Cardiac Biomarkers for Risk Stratification of Patients With Acute Pulmonary Embolism

Nils Kucher, MD; Samuel Z. Goldhaber, MD

Patients with pulmonary embolism (PE) present with a wide spectrum of clinical acuity that necessitates different therapeutic strategies. Most patients maintain normal systolic arterial pressure and normal right ventricular function. With therapeutic levels of anticoagulation, they will likely have a benign clinical course. Unfortunately, some PE patients suffer rapid clinical deterioration with adverse clinical events, including death from right ventricular failure or the need for cardiopulmonary resuscitation, mechanical ventilation, or administration of pressors for systolic arterial hypotension. Selected patients will benefit from thrombolysis or surgical embolectomy in addition to anticoagulation.1,2

Severe dyspnea, cyanosis, and syncope indicate life-threatening PE. The clinical examination may reveal signs of acute right ventricular dysfunction, including tachycardia, a low arterial blood pressure, distended neck veins, an accentuated P 2, or a tricuspid regurgitation murmur. On the ECG, T-wave inversion or a pseudoinfarction pattern (Qr) in the anterior precordial leads indicates right ventricular dilation and dysfunction.3 Chest computed tomography or magnetic resonance imaging may not only confirm PE but also demonstrate right ventricular dilation.

Echocardiography has emerged as the principal tool for risk stratification in acute PE. From a prognostic point of view, echocardiography helps to classify patients with PE into 3 groups: Low-risk PE (no right ventricular dysfunction), with a hospital mortality of <4%, submassive PE (right ventricular dysfunction and a preserved arterial pressure), with a hospital mortality of 5% to 10%, and massive PE (right ventricular dysfunction and cardiogenic shock), with a hospital mortality of approximately 30%.4 Right ventricular dysfunction on the echocardiogram is an independent and powerful predictor of early death in patients with acute PE.5 Indirect signs are systolic pulmonary artery hypertension manifested by an increased tricuspid regurgitant velocity >2.6 m/sec and reduced inspiratory collapse of a dilated inferior vena cava due to elevated central venous pressure.6

The major drawbacks of echocardiography are its limited round-the-clock availability and its cost. Another problem is occasional poor imaging quality of the right ventricle, particularly in patients with obesity or chronic lung disease. This latter problem can be circumvented by transesophageal echocardiography, an imaging modality requiring even more specialized skills, expense, and procedure-related risk.

Cardiac biomarkers, including troponins and natriuretic peptides, have emerged as promising tools for risk assessment of patients with acute PE. We will summarize results of contemporary trials on cardiac biomarkers for risk stratification, and we will provide practical recommendations on how to incorporate biomarker test results into the management strategy of patients with acute PE.

Pathophysiology of Cardiac Biomarker Elevation in Pulmonary Embolism

Troponins

Cardiac troponins are the most sensitive and specific biomarkers of myocardial cell damage, reflecting microscopic myocardial necrosis.7 Elevated troponin levels predict adverse outcomes in patients with acute myocardial infarction and in critically ill patients without acute coronary syndromes.8

Troponin is a regulatory protein of the thin filament of striated muscle, and consists of three subunits: C at 18
kDa, I at 21 kDa, and T at 37 kDa. The concentration of the troponin I and T subunits is increased in blood for many days after myocardial infarction, because release from the structural elements requires degradation of the myofibril itself. Elevations of troponin levels in PE patients are mild and of short duration compared with elevations in patients with acute coronary syndromes. In acute PE, troponin levels correlate well with the extent of right ventricular dysfunction. Some PE patients have initially negative troponin test results but may show a release of troponin 6 to 12 hours later. Myocardial ischemia and micro-infarction due to alterations in oxygen supply and demand of the failing right ventricle probably play a major role in the pathogenesis of troponin release (Figure 1). Release of troponin can occur in patients with PE in the absence of angiographic coronary artery disease. An abrupt increase in right ventricular wall tension with compression of the right coronary artery and direct myocardial micro-injury is a possible explanation.

Natriuretic Peptides
The natriuretic peptides are useful diagnostic and prognostic biomarkers for patients with congestive heart failure. In contrast to atrial natriuretic peptide that originates mainly from atrial tissue, brain natriuretic peptide (BNP) is produced to a larger degree from ventricular myocytes. The principal stimulus for BNP synthesis and secretion is cardiomyocyte stretch. BNP is a 32 amino acid peptide hormone first isolated from porcine brain tissue. The human BNP gene is located on chromosome 1. In plasma, the intact 108 amino acid prohormone (proBNP), the biologically active BNP (plasma half life 20 minutes), and the remaining part of the prohormone, N-terminal (NT)-proBNP (76 amino acids, plasma half life 60 to 120 minutes), can be measured by immunoassay.

Prohormones in normal ventricular myocytes are not stored to a significant amount. Thus, it takes several hours for the plasma natriuretic peptide levels to increase significantly after the onset of acute myocardial stretch. This process includes myocardial BNP messenger ribonucleic acid (mRNA) synthesis, prohormone synthesis, and prohormone release into the circulation (Figure 1). Similar to cardiac troponins, elevations in BNP and NT-proBNP are associated with right ventricular dysfunction in acute PE. Natriuretic peptide levels are also increased in patients with right ventricular pressure overload due to causes other than PE, including primary pulmonary hypertension, chronic thromboembolic pulmonary hypertension, and chronic lung disease.

Accuracy of Cardiac Biomarkers for the Prediction of Adverse Clinical Outcomes
Troponins and natriuretic peptides are accurate in identifying low-risk PE patients and have a high negative predictive value for in-hospital death (Table). The cut-off levels for troponins are the lower detection limits for myocardial ischemia reported by the manufacturer. However, the cut-off level for the BNP Triage assay to predict a benign clinical outcome in PE patients is lower (<50 pg/mL) than the congestive heart failure cut-off level of 90 pg/mL.

