Acute pulmonary embolism risk stratification

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Acute pulmonary embolism (PE) is a complex heterogenous condition that affects 0.5 - 1 per 1000 persons in the general population each year, and is one of the most common preventable causes of death among hospitalized patients.[1] In the United State, PE kills more than 200,000 patients every year; more than breast cancer, HIV, and motor vehicle accidents combined.[2] Pulmonary embolism has varying early and long-term outcomes. The mortality rate of acute PE varies from almost 0% (in asymptomatic small PE) to more than 60% in life-threatening major PE patients, who present in cardiac arrest;[3] most deaths, however, occur in the first 2 hours of presentation. Overall, the mortality rate in PE patients is found to be higher than in patients with acute myocardial infarction, exceeding 10% at 30 days and 16% at 3 months.[4] Within 30 days, the most common cause of death is right ventricular failure and pulmonary hypertension, while most deaths beyond 30 days are often due to the underlying comorbid chronic conditions, such as congestive heart failure, chronic obstructive lung disease, or malignancy. As of this variable result, one of the most important task of the treating physician is to apply a clear, evidence-based risk stratification strategy, in order to detect those patients who are likely to have a complicated and poor result and to institute a proper early therapeutic intervention. By applying risk stratification model, patients estimated to be at low risk could be discharged early or managed entirely as outpatients using low-molecular-weight heparin, whereas patients estimated as high risk should be admitted for extensive and supervised therapy. The 5 steps that are required for adequate risk stratification of acute PE are as following:

1. Clinical assessment. The presence of comorbid illnesses (such as advanced age, congestive heart failure, malignancy, or chronic lung disease) increases the risk of adverse clinical events, even in the presence of anatomically small PE. In the International Cooperative Pulmonary Embolism (ICOPER) registry,[4] the presence of comorbidities was associated with an approximately 2-fold increase in the risk of death at 3-month. Clinically, the presence of severe dyspnea and syncope usually indicate hemodynamically significant PE. The clinical examination might support this by showing signs of acute right ventricular dysfunction, including tachycardia, distended neck veins, an accentuated pulmonic component of the second heart sound, or a tricuspid regurgitation murmur. The presence of hemodynamic instability or shock status has a prognostic value and significant increase in mortality compared to hemodynamically stable patients (30% versus <5%). Patients who present with cardiac arrest have a mortality rate approaching 60%.

The Geneva Prognostic Index (GPI) has been developed as a tool for severity assessment to identify low-risk patients. It is based on the findings from the medical history and the clinical examination. Using GPI, risk stratification is performed using an 8-point scoring system and identifies 6 predictors of adverse result: 2 points each for cancer and hypotension and 1 point each for heart failure, previous deep vein thrombosis (DVT), arterial hypoxemia, and ultrasound-proven DVT. The higher the scoring points, the worse the result. Patients who score less than 2 were found to have an extremely good prognosis.[4] Finally, the presence of prior and idiopathic PE, younger age, or a large perfusion defect on perfusion scan has been shown to be associated with increased risk for the developing chronic thromboembolic pulmonary hypertension (CTEPH) during the ensuing 2 years.[5]

2. Electrocardiogram (ECG). Electrocardiogram has gain recent interest in the process of risk stratification in acute PE. From one aspect, it can help excluding other conditions, such as acute ST elevation myocardial

