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Caveats in the Management of Patients with Acute Pulmonary Thromboembolism and Possible New Pathways

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Background

Acute Pulmonary Embolism (PE) is the third most common cause of vascular death after myocardial infarction and stroke with the incidence being approximately 100 per 100,000 persons per year [1]. Early mortality is closely related to clinical presentation with or without acute heart failure and respiratory failure. In addition, mortality depends on comorbidities, very often present in PE patients, especially malignancy and autoimmune diseases. Treatment of acute PE is based on the risk assessment of patients which should be estimated continuously during the early treatment [2]. The patients with high risk are hypotensive, in circulatory shock, and have hospital mortality rate above 20%. High-risk patients need immediate reperfusion therapy with either systemic, or catheter-guided thrombolysis, or even mechanical removal of the thrombus by surgical or percutaneous techniques. The differential diagnosis of acute circulatory shock includes variety of diseases which can mimic or even be associated with PE. The biggest problems are acute heart failure and internal bleeding after surgery in various settings. However, severe dyspnea, which is characteristic of large PE with nonspecific electrocardiography changes, leads to proper diagnostic algorithm using urgent cardiac ultrasound and multidetector computed tomographic pulmonary angiography (MDCT-PA). Patients with intermediate risk PE have the right ventricle (RV) dysfunction caused by the thrombus presence in pulmonary tree leading to high systolic pressure, larger diastolic diameter, hypo or akinesia of the free RV wall (McConnell sign) [3] and impaired tricuspid annulus movements. Transthoracic cardiac ultrasound is the most commonly used for the estimation of RV function in PE at admission and afterwards [4]. However, some changes in RV function may exist before development of acute PE. Hence, sometimes is very difficult to distinguish those premorbid and PE caused changes in RV function. The most common premorbid comorbidities, which can influence chronic RV changes, are left ventricle heart failure and chronic lung diseases, especially chronic obstructive lung disease. Some acute events can also cause acute RV dysfunction such as: severe pneumonia, acute left heart failure and acute respiratory distress. A variety of laboratory and clinical markers can further assist in risk assessment in intermediate risk PE patients [5]. Simplified Pulmonary Embolism Severity Index (sPESI) is clinical score which is also used in the risk stratification of intermediate risk PE (Table 1) [6]. Simplified PESI is consisted of several easily obtained patients' characteristics. Three of them are related to the clinical state of patients at presentation (oxygen saturation, arterial pressure and heart rate) and other three, the most important parameters, are characteristics of the patients (age, presence of chronic lung or heart failure and presence of malignancy). The presence of at least one sPESI risk factor means 10% risk of one-month mortality, compared to almost 0% mortality risk in patients without any of them. Therefore, patients with intermediate risk PE, without positive biomarkers (troponin, BNP), but with sPESI of at least one or higher, should be hospitalized. Real low risk patients are those without positive biomarkers and RV dysfunction on imaging, who are hemodynamically stable and with sPESI = 0. They can be treated in outpatient settings. Thus management of PE patients is based on the early PE diagnosis and risk assessment (Table 2).

Simplified PESI Score	
Age > 80 years	1 point
History of cancer	1 point
History of chronic cardiopulmonary disease	1 point
Heart rate ≥ 110 beats per minute	1 point
Systolic plod pressure < 100 mmHg	1 point
O2 saturation < 90%	1 point

Table 1: Simplified PESI score.

There are several caveats with current PE recommendation management mainly based on European Society of Cardiology guidelines [2].

Risk Assessment According to Age

Risk assessment method probably should be different for younger and elderly patients. The cardiovascular reaction to acute obstruction of pulmonary artery with thrombus depends on age. Younger patients are very difficult to deteriorate and they will hold arterial blood pressure with compensatory tachycardia to enormous extent with sudden breakdown of arterial pressure. Thus tachycardia should be better and also earlier sign of hemodynamic compromise than arterial hypotension in younger patients. On the opposite, it is very likely that elderly patients do not achieve such extreme compensatory heart rate and they develop arterial hypotension before extreme tachycardia.