Accuracy of Cardiac Biomarkers for the Prediction of In-Hospital Death in Pulmonary Embolism

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Biomarker</th>
<th>Assay</th>
<th>Cut-Off Level</th>
<th>Test +, %</th>
<th>NPV, %</th>
<th>PPV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Konstantinides et al</td>
<td>106</td>
<td>cTnl</td>
<td>Centaur (Bayer)</td>
<td>0.07 ng/mL</td>
<td>41</td>
<td>98</td>
<td>14</td>
</tr>
<tr>
<td>Konstantinides et al</td>
<td>106</td>
<td>cTnT</td>
<td>Elecsys (Roche Pharmaceuticals)</td>
<td>0.04 ng/mL</td>
<td>37</td>
<td>97</td>
<td>12</td>
</tr>
<tr>
<td>Giannitsis et al</td>
<td>56</td>
<td>cTnT</td>
<td>TropT (Roche Pharmaceuticals)</td>
<td>0.10 ng/mL</td>
<td>32</td>
<td>97</td>
<td>44</td>
</tr>
<tr>
<td>Janata et al</td>
<td>106</td>
<td>cTnT</td>
<td>Elecsys (Roche Pharmaceuticals)</td>
<td>0.09 ng/mL</td>
<td>11</td>
<td>99</td>
<td>34</td>
</tr>
<tr>
<td>Pruszczynska et al</td>
<td>64</td>
<td>cTnT</td>
<td>Elecsys (Roche Pharmaceuticals)</td>
<td>0.01 ng/mL</td>
<td>50</td>
<td>100</td>
<td>25</td>
</tr>
<tr>
<td>ten Wolde et al</td>
<td>110</td>
<td>BNP</td>
<td>Shionoria (CIS Bio International)</td>
<td>21.7 pmol/L</td>
<td>33</td>
<td>99</td>
<td>17</td>
</tr>
<tr>
<td>Kucher et al</td>
<td>73</td>
<td>NT-proBNP</td>
<td>Elecsys (Roche Pharmaceuticals)</td>
<td>500 pg/mL</td>
<td>58</td>
<td>100</td>
<td>12</td>
</tr>
<tr>
<td>Kucher et al</td>
<td>73</td>
<td>BNP</td>
<td>Triage (Biosite Technologies)</td>
<td>50 pg/mL</td>
<td>58</td>
<td>100</td>
<td>12</td>
</tr>
<tr>
<td>Pruszczynska et al</td>
<td>79</td>
<td>NT-proBNP</td>
<td>Elecsys (Roche Pharmaceuticals)</td>
<td>153 to 334* pg/mL</td>
<td>66</td>
<td>100</td>
<td>23</td>
</tr>
</tbody>
</table>

NPV indicates negative predictive value; PPV, positive predictive value.
*Age and gender adjusted cut-off levels according to the manufacturer.
At this time, none of the biomarkers have been proven superior over others. Keeping in mind that troponin and BNP release into the circulation may take several hours after the onset of myocardial injury, a second biomarker test 6 to 12 hours after an initially negative test should be obtained in a PE patient with a symptom duration <6 hours. Similar to troponin assays, bedside point-of-care BNP assays, using whole blood or plasma samples, have precision, analytical sensitivity, stability, and a rapid turnaround time.

Incorporation of Cardiac Biomarkers Into Risk Stratification

The principal role for cardiac biomarkers in PE patients is to differentiate between low risk and intermediate risk (Figure 2). Biomarker tests are not necessary in patients with obvious PE-related shock. According to the European Pulmonary Embolism Task Force Guidelines and the results from the largest PE thrombolysis study (Management Strategy and Prognosis in Pulmonary Embolism Trial-3), fibrosis should be considered not only for patients with PE-related shock but also for patients with a preserved arterial pressure and evidence of right ventricular dysfunction in the absence of an increased bleeding risk. In hemodynamically stable PE patients with increased troponin and/or BNP levels, further risk stratification with echocardiography should be undertaken. Elevated cardiac biomarkers have not yet been incorporated into formal guidelines for treatment decisions (anticoagulation alone versus thrombolysis versus embolectomy) regarding PE patients. In patients with normal biomarker levels, echocardiography need not ordinarily be ordered because right ventricular function will almost always be normal.

Future Research Perspectives on Cardiac Biomarkers

An elevated biomarker level in combination with echocardiographic right ventricular dysfunction may help to identify a subgroup of hemodynamically stable patients at especially high risk of adverse clinical events. Future research will investigate whether the natriuretic peptides have incremental prognostic information in the presence of troponin release. Because of the short half-life of the natriuretic peptides, particularly BNP, these biomarkers may also be helpful in serial monitoring and gauging the success of different PE treatment regimens.

In conclusion, low cardiac troponin and natriuretic peptide values identify low-risk patients through their high negative predictive value for adverse outcomes. In PE patients with normal biomarker levels, echocardiography may not be necessary. In hemodynamically stable PE patients with increased cardiac troponin or BNP levels, however, right ventricular dysfunction should be confirmed by echocardiography. Finally, the prognostic implications of elevated biomarkers and abnormal echocardiography require further investigation.

References

Cardiac Biomarkers for Risk Stratification of Patients With Acute Pulmonary Embolism
Nils Kucher and Samuel Z. Goldhaber

Circulation. 2003;108:2191-2194
doi: 10.1161/01.CIR.0000100687.99687.CE

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/108/18/2191

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/