</td>
</tr>
<tr>
<td>Thromboembolic risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent surgery</td>
<td>15 (27)</td>
<td>7 (39)</td>
</tr>
<tr>
<td>Use of contraceptives</td>
<td>3 (5)</td>
<td>...</td>
</tr>
<tr>
<td>Previous thromboembolic event</td>
<td>9 (16)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Disorder of hemostasis</td>
<td>4 (7)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Deep-vein thrombosis</td>
<td>22 (39)</td>
<td>8 (44)</td>
</tr>
<tr>
<td>History of deep-vein thrombosis</td>
<td>14 (25)</td>
<td>3 (17)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>6 (11)</td>
<td>4 (22)</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; CAD, coronary artery.
Values are given as absolute numbers with relative frequencies in parentheses or as means ± SD.
system, Roche Diagnostics). The qualitative assay with a detection limit of 0.1 μg/L\(^{19}\) was used in 41 (73.2%) of 56 patients. For practical reasons, qualitative and quantitative cTnT values exceeding the discriminator value are reported as positive.

All patients were followed up prospectively for in-hospital death related to PE.

### Statistical Analysis

Mean values were calculated for continuous variables and absolute and relative frequencies for discrete variables. Univariate comparison of continuous data were performed with the use of the unpaired Student’s \(t\) test or Wilcoxon test. For comparison of discrete variables, a \(\chi^2\) test or Fisher’s exact test was used. Multiple logistic regression analysis was performed for prediction of in-hospital death. Only variables with significant univariate association were included in different models. Many variables were highly correlated. We therefore adjusted for those variables that were most strongly associated with in-hospital death, were less likely to be intercorrelated, and appeared to address different issues. The variables included in the final model are listed in Table 4. A 2-tailed
probability value of <0.05 was considered significant. The cumulative survival curves were constructed with the use of the Kaplan-Meier method, with death from PE as an end point. Statistical analysis was performed with the use of a commercially available statistical package (SPSS for Windows, Version 5.0.2).

Results

Study Group

From April 1996 to November 1998, 56 consecutive patients with confirmed diagnosis of PE were included. PE was confirmed by pulmonary angiography in 18 (32%) and high-probability lung scintigraphy in 22 (39%) patients. In 16 (28.6%) patients, diagnosis of PE was based on echocardiography in combination with clinical presentation in the absence of a preexisting chronic pulmonary disease. Diagnosis of PE was strongly supported by elevated pulmonary artery pressures, which were measured invasively in 14 (25%) or by Doppler echocardiography in 32 (57%), objective evidence of deep-vein thrombosis in 22 (39.3%), or the result of a d-dimer test, which was performed in 21 patients and was positive in 17 (80.9%) cases. Absolute and relative frequencies of diagnostic subsidiary analyses in different diagnostic categories, that is, confirmed PE by pulmonary angiography (n=18), ventilation-perfusion lung scan (n=22), either angiography or lung scan (n=40), and neither angiography or lung scan (n=16) are displayed in Table 1.

Diagnosis of PE was confirmed after a median of 2 hours (range 0.5 to 22) after admission. Median time from onset of symptoms suggestive of acute PE or symptomatic recurrence of silent PE was 3 days (range 1 to 12).

Baseline clinical variables of the entire group and of cTnT groups are displayed in Table 2. A positive cTnT was detected in 18 (32%) patients and only among those with moderate and severe PE. No significant differences were observed between cTnT groups.

According to the predefined criteria adapted from Goldhaber et al,17 17 (30%) were diagnosed as having massive PE, 26 (46%) patients moderate to large PE, and 13 (23%) patients small PE (Table 3). Sixteen patients received thrombolytic therapy for massive or moderate to large PE. All but 1 patient who had previously undergone a major surgical intervention received intravenous heparin therapy adjusted to a 2-fold increase of activated partial thromboplastin time.

Diagnostic Findings According to Levels of cTnT

RV dysfunction was more often found in patients with elevated cTnT. These patients also revealed more often a right bundle-branch block and abnormal right precordial repolarization. Mean pulmonary artery pressures as measured invasively and systolic RV pressures were comparable.

Activities of CK and CK-MB were higher in cTnT-positive patients. In 4 (7.1%) patients, the profile of cardiac enzymes (CK activity >2 times the upper limit of normal in combination with a CK-MB/CK ratio ≥0.06) was suggestive of AMI without characteristic ECG changes. Details are given in Table 3.

