Prognostic Role of Right Ventricular Dilatation and Troponin I Elevation in Acute Pulmonary Embolism

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SUMMARY

Acute pulmonary embolism continues to cause significant morbidity and mortality despite advances in diagnosis and treatment. This retrospective analysis aimed to determine whether the combination of elevated troponin I and right ventricular dilatation (RVD) could provide a more powerful predictor for risk evaluation.

The study data comprised records of 110 patients with either high-probability ventilation/perfusion lung scan or positive spiral computed tomography. All cause 100-day mortality was 18.2%. The hypotension and RVD variables significantly influenced 100-day mortality. For the combination of RVD and raised troponin I, the 100-day mortality rate was 31%. Notably, the group with elevated troponin I and no RVD had a 100-day mortality rate of only 3.7%. The combination of RVD and elevated troponin had a positive predictive value of 31% and a negative predictive value of 88% for 100-day mortality. Compared with existing reports, conflicting conclusions for the individual prognostic role of elevated troponin I, cancer, and heart failure were obtained. These conflicting conclusions most likely resulted from inappropriate cut-off troponin I values and the modest sample size.

In conclusion, the combination of elevated troponin and RVD was able to identify a subset of patients most likely to benefit from aggressive therapy. (Int Heart J 2006; 47: 775-781)

Key words: Pulmonary embolism, Right ventricular dilatation, Troponin I

PULMONARY embolism (PE) remains a major cause of morbidity and mortality among the general population, with an estimated incidence of 0.5 per 1000 people1) and a case-fatality rate of 15% at 3 months.2) Patients with pulmonary embolism present with a wide range of clinical acuity, thus necessitating different therapeutic strategies. Shock or systemic hypotension with systolic BP < 90 mmHg are the generally accepted indications for urgent thrombolysis in patients with acute PE.1)
Right ventricular dysfunction was the single most important predictor of in-hospital death in the international registry of 2454 patients with pulmonary embolism.\textsuperscript{2,3} Although the in-hospital mortality rate in a subgroup of normotensive patients with signs of right ventricular (RV) pressure overload on echocardiography has been reported to be as high as 12.6 to 15.9%, whether such patients should receive thrombolysis or anticoagulation therapy remains controversial.\textsuperscript{1,4}

Cardiac troponin is another important prognostic factor. It is the most sensitive and specific biomarker of myocardial cell damage, reflecting microscopic myocardial necrosis. Elevated troponin levels predict adverse outcomes in patients with acute myocardial infarction and in critically ill patients without acute coronary syndromes.\textsuperscript{5} Raised concentrations of cardiac troponins have also been reported to be associated with early mortality and a complicated hospital course in patients with pulmonary embolism.\textsuperscript{6,7}

This study tested the hypothesis that elevated troponin I and RV dilation have an incremental prognostic value in PE patients. Moreover, this study also examined whether this combination can translate into a realistic therapeutic alternative in patients experiencing adverse events.

**Methods**

**Patients:** This investigation retrospectively identified 110 patients discharged from Chang-Gung Memorial Hospital, Taiwan with a diagnosis of acute pulmonary embolism (PE) from June 1999 to June 2004. The diagnosis of PE was confirmed by either spiral computed tomography or a high probability ventilation and perfusion lung scan. Clinical characteristics and treatment were abstracted from the medical records. Right ventricular and left ventricular (LV) end-diastolic diameters were reviewed using echocardiography from the apical 4-chamber view. The maximal distance between the endocardium of the right ventricular free wall and the interventricular septum, perpendicular to the long axis of the ventricle, was measured at the beginning of the QRS-complex. RV dilatation (RVD) was defined as an RV/LV ratio $\geq$ 1. The laboratory cut-off value for troponin I was 0.4 ng/mL. Troponin I levels were determined in all 110 patients either on admission or within 24 hours after arrival at hospital. Patients with a moderate probability or low probability lung ventilation/perfusion scan and/or suspected septic embolism were excluded from the study.

Acute pulmonary embolism was treated pharmacologically in all cases. During the acute phase, all patients received anticoagulation with unfractionated heparin dosed according to the activated partial thromboplastin time (APTT) or weight-adjusted low molecular heparin administered subcutaneously. Thrombolysis was performed in 8 patients, and consisted of a 2 hour intravenous infusion
of 100 mg of recombinant tissue plasmin activator (rtPA) without concomitant
heparin. Oral warfarin with an international normalized ratio (INR) of 2.0-3.0
was used for at least 6 months of treatment in all discharged patients.

Statistical analysis: The end point was all-cause 100-day mortality. Student's t
test was used to compare continuous variables, while the chi-square test was used
for categorical variables. Multivariate Cox regression analysis, focusing on
patients with no evidence of RVD or with raised troponin I as a reference group
while adjusting for age and the presence of hypotension, was used to assess the
influence of RVD and cardiac troponin I on mortality.

