Incremental prognostic value of troponin I and echocardiography in patients with acute pulmonary embolism

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Background To test the hypothesis that troponin I and echocardiography have an incremental prognostic value in patients with pulmonary embolism (PE).

Methods and results In 91 patients with acute PE, echocardiography was performed within 4 h of admission. Troponin I levels were obtained on admission and 12 h thereafter. The 0.06 µg/l troponin I cut-off level was identified as the most useful, high-sensitivity cut-off level for the prediction of adverse outcome by receiver operating characteristic analysis with a sensitivity and specificity of 86%, respectively. Twenty-eight (31%) patients had elevated troponin I levels (4.9±3.8 µg/l). Twenty-one (23%) patients had adverse clinical outcomes including in-hospital death in five, cardiopulmonary resuscitation in four, mechanical ventilation in six, pressors in 14, thrombolysis in 14, catheter fragmentation in three, and surgical embolectomy in three. The area under the receiver operating characteristic curve from multivariate regression models for predicting adverse outcome without troponin I and echocardiography (0.765), with troponin I (0.890) or echocardiography alone (0.858), and the combination of both tests (0.900) was incremental. Three-month survival rate was highest in patients with both a normal troponin I level and a normal echocardiogram (98%). Positive predictive value for adverse clinical outcomes of the combination of echocardiography and troponin I was higher (75% (95%CI 55–88%)) compared with each test alone (echocardiography: 41%, 95% CI 28–56%; troponin I: 64%, 95% CI 46–79%).

Conclusions While troponin I measurements added most of the prognostic information for identifying high-risk patients, a normal echocardiogram combined with a negative troponin I level was most useful to identify patients at lowest risk for early death.

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KEYWORDS
- Pulmonary embolism
- prognosis
- echocardiography

Introduction

Right ventricular dysfunction was the single most important predictor of in-hospital death in the international registry of 2454 patients with pulmonary embolism (PE). Therefore, echocardiography has emerged as important diagnostic tool for assessing the degree of right ventricular dysfunction in patients with acute PE.

Recently, cardiac troponins I and T have also been shown to be associated with early mortality and a complicated hospital course in patients with PE. However, the prognostic role of cardiac troponins in PE patients who undergo risk stratification, including assessment of right ventricular function by echocardiography, is less clear. We aimed to test the hypothesis that troponin I and echocardiography have an incremental prognostic value in PE patients.
Methods

Patients

In consecutive symptomatic PE patients from the Emergency Department of the University Hospital of Bern, the diagnosis was confirmed by spiral computed tomography (CT) in 86, high probability ventilation perfusion scan in three, and pulmonary angiography in two patients during a study period of 18 months. Troponin I levels were taken in all 91 patients on admission and 12 h thereafter using a microparticle enzyme immunoassay (Abbott, USA). The study protocol was approved by the local ethics committee, and written informed consent was obtained from all patients.

Spiral computed tomography, ventilation perfusion scan, and pulmonary angiography

Pulmonary embolism was diagnosed by spiral CT when there was at least one intravascular filling defect in a pulmonary artery using a standard protocol. Troponin I levels were considered significant at ≥0.06 µg/l (Fig. 1). Three-month survival rate was higher in patients with normal troponin I levels (4.9±3.8, range 0.7–14.6 µg/l). Syncope and dyspnea were more prevalent in patients with a troponin I level than in patients with a normal troponin I level (Table 1). The history and risk factors for coronary artery disease were similar in patients with and without troponin I elevation. Haemodynamic changes were more severe and moderate to severe right ventricular dysfunction more frequent in patients with than without elevated troponin I levels. Right ventricular dilatation was pronounced, and tricuspid pressure gradients were also higher in patients with elevated troponin I levels. More patients had paracentral or central pulmonary artery filling defects as assessed by spiral CT in the elevated troponin I group.