In-Hospital Course According to Levels of cTnT

Total in-hospital mortality rate was 16%. Marked differences in mortality rates were observed in patients with massive versus moderate PE (41.1% versus 7.7%, P=0.002) (Figure 1).

TnT was highly discriminative with respect to mortality, being 44% in cTnT-positive versus 3% in cTnT-negative patients (P<0.001) (Figure 2). Indicators of a more severe PE such as prolonged hypotension and shock, severe hypoxemia, need for resuscitation, inotropic therapy, or mechanical ventilation were also more frequently present in the cTnT-positive patients. Moreover, cTnT-positive patients had a significantly longer stay in the intensive care unit than did cTnT-negative patients (P=0.003). It is tempting to speculate that CAD may be more prevalent in cTnT-positive patients. However, coronary angiography disclosed significant CAD in an equal distribution between cTnT-positive and cTnT-negative patients.

Of the 16 patients treated with thrombolytic agents, 8 were cTnT positive and another 8 were cTnT negative. Details on in-hospital outcomes are given in Table 4.

Predictors of In-Hospital Death

The clinical severity of PE proved valuable for prediction of inhospital death (massive versus moderate PE, [OR 8.4; 95% CI 1.5 to 47.7]). Moreover, cTnT indicated an increased hazard for in-hospital death (cTnT ≥0.1 versus cTnT <0.1 µg/L, [OR 29.6; 95% CI 3.3 to 265.3]). Univariate analysis revealed an association of death with syncope at presentation (OR 7.1; 95% CI 1.5 to 33.3), prolonged hypotension and cardiogenic shock (OR 11.4; 95% CI 2.1 to 63.4), need for mechanical ventilation (OR 78.8; 95% CI 9.5 to 653.2), resuscitation (OR 18; 95% CI 2.6 to 124.3) or need for inotropic support (OR 37.6; 95% CI 5.8 to 245.6), severe hypoxemia as suggested by $p_{O_2}/FIO_2$ ratio <250 mm Hg (OR 9.9; 95% CI 1.1 to 85.6), and evidence of concomitant AMI (OR 18.3; 95% CI 3.2 to 106.5). In logistic regression analysis, cTnT remained the only independent predictor of
in-hospital death (adjusted OR 15.2; 95% CI 1.22 to 190.37) and was superior to CK activity, which was not independently predictive (Table 5).

**Discussion**

In the present study, cTnT levels ≥0.1 μg/L were frequently found in patients with moderate and severe PE. Along with rises in total CK and CK-MB activities, circulating cTnT indicates irreversible myocardial cell damage. Since elevations of cTnT were observed even in patients without CAD, it is likely that release of cTnT from myocardium results from acute RV pressure overload, impaired coronary blood flow, and severe hypoxemia caused by PE. Moreover, our data demonstrate that patients with elevated cTnT are at considerably higher risk for subsequent in-hospital death. Thus, this study not only confirms previous experimental and clinical studies showing an association between myocardial ischemia and RV dysfunction but also provides strong evidence that myocardial cell injury is a major risk factor in patients with PE.

**Myocardial Ischemia in RV Dysfunction**

That PE may cause myocardial ischemia and AMI has been recognized for >50 years. Acute pressure overload in acute PE may result in regional myocardial ischemia as the result of increased wall tension and oxygen demand and reduced coronary perfusion and oxygen supply. Limitation of pericardial expansion in the presence of a dilated right ventricle together with leftward shift of the interventricular septum appear to contribute to the diminished left ventricular preload and resultant decreased cardiac output. Hypoxemia, systemic arterial hypotension, and cardiogenic shock may further increase the propensity to ischemic damage, and preexisting cardiopulmonary abnormalities may contribute to both the hemodynamic alteration and the risk of ischemia and infarction induced by PE. Accordingly, RV failure has been reported to develop more likely in patients with coexistent CAD. On the other hand, RV infarction has been reported to occur with either normal or mildly to moderately diseased coronary vasculature.

The role of the highly cardio-specific troponins for identification of AMI and minor myocardial damage is well established. The incidence, however, of elevated cTnT in the setting of acute PE remains largely undetermined. Recently, a small French prospective cohort that enrolled 29 patients with acute PE found elevated levels of troponin I in 2 patients. Both patients had submassive PE and survived. In our cohort, elevated cTnT levels were found in 18 (32%) of 56 consecutive patients and exclusively among patients with moderate and severe PE.