RESULTS

Follow-up assessment of patients was performed after at least one year. The
baseline characteristics of the 110 patients are presented in Table I. All cause 100-
day mortality was 18.2% (15.4% in hospital). Echocardiographic parameters and
troponin levels are also shown in Table I. Troponin I values, which ranged from
less than 0.4 ng/mL to 17.7 ng/mL, were elevated in 56% of the patients. How-
ever, in most cases the elevation was minor, ranging from less than 0.4 ng/mL to
5.4 ng/mL. Only 2 patients had high troponin I levels (14.6 ng/mL and 17.7 ng/
/mL). Both of these patients agreed to undergo coronary angiography and did not
have significant stenosis of coronary arteries. The patient with a troponin I level
of 14.6 ng/mL died, while the patient with the higher level of 17.7 ng/mL sur-

Table I. Clinical Characteristics, Echocardiographic Parameters, and Cardiac Troponin I in PE
Survivors and Patients Who Died at 100 Days

<table>
<thead>
<tr>
<th>Variable</th>
<th>100-day survival (n = 90)</th>
<th>100-day death (n = 20)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical characteristic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>65.6 ± 13.5</td>
<td>67.7 ± 17.6</td>
<td>0.724</td>
</tr>
<tr>
<td>Duration of symptoms (days)</td>
<td>5.06 ± 7.25</td>
<td>4.05 ± 4.51</td>
<td>0.554</td>
</tr>
<tr>
<td>Women</td>
<td>48/90 (53%)</td>
<td>12/20 (60%)</td>
<td>0.769</td>
</tr>
<tr>
<td>Cancer</td>
<td>12/90 (13.3)</td>
<td>6/20 (30%)</td>
<td>0.070</td>
</tr>
<tr>
<td>Hypotension (SBP &lt; 100 mmHg)</td>
<td>8/90 (8.9%)</td>
<td>6/20 (30%)</td>
<td>0.020*</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>24/90 (27%)</td>
<td>3/20 (15%)</td>
<td>0.275</td>
</tr>
<tr>
<td>Hypertension</td>
<td>34/90 (38%)</td>
<td>6/20 (30%)</td>
<td>0.513</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>9/90 (10%)</td>
<td>2/20 (10%)</td>
<td>1.000</td>
</tr>
<tr>
<td>DVT</td>
<td>25/90 (28%)</td>
<td>4/20 (20%)</td>
<td>0.475</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tissue plasmin activator (tPA)</td>
<td>8/90 (8.8%)</td>
<td>0/20 (0%)</td>
<td>0.168</td>
</tr>
<tr>
<td>Echocardiography and troponin I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RVD (RV/LV ≥ 1)</td>
<td>43/90 (47.7%)</td>
<td>15/20 (75%)</td>
<td>0.027*</td>
</tr>
<tr>
<td>TnI ≥ 0.4</td>
<td>50/90 (55%)</td>
<td>12/20 (60%)</td>
<td>0.717</td>
</tr>
<tr>
<td>TnI ≥ 0.4 and RV/LV ≥ 1</td>
<td>24/90 (26.6%)</td>
<td>11/20 (55%)</td>
<td>0.014*</td>
</tr>
</tbody>
</table>

*: P < 0.05

TnI indicates troponin I; RVD, right ventricular dilatation; and SBP, systolic blood pressure.
None of the 8 patients who accepted thrombolysis experienced any major bleeding.

For the combination of RV enlargement and elevated troponin I, which occurred in 32% of the subjects, the 100-day mortality rate was 31%. In contrast, patients with neither RV enlargement nor raised troponin I had a 100-day mortality of 16%. Compared with a reference group without RV enlargement or elevated troponin, the adjusted hazard ratio for death at 100 days associated with RV enlargement and normal troponin I was 0.971 (95% confidence interval [CI]: 0.530 to 1.779), with elevated troponin I and no RV enlargement 0.906 (95% CI 0.501 to 1.636), and with the combination of elevated troponin I and RV enlargement 2.584 (95% CI 1.451 to 4.602). The survival curves of these 4 groups are.

### Table II. Four Different Combinations of Troponin I and Echocardiographic Findings

<table>
<thead>
<tr>
<th>Combination Group</th>
<th>Patient No.</th>
<th>100-day death</th>
<th>Mortality rate</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TnI &lt; 0.4 &amp; RV/LV &lt; 1 (Group 1)</td>
<td>25</td>
<td>4</td>
<td>4/25 (16%)</td>
<td>1</td>
</tr>
<tr>
<td>TnI ≥ 0.4 &amp; RV/LV &lt; 1 (Group 2)</td>
<td>27</td>
<td>1</td>
<td>1/27 (3.7%)</td>
<td>0.906 (0.501-1.636)</td>
</tr>
<tr>
<td>TnI &lt; 0.4 &amp; RV/LV ≥ 1 (Group 3)</td>
<td>23</td>
<td>4</td>
<td>4/23 (17%)</td>
<td>0.971 (0.530-1.779)</td>
</tr>
<tr>
<td>TnI ≥ 0.4 &amp; RV/LV ≥ 1 (Group 4)</td>
<td>35</td>
<td>11</td>
<td>11/35 (31.4%)</td>
<td>2.584*** (1.451-4.602)</td>
</tr>
</tbody>
</table>