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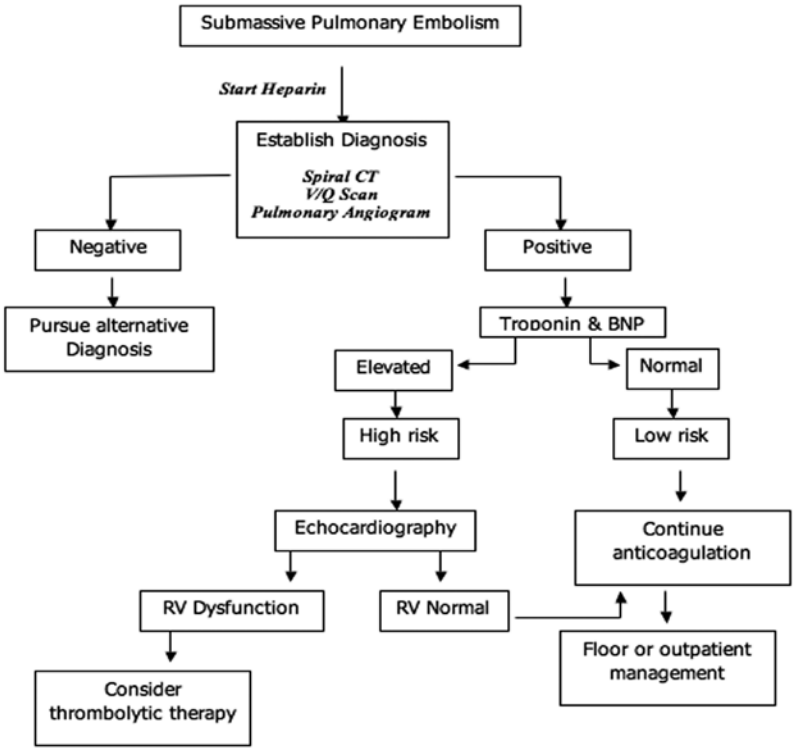

Figure 1 - The algorithm of management of submassive pulmonary embolism. RV - right ventricular, BNP - brain natriuretic peptides.

infarction. Unfortunately, approximately 25% of the patients with acute PE may have a non-specific ECG that has no risk stratification value.

In a recent study,[6] atrial arrhythmias, complete right bundle branch block, low voltage, Q waves in leads III and aVF, and ST segment changes (elevation or depression) over the left precordial leads, were all significantly more frequent in patients with a fatal result. Overall, 30% in-hospital mortality was found in patients who had at least one of these abnormalities on admission compared to 11% in patients without pathological ECG findings. The ECG can reflect the cardiac status in patients with acute PE. The presence of T wave inversion in the anterior precordial leads (V2 and V3) and Qr in V1 may indicate right ventricular dilation and dysfunction. Both findings were found to predict adverse clinical outcomes, including death, cardiopulmonary resuscitation, mechanical ventilation, and the administration of Vasoactive pressors or thrombolysis. The pattern of S1Q3T3 described by McGinn in 1935 has also shown to have both diagnostic and prognostic significance, but it only present in a minority of patients.

Finally, the correlation between ECG abnormalities and cardiac biomarkers has been described. Right ventricular strain pattern in ECG often present with elevated cardiac biomarker levels, including cardiac troponins and natriuretic peptides, suggesting that ECG signs correlate with the extent of right ventricular dilation and dysfunction.

3. Echocardiography. Transthoracic echocardiography is an important tool for risk stratification in acute PE for the following reasons:

- Right ventricular dysfunction on the echocardiogram is a powerful and independent predictor of mortality even in hemodynamically stable patients.[7] Right ventricular dysfunction in PE patients may be a marker of a larger thrombus load or a poor outcome. The echocardiographic criteria for right ventricular dysfunction include: 1) right ventricular dilatation, 2) right ventricular systolic free wall hypokinesia, 3) elevated systolic pulmonary arterial pressure, or 4) indirect signs of right ventricular pressure overload, such as flattened inter-ventricular septum, paradoxical systolic motion of the inter-ventricular septum toward the left ventricle, or a dilated inferior vena cava with reduced respiratory variability.[8] However, which of

these signs, if any, is better than the others as a marker for risk stratification, has not been determined. Despite the fact that patients with RV dysfunction have a worse prognosis than those without RV dysfunction, it is important to realize that the positive predictive value of RV dysfunction on echocardiography is rather poor. There is still no definitive consensus whether or not to thrombolyse patients with right ventricular strain but no arterial hypotension (so-called submassive PE [**Figure 1**]). However, a major European trial addressing this question was started in early 2007. If the results of this trial are positive, then right ventricular function assessment by echocardiography will be mandatory in all hemodynamically stable PE patients.