Some of these patients had concomitant significant CAD, increasing the propensity for myocardial ischemia. However,
a considerable proportion developed elevated cTnT in the absence of CAD, which underscores the hypothesis that cTnT is being released as a consequence of ischemic injury to the right ventricle.6–8

**Role of cTnT for Risk Assessment**

Risk stratification in PE is paramount because prognosis strongly influences selection of appropriate management strategies. Hemodynamic instability and cardiogenic shock are regarded as indicators for thrombolytic therapy,9 whereas the optimal therapy for normotensive patients with RV dysfunction is still controversial. More recently, there is accumulating evidence that RV dysfunction indicates a high-risk subgroup and that improved outcome and lower rates of recurrent PE are achieved with thrombolytic therapy in these patients.1,3,9 RV dysfunction may be identified by echocardiography even in critically ill patients, demonstrating evidence of RV dysfunction in 46% to 81% of cases with acute PE.1,4,28

In addition to RV dysfunction, there are some other indicators of increased risk for early death such as hemodynamic instability, prolonged arterial hypotension, older age, syncope at presentation, need of cardiopulmonary resuscitation, chronic pulmonary disease, and cardiovascular disease.3,19,29

The present study identifies a subgroup of patients with cTnT ≥0.1 μg/L at increased risk of subsequent death. In-hospital mortality rate was 44% in patients with elevated cTnT compared with only 3% in patients with normal cTnT. The predictive value of cTnT persisted even after adjustment for severity of PE, thus correcting for hemodynamic instability and presence of RV dysfunction. An even less favorable outcome was found for those patients with cTnT and a concomitant ≥2-fold increase of CK activity reflecting more severe myocardial ischemia. All 4 patients with cTnT and positive cardiac enzymes had massive PE requiring mechanical ventilation and catecholamines and died subsequently from progressive right heart failure and cardiogenic shock. In 3 of these patients, an underlying CAD was ruled out by coronary angiography.

In this study, diagnosis of PE was confirmed by pulmonary angiography in 32% and lung scan in 39% of all patients. Thus, the diagnostic workup in this study is comparable to that of 2 recent large-scaled registries reporting use of pulmonary angiography in 17% to 19% and lung scan in 47% to 55% of cases.5,18 In both registries and in the present study, PE was more frequently diagnosed by bedside echocardiography in combination with high clinical suspicion. Conversely, a diagnostic strategy seeking more definite confirmation of PE by use of pulmonary angiography and lung scan may lead to selection of a patient cohort with a more benign clinical outcome because transportation from the intensive care unit to the diagnostic facilities is possible only in the less critically ill patients.18

Interestingly, the total in-hospital mortality rate of our cohort was 16% and similar to the 17% to 22% mortality rates found in both large-scaled multicenter registries.5,18 Moreover, mortality rates in particular subgroups were comparable to earlier reports ranging from 4.1% for stable patients without RV dysfunction2 to 32% for massive PE presenting with hemodynamic instability.16,30

**Limitations**

The present study is limited by 2 shortcomings. First, sample size is not sufficiently large to allow detailed statistical investigation of all competing prognostic risk factors. However, prognostic risk factors that usually contribute to patient risk stratification were taken into account in the multiple regression model. In particular, RV dysfunction and hemodynamic instability were partially controlled because these variables represented defining criteria for massive and large PE. Second, the prevalence of CAD (42%) is higher than commonly reported in unselected cohorts. However, the present study sought to determine the cause of cTnT elevation in patients with PE. Therefore, all patients except those who refused or died underwent coronary angiography during early diagnostic workup or at least before discharge, which may explain some discrepancies to other registries with respect to the prevalence of CAD. Although there were patients in whom significant CAD may have contributed to myocardial ischemia during acute PE, our data clearly demonstrate that cTnT elevations occur even in absence of CAD.

**Conclusions**

Increased cTnT levels are not uncommon during moderate and severe PE. Although the exact pathomechanism remains unclear, the association between cTnT and RV dysfunction in the absence of significant CAD suggests a link between acute increase of RV afterload and severe and possible irreversible myocardial ischemia. Moreover, cTnT was an independent predictor of in-hospital death and thus may aid risk stratification and guidance of the appropriate therapeutic management of acute PE.

**Acknowledgment**

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**References**


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