***: $P < 0.001$
shown in the Figure.

The combination of RV enlargement and elevated troponin had a positive predictive value of 31% and a negative predictive value of 88% for 100-day mortality. The combination of RV enlargement and elevated troponin I significantly increased 100-day mortality (31.4%) compared to patients with elevated troponin I alone (3.7%), RV dilation alone (17%), or neither (16%)(Table II).

**DISCUSSION**

Hypotension and RVD significantly influenced 100-day mortality. In the ICOPER study, the authors claimed that mortality was 58.3% and 15.1% in hemodynamically unstable and stable patients, respectively. Our results are similar. Furthermore, RVD was proven again to be an important prognostic factor for pulmonary embolism.

However, there are conflicts between our results and those of previous reports. A review of relevant articles revealed troponin I has been identified as having an independent prognostic value in acute pulmonary embolism. Analysis of the present results yields conflicting conclusions regarding the influence of troponin I in patients with acute pulmonary embolism. There are 3 possible explanations for this phenomenon. The most likely explanation is an inappropriate cut-off value for troponin I. Our hospital biochemical laboratory has used 0.4 ng/mL as the cut-off value over the past several years. Cardiac troponin levels correlate closely with the extent of right ventricular dysfunction. Although high troponin concentrations on admission indicate right ventricular microinfarction and also identify patients at high risk of a complicated hospital course, elevated troponin levels in PE patients are mild and of short duration compared to those in patients with acute myocardial infarction. Compared with numerous reports, the more appropriate cut-off value for troponin is 0.06 to 0.07 ng/mL.

Second, the use of cardiac troponin I for risk stratification of acute pulmonary embolism may be limited to those patients presenting early after the onset of symptoms. This study noted that the time elapsed from the time of the onset of symptoms of the first event of pulmonary embolism was markedly shorter in patients with raised troponin I. Gopikrishna, et al noted that none of the patients with a duration of symptoms exceeding 72 hours had elevated cardiac troponin I levels despite having right ventricular dysfunction. Gopikrishna, et al thus concluded that the dynamics of cardiac troponin I release in acute pulmonary embolism patients presenting with symptoms ≤ 72 hours duration could differ from patients who present with a longer duration of symptoms. If a patient with severe pulmonary embolism comes to hospital after the symptoms have lasted for more than 3 days, he or she may have a normal troponin I level on admission. The prog-
nosis of the patient may deteriorate because of a delay in treatment.

Third, in the landmark PIOPED study, only 41% of the patients with pulmonary embolism had a high-probability lung scan. Most patients with pulmonary embolism (57%) had an intermediate probability or low-probability scan. The retrospective PIOPED study did have selection bias for patients with acute pulmonary embolism. Patients with intermediate and low probability lung scans were excluded at the beginning. The excluded patients were suspected of having low troponin I values and less severe acute pulmonary embolism.

Another conflict is that cancer has no prognostic power. In the Geneva score, cancer was an important predictor of death, and the present data only showed a trend towards mortality. Furthermore, congestive heart failure did not exhibit a significant influence. These unmatched results are most likely due to the small number of enrolled patients.

Notably, the use of a combination of echocardiography and troponin I measurement can identify patients at high risk of mortality following PE; this is valid even in normotensive patients. These patients with both raised troponin I and RVD may be the most likely to benefit from aggressive therapies, such as thrombolysis or thrombectomy.

This study has several notable limitations. First, the sample size is limited. Moreover, this retrospective study has a selection bias. Consequently, the present analysis has limited statistical power to reliably detect clinically worthwhile differences in individual risk factors. In addition, some risk factors such as protein C, protein S, antithrombin III, antiphospholipid antibody, and homocysteine level could not be completely collected for all 110 patients. This made it difficult to speculate on the sources of the emboli for every patient.

Conclusion: Adverse outcomes remain common in patients with PE. Despite a wide spectrum of severity at presentation, the large majority of patients with PE receive similar antithrombotic treatment. We found that, no matter what the previous risk factors were for these patients, the combination of the initial troponin I level and echocardiographic findings still had the ability to predict the 100-day prognosis for these acute pulmonary embolism patients. The combination of elevated troponin I and RV dilatation was used to identify a subset of patients most likely to benefit from thrombolytic therapeutic strategies. In the future, a more sensitive cut-off value of troponin I needs to be used to further clarify its predictive power. Further assessment of the efficacy and safety of thrombolytic therapy for treating high-risk patients with acute pulmonary embolism appears warranted.
REFERENCES