• Echocardiography is also useful in detecting the presence of a patent foramen ovale, which identify patients at risk for paradoxical embolism and stroke, and may predict mortality.[9]

• Echocardiography is important diagnostic tool for the presence of free floating right heart thrombi, which increases the risk for adverse clinical events. In International Cooperative Pulmonary Embolism Registry (ICOPER) study,[4] the overall mortality rate at 14 days (21 versus 11%) and at 3 months (29 versus 16%) was higher in patients with right heart thrombi compared to those without such diagnosis.

• Echocardiography has also found to have a predictive value for long-term complication, namely CTEPH. An estimated systolic pulmonary artery pressure of greater than 50 mm Hg at the time of acute PE diagnosis has been found to be associated with CTEPH at one year.[10] Echocardiographic follow-up at 6 weeks after the diagnosis can identify patients with CTEPH and may be of value in planning the long term care of these patients.

4. Cardiac biomarkers. The optimal therapeutic strategy for normotensive patients with evidence of right ventricular dysfunction on echocardiography is controversial. For this group of patients, biomarkers such as cardiac troponin and brain natriuretic peptides (BNP) could be extremely useful for risk stratification. The role of cardiac troponin as indicators of irreversible cell injury is well established.[11] Unlike acute myocardial infarction when cardiac troponin may remain elevated for >7 days, in PE the time period of troponin marker elevation is 1-3 days only. Currently, it is believed that cardiac troponin elevation in patients with acute PE is related to the myocardial damage resulting from the acute increase of right ventricular after load, which lead to decreased cardiac output, reduced coronary blood flow, and diminished oxygen supply. Similarly, elevation of both BNP and NT-proBNP in acute PE is presumably related to increase right ventricular stretching secondary to right ventricular strain, explaining the close association of circulating levels of these biomarkers with the presence of right ventricular dysfunction and dilatation as detected by echocardiography. From risk stratification point of view, both cardiac troponin and natriuretic peptides were found to have high negative predictive value, which is in the range of 97-99%, giving them an important clinical relevance. Thus, a patient with negative biomarker results has an extremely low risk for death or in-hospital complications, such as hemodynamic deterioration, mechanical ventilation, or need for inotropic support. In the risk stratification algorithm for acute PE, the combination of biomarkers with echocardiography increases the positive predictive value of cardiac troponin T or natriuretic peptides. Such combination may allowed to distinguish a low-risk group in which both biomarkers and echocardiography are normal; an intermediate-risk group in which either biomarkers or echocardiography is abnormal; and a high-risk group in which biomarkers and echocardiography are both abnormal. It has been found that the high-risk group has a 10-12-fold higher rate of complications compared to the other 2 groups.[12] Recently, other cardiac biomarkers have gained attention for their importance for risk stratification in acute PE. Cytoplasmic heart-type fatty acid binding protein (H-FABP), which is a sensitive and specific biomarker of myocardial damage, and plasma concentration of myoglobin were evaluated for risk stratification in acute PE and found to predict fatal outcome.[13] More recently, Growth-differentiation factor-15 (GDF-15), which is a cytokine induced in the heart after ischemia or pressure overload, was emerged as an independent predictor of a complicated 30-day outcome.[14]

5. Contrast-enhanced multi-detector computed tomography. Contrast enhanced chest computed tomography (CT) is increasingly used as the first-line diagnostic imaging tool for acute PE. However, the advent of multi-detector CT (MDCT) with its ability to visualize smaller sub-segmental emboli that may be missed with single-slice technology and increasing familiarity with the technique has definitely improved the diagnostic yield. However, another advantage of MDCT is in its value as a risk stratifying tool. Using MDCT, standardized cardiac views are easily obtained in almost all patients. In the reconstructed 4-chamber view, right (RVD) and left ventricular dimensions (LVD) are measured by identifying the maximal distance between the ventricular endocardium and the interventricular septum, perpendicular to the long axis of the heart. Right ventricular enlargement is then defined as RVD/LVD ratio >0.9. Right ventricular enlargement on the reconstructed MDCT 4-chamber view has shown to correlate with the presence of right ventricular dysfunction on echocardiogram[15] and to be an independent predictor of 30-day mortality.[16]

Finally, the presence of "Saddle" or large proximal or bilateral PE on CT scan has been suggested to carry a worse outcome.