In-hospital mortality was 5%, and all five deaths were attributed to right ventricular failure. Four of these patients had elevated troponin I levels, Twenty one (23%) patients had elevated troponin I levels. Twenty eight (31%) patients had elevated troponin I levels (4.9±3.8, range 0.7–14.6 µg/l). Syncope and dyspnea were more prevalent in patients with a troponin I level than in patients with a normal troponin I level (Table 1). The history and risk factors for coronary artery disease were similar in patients with and without troponin I elevation. Haemodynamic changes were more severe and moderate to severe right ventricular dysfunction more frequent in patients with than without elevated troponin I levels. Right ventricular dilatation was pronounced, and tricuspid pressure gradients were also higher in patients with elevated troponin I levels. More patients had paracentral or central pulmonary artery filling defects as assessed by spiral CT in the elevated troponin I group.

Reperfusion therapy, including thrombolysis, catheter fragmentation, or surgical embolectomy was performed in patients with PE and a shock index ≥1 (heart rate divided by systolic blood pressure). Thrombolysis was also considered in the absence of contraindications according to the Task Force of the European Society of Cardiology (ESC) in patients with a shock index <1 but moderate to severe right ventricular dysfunction. All patients with normal/near normal right ventricular function on the echocardiogram were treated with heparin alone.

Table 1 and Table 2 data are presented as numbers of patients with proportions in parentheses or mean±SD values.

Statistical analysis

Adverse clinical outcome was defined as in-hospital death or the need for cardiopulmonary resuscitation, mechanical ventilation, pressors, thrombolysis, catheter fragmentation, or surgical embolectomy according to the MAPPET-3 criteria. Receiver operating characteristic (ROC) analysis was performed to identify the most useful troponin I cut-off level for the prediction of adverse outcome. Nominal data comparison between the troponin groups (cut-off 0.06 µg/l) was performed using a χ² test. Continuous echocardiographic and haemodynamic data between the troponin groups were compared with the Student t-test.

Multivariate logistic regression was performed on univariately significant continuous and categorical variables (P<0.05) from Table 1 for predicting adverse clinical outcomes. To investigate whether troponin I and echocardiography have incremental prognostic value in addition to clinical parameters, we also calculated resulting areas under the ROC curve for multivariate models without troponin and echocardiography, with troponin I and echocardiography alone, and with the combination of both tests. All models were adjusted for univariately significant (P<0.05) predictors of adverse outcome from Table 1.

Kaplan–Meier analyses were performed to investigate cumulative 3-month survival rates according to troponin I levels and the presence or absence of right ventricular dysfunction. Data were considered significant at P<0.05.

Results

None of the 91 patients had evidence for acute coronary syndromes, including right ventricular infarction, based on electrocardiograms, echocardiograms, and creatine kinase-MB levels. Twenty eight (31%) patients had elevated troponin I levels (4.9±3.8, range 0.7–14.6 µg/l). Syncope and dyspnea were more prevalent in patients with a troponin I level than in patients with a normal troponin I level (Table 1). The history and risk factors for coronary artery disease were similar in patients with and without troponin I elevation. Haemodynamic changes were more severe and moderate to severe right ventricular dysfunction more frequent in patients with than without elevated troponin I levels. Right ventricular dilatation was pronounced, and tricuspid pressure gradients were also higher in patients with elevated troponin I levels. More patients had paracentral or central pulmonary artery filling defects as assessed by spiral CT in the elevated troponin I group.

In-hospital mortality was 5%, and all five deaths were attributed to right ventricular failure. Four of these patients had elevated troponin I levels. Twenty one (23%) patients had adverse clinical outcomes including cardiopulmonary resuscitation in four, mechanical ventilation in six, pressors in 14, thrombolysis in 14, catheter fragmentation in three, and surgical embolectomy in three patients. Detailed combinations of adverse clinical outcomes are shown in Table 2. The 0.06 µg/l troponin I cut-off level was identified as the most useful, high-sensitivity cut-off level for the prediction of adverse outcome by receiver operating characteristic analysis with a sensitivity and specificity of 86%, respectively.

