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Elevated Heart-Type Fatty Acid-Binding Protein Levels on Admission Predict an Adverse Outcome in Normotensive Patients With Acute Pulmonary Embolism

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Objectives We assessed the predictive value of heart-type fatty acid-binding protein (H-FABP) in normotensive patients with acute pulmonary embolism (PE).

Background Risk stratification of initially normotensive patients with PE on the basis of right ventricular dysfunction or injury remains controversial. Previous studies investigating biomarkers or imaging modalities included unselected patients, some of whom presented with cardiogenic shock.

Methods We included 126 consecutive normotensive patients with confirmed PE. Complicated 30-day outcome was defined as death, resuscitation, intubation, or use of catecholamines. Long-term survival was assessed by follow-up clinical examination.

Results During the first 30 days, 9 (7%) patients suffered complications. These patients had higher baseline H-FABP values (median, 11.2 ng/ml [interquartile range: 8.0 to 36.8 ng/ml]) compared with patients with an uncomplicated course (3.4 ng/ml [2.1 to 4.9 ng/ml]; $p < 0.001$). H-FABP values were above the calculated (by receiver operating characteristic curve analysis) cutoff value of 6 ng/ml in 29 patients. Eight (28%) of them suffered complications versus 1 of 97 patients with low H-FABP (negative predictive value, 99%; $p < 0.001$). By logistic regression, elevated (≥6 ng/ml) H-FABP was associated with a 36.6-fold increase in the death or complication risk. The combination of H-FABP with tachycardia was a particularly useful prognostic indicator. H-FABP also predicted long-term mortality over 499 (interquartile range: 204 to 1,166) days (hazard ratio: 3.6; 95% confidence interval: 1.6 to 8.2; $p = 0.003$).

Conclusions The H-FABP might be a useful biomarker for risk stratification of normotensive patients with acute PE. (J Am Coll Cardiol 2010;55:2150–7) © 2010 by the American College of Cardiology Foundation

Acute pulmonary embolism (PE) is a relatively frequent cardiovascular emergency (1–3) and a major cause of morbidity and mortality in the population (4). At an average case fatality rate of 11% (1), venous thromboembolism is responsible for up to 15% of all in-hospital deaths (5). However, early or in-hospital death rates might vary widely, mostly depending on the clinical severity of PE at presentation (1,6). Accordingly, recent guidelines have proposed immediately classifying patients presenting with acute PE into a high-risk and a non–high-risk group (7). Patients belonging to the "high-risk" group are those presenting with hemodynamic instability (i.e., cardiogenic shock or persistent arterial hypotension due to overt right ventricular [RV] failure). The treatment of these patients should definitely include immediate thrombolysis or mechanical removal of the thrombus in addition to standard heparin anticoagulation (7,8). By contrast, the optimal management of initially normotensive patients with "non–high-risk" PE is less clearly defined. In particular, further risk stratification of this seemingly stable group, focusing on the identification of patients who present with (subclinical) RV dysfunction or myocardial injury and might have an "intermediate" death risk of 3% to 15% (9–11), continues to pose a challenge in clinical practice.

See page 2158

Over the past years, a number of studies evaluated the use of echocardiography, computed tomography, and N-terminal

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pro-brain natriuretic peptide (NT-proBNP) for the detection of RV dysfunction and the use of the cardiac troponins T and I for diagnosis of myocardial injury resulting from acute PE. Recent meta-analyses of these studies generally confirmed the prognostic value of these modalities but also brought to light the marked heterogeneity and the numerous methodological limitations of the individual studies (7,10–12). An important obstacle to translating their data into a prognostic algorithm for clinical practice is that the vast majority of these studies included unselected (i.e., both high-risk and non–high-risk) patients with PE, instead of focusing on the risk stratification of the normotensive group.