Patient management based on risk stratification:

a) Simple, uncomplicated acute PE: (normal hemodynamics and normal RV function): The prognosis of patients with acute PE, who found to have stable hemodynamics and normal RV function, is extremely good. On treatment with anticoagulation alone, the mortality in these patients is very low (<1%).[17] Treatment of such low-risk patients is anticoagulation alone and thrombolytic therapy (TT) is not required.

b) Massive acute PE (hemodynamic instability/ shock): Shock is the most important risk stratifying parameter, at which the mortality increased dramatically. As mentioned earlier, the majority of patients with massive acute PE die within 2 hours and before diagnosis or treatment can be instituted. A single trial (that was terminated prematurely) studied those patients with acute PE who presented in cardiogenic shock. After inclusion of 8 patients only, all 4 patients treated with streptokinase survived while all those treated with heparin died.[18] Based on this trial, and the observed rapid lysis of clot with TT, it is now considered that TT is a very reasonable option (and may be considered as the standard of care) in the management of massive acute PE, unless contraindicated.

c) Sub-massive acute PE (normal hemodynamics, and RV dysfunction): Nearly one third of patients with acute PE has normal blood pressure but some evidence of RV dysfunction on echocardiography. Despite the clear increase in mortality of this group compared to the group with simple (uncomplicated) PE, it is important to mention that the management of this group of patient is still controversial. Several studies[19,20] have confirmed the reliability of RV dysfunction on echocardiography as a marker of poorer prognosis. One study reported that the 30-day mortality in 172 hemodynamically stable patients who did not have RV dysfunction was 4.1% compared to 10% among 380 such patients with RV dysfunction.[21] Another study reported a mortality rate of 4% in 216 patients with RV dysfunction, compared to 0.9% without RV dysfunction.[22]

Despite the fact that many authorities recommend treating this group of patients with TT if there is evidence of RV dysfunction, the clinical consequences of this rapid reversal of RV dysfunction are uncertain. In a randomized study of 101 patients who received either r-TPA or heparin,[23] greater improvement on echocardiogram occurred in patients receiving r-TPA at 3 and 24 hours, confirming the efficacy of TT in rapid clot lysis. However, there were no clear clinical advantages to this rapid clot lysis. Studies that looked at clinical endpoints showed conflicting results. For example, in the MAPPET registry,[20] the 30-day mortality was 4.7% in patients with RV dysfunction treated with TT, compared to 11.1% in heparin-treated patients. On the contrary, another single-center registry reported fewer deaths among patients receiving unfractionated or low-molecular weight heparin (0%; 0 of 64 patients) than among those receiving TT (6.3%; 4 of 64 patients).[24] Recently, a randomized trial comparing heparin plus alteplase with heparin plus placebo in the treatment of submassive PE in 256 patients has been reported.[19] The primary endpoint was in-hospital death or clinical deterioration requiring an escalation of treatment (defined as catecholamine infusion, secondary thrombolysis, endotracheal intubation, cardiopulmonary resuscitation, emergency surgical embolectomy, or catheter fragmentation of the thrombus). The results showed no difference in the primary endpoint between the two groups (3.4% in the alteplase group, 2.2% in the placebo group). However, the need to escalate treatment was significantly less in TT group (24.6% in the placebo group; 10.2% in the TT group, p=0.004). The 30-day event-free survival was higher in the heparin plus alteplase group.

As there is no conclusive evidence for mortality benefit from using TT is sub-massive PE (and the end-point of escalation of therapy is soft and inadequately objective), the controversy is likely to continue until the results of the large European study become available. At the moment, and because of lack of enough evidence, it might be reasonable to consider TT in patient who presented with acute PE, and found to have both RV dysfunctions by echocardiography and abnormally elevated cardiac biomarkers. Conversely, the relatively low positive predictive value of the biomarkers results when used alone, it is probably not justified to administer TT and exposing the patient to the risk of intracranial or other major bleeding associated with TT.

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