Normal troponin I levels were associated with a higher 3-month survival rate than in patients with troponin I levels ≥0.06 µg/l (Fig. 1). Three-month survival rate was highest in patients with both a normal troponin I level and a normal echocardiogram (Fig. 2).

Specificity and positive predictive value for adverse clinical events were higher using the combination of
troponin I and echocardiography compared with that of each test individually (Table 3). Sensitivity and negative predictive value for adverse outcomes were similar for troponin I, echocardiography, and the combination of both tests.

In a multivariate regression model, troponin I elevation was an independent predictor of adverse outcome when adjusted for right ventricular function on the echocardiogram and other univariate predictors of adverse outcome (Table 4). The area under the ROC curve...
obtained from multivariate regression models were: 0.765 for the model without troponin I and echocardiography, 0.890 for troponin I alone, 0.858 for echocardiography alone, and 0.900 for the combination of both tests.

**Discussion**

In the present study of 91 patients with acute PE, the combination of troponin I and echocardiography had additional prognostic information compared with troponin I or echocardiography alone. The area under the ROC curve from multivariate regression models for predicting adverse outcome without troponin I and echocardiography (0.765), with troponin I (0.890) or echocardiography alone (0.858), and the combination of both tests (0.900) was incremental. The biggest addition of prognostic information was obtained with troponin I measurements. Although the area under the curve did no increase much
with addition of echocardiography to troponin I results, it appears to be useful in identifying low-risk patients because patients with a normal troponin I level and a normal echocardiogram had the lowest mortality rate (Fig. 2). The positive predictive value and specificity for predicting adverse outcomes were higher with the combination of troponin I and echocardiography compared with each test alone (Table 3).

The prevalence of increased cardiac troponin I levels was 31%. A similar prevalence was also found in three recent studies in patients with PE using different troponin assays: 18 (32%) of 56 patients using a qualitative troponin T assay, 4 14 (39%) of 36 patients using a qualitative troponin I assay, 3 and 43 (41%) of 106 patients using a quantitative troponin I assay. 2 In the cited and in the present study, cardiac troponin was a predictor of right ventricular dysfunction and adverse clinical outcomes in patients with PE.

In the present study, four of the 28 patients with a troponin I leak had preserved right ventricular function on echocardiography. Thus, right ventricular dysfunction should be confirmed in all troponin-positive PE patients with risk factors for coronary artery disease. Echocardiography is an important diagnostic and prognostic tool in patients with PE, and an increasing number of hospitals use echocardiography for risk stratification of their PE patients.

The present study is limited by the selection of adverse clinical outcomes used to define the combined end-point, including the need for thrombolysis and embolectomy. Ten of 13 patients who received thrombolysis fulfilled the criteria for clinically massive PE with shock or systemic hypotension according to the ESC guidelines. 11 The remaining three patients with thrombolysis had submassive PE, defined as a preserved systolic arterial pressure and evidence of right ventricular dysfunction. According to the ESC guidelines, 11 thrombolysis may also be considered in patients with submassive PE when no contraindications to thrombolysis are present. In contrast to MAPPET-3, 12 the decision to initiate reperfusion therapy was based on the initial clinical presentation of the patient, particularly on shock index and echocardiographic findings, and not on secondary clinical deterioration. Thus, this study allows no conclusion about the prognostic value of echocardiography and troponin I in the prediction of secondary clinical deterioration in patients with elevated troponin I levels and right ventricular dysfunction who receive standard treatment with heparin alone.

### Conclusions

In patients with acute PE, troponin I and echocardiography have an incremental prognostic value for adverse clinical outcomes including death, the need for cardiopulmonary resuscitation, mechanical ventilation, pressors, thrombolysis, catheter fragmentation, and surgical embolectomy. While troponin I measurements added most of the prognostic information for identifying high-risk patients, a normal echocardiogram combined with a negative troponin I level was most useful to identify patients at lowest risk for early death.

### References