Heart-type fatty acid-binding protein (H-FABP) is an early, highly sensitive marker of myocardial injury that has been evaluated for emergency triage of patients with acute coronary syndromes (13). Fatty acid-binding proteins are relatively small cytoplasmic proteins (12 to 15 kDa) that are abundant in tissues with active fatty acid metabolism, including the heart (14). After myocardial cell damage, H-FABP diffuses much more rapidly than troponins through the interstitial space and appears in the circulation as early as 90 min after symptom onset, reaching its peak within 6 h (13). Recent studies in unselected patients with acute PE suggested that H-FABP levels on admission might predict an adverse early clinical outcome with a sensitivity and specificity superior to that of cardiac troponins or natriuretic peptides (15,16). Moreover, H-FABP levels were associated with the risk of death during long-term follow-up in patients with chronic thromboembolic pulmonary hypertension (17). On the basis of these promising observations, we conducted the present study to determine whether H-FABP, alone or in combination with clinical or echocardiographic findings, might reliably predict a poor early and long-term prognosis in normotensive patients with acute PE and thus help identify a true "intermediate-risk" group.

Methods

Patient population and study design. We prospectively followed consecutive patients who were diagnosed with acute symptomatic PE (symptom onset, ≤4 weeks), at the University Hospital of Goettingen over a 42-month period (between 2003 and 2007), and who were normotensive on admission. Of 187 patients with confirmed PE, 61 were not considered for further analysis, because they met at least 1 of the following exclusion criteria: 1) hemodynamic instability (i.e., persistent arterial hypotension or shock), defined as systolic blood pressure <90 mm Hg or a pressure drop of ≥40 mm Hg for >15 min at presentation if not caused by new-onset arrhythmia, hypovolemia, or sepsis (6) (n = 24); 2) denial or withdrawal of written consent for participation in the study (n = 4); 3) lost to follow-up (n = 14); and 4) unexpected or accidental diagnosis of PE (patients undergoing diagnostic tests for another suspected disease) or PE coinciding with acute decompensation of left ventricular (LV) failure or acute myocardial infarction (n = 19).

Abbreviations and Acronyms

AUC = area under the curve
CI = confidence interval
cTnT = cardiac troponin T
H-FABP = heart-type fatty acid binding protein
IQR = interquartile range
LV = left ventricle/ventricular
OR = odds ratio
PE = pulmonary embolism
ROC = receiver operating characteristic curve
RV = right ventricle/ventricular

The time period covered by the present study (2003 to 2007) partly overlapped with that (2003 to 2005) of a previous publication by our own group (15); of that latter patient population (n = 107), 73 patients were also included in the present study, whereas 34 were excluded due to hemodynamic instability (n = 10), loss to follow-up (n = 14), and acute PE coinciding with acute decompensation of LV failure or acute myocardial infarction (n = 10). Between 2005 and 2007, 53 additional patients were included. Thus, a total of 126 patients were finally considered for analysis.

The diagnostic workup for patients with suspected acute PE complied with existing guidelines during the study period (18). Patients with high clinical (pre-test) probability of PE on the basis of the standardized Wells Score (19) and those with intermediate or low clinical probability and a positive D-dimer test using a quantitative assay (Tinaquant, Roche Diagnostics, Germany) underwent an imaging procedure, preferably multidetector-row (64-slice) computed tomography, to confirm the disease (88 patients; 70% of the study population). Alternatively, in 31 (25%) patients PE was confirmed by a diagnostic ventilation-perfusion lung scan. In 5 patients (4%), the diagnosis was based on the patients' clinical presentation and the confirmation of deep vein thrombosis by compression ultrasonography. Pulmonary angiography was rarely necessary to confirm PE (2 patients; 2%).

The study protocol strongly recommended a transthoracic echocardiogram within 2 h of PE diagnosis. Of 112 patients (89% of the study population) who underwent cardiac ultrasound, 44 (39%) were diagnosed with RV dysfunction. The latter finding was prospectively defined as dilation of the RV (end-diastolic diameter >30 mm from the parasternal view or a RV/LV diameter ratio >1.0 from the subcostal or apical views), combined with right atrial hypertension (absence of the inspiratory collapse of the inferior vena cava) in the absence of LV or mitral valve disease (15).

In all cases, blood was drawn immediately for measurement of baseline (admission) biomarker levels before further diagnostic workup. After confirmation of the diagnosis, patients were asked to sign the informed consent form. Subsequently, complete data on baseline clinical, hemodynamic, and laboratory parameters were obtained with a standardized questionnaire by investigators unaware of the patients' biomarker levels.