Slow Thrombolytic Protocols for Intermediate-High Risk PE

Avoidance of thrombolytic therapy in intermediate risk PE is recommended after results of large randomized PEITHO study which investigated the role of tenecteplase in patients with troponin positive intermediate risk PE [7]. Tenecteplase did not decrease mortality but increased major bleeding including intracranial bleeding. However, there are some serious concerns about the methodology in this study. More than one third of patients in this study were 75 years or older, echocardiography criteria was "soft" and use of troponin at any level above normal favorites elderly patients with renal dysfunction. The second problem is that tenecteplase is a thrombolytic that causes intracranial bleeding more often than other thrombolytics [8]. Hence, why should we use full dose bolus thrombolysis like in PEITHO study with no chance to control anything after the "bomb" is delivered? Slow protocol

Key Points for Treatment of Patients with PE According to Risk Assessment	
Low-risk	No hemodynamic compromise No RV dysfunction • sPESI should be zero for the really low-risk PE • For diagnosis d-dimer, clinical probability assessment and MDCT-PA are mandatory • Trend to outpatient treatment • Introduction of direct oral anticoagulant drugs without heparin therapy • Good prognosis
Intermediate-low risk	No hemodynamic compromise RV dysfunction is present Negative biomarkers • For diagnosis d-dimer, clinical probability assessment and MDCT-PA are mandatory • If sPESI is 0 – outpatient treatment should be considered • Early introduction of direct oral anticoagulants • Mortality depends on comorbidities • Good prognosis in majority
Intermediate-high risk	Patients are at the edge of hemodynamic compromise Echocardiography assessment is very important Biomarkers are positive • MDCT-PA in-hospital mortality is probably higher than 10% • It would be wiser to start anticoagulant therapy with heparins considering the possibility of deterioration and renal function • Monitoring is necessary whenever patient is unstable • Patients who developed hemodynamic deterioration should be treated with reperfusion and other necessary symptomatic therapy
High-risk	Patients are in shock • The state can be extremely unstable • Diagnostic procedure is very cumbersome but every effort should be made to perform MDCT-PA • Echocardiography and Doppler venosonography can be surrogate for MDCT-PA • Fast reperfusion therapy is necessary with systemic thrombolysis in patients with low risk for major-uncontrolled bleeding • In patients with firm contraindication for systemic thrombolysis catheter thrombolysis or mechanical removal of thrombus should be performed. • In hospital mortality is higher than 30%. • Careful bridging from heparins to oral anticoagulants

Table 2: Management and some key points for treatment of patients with PE according to risk assessment at presentation.

(streptokinase 100.000 IU/h or alteplase 5 mg/h or catheter thrombolysis with even slower alteplase infusion) may be safer because we can interrupt thrombolysis at the minor suspicion of bleeding. During the slow protocol of thrombolysis we have enough time to monitor patient carefully and measure several parameters in order to estimate the risk of bleeding or to spot the ongoing bleeding (like fibrinogen, red blood cells, hematocrit etc.).

Assessment of Bleeding Risk

In the current guidelines, there are very little data about the estimation of the risk of bleeding. We think that intermediate-high risk PE patients, especially younger patients should be treated with reperfusion therapy using the estimation of bleeding risk. The appropriate score should take into account some important features of PE patients, very often presence of recent surgery, malignant disease, previous use of drugs which can contribute to bleeding, renal function, history of bleeding, older age etc.

Management of PE Patients Admitted in Resuscitation

How to diagnose and treat patients with PE admitted in resuscitation? Risk factors for PE and signs of deep vein thrombosis could lead to suspicion of PE. ECG may be very variable, tachycardia with signs of acute RV overload, bradycardia, AV blocks, supraventricular tachyarrhythmias etc. The presence of dyspnea before loss of conscious witnessed by bystander may be a lead to PE diagnosis [9]. Urgent echocardiography should be used during the resuscitation, however it is not easy to interpret the imaging and its quality is not satisfactory in a large number of patients. Nevertheless, if we have a high suspicion for PE, what therapy should be given? Tenecteplase, the only bolus thrombolytic agent is expelled from the guidelines. The right choice of thrombolytic protocol may be of importance even here. Intravenous bolus of reduced dose (1 / 2 of usual dose) of alteplase may be a solution [10].

Treatment of various diseases is based on guidelines which

are based on clinical trials and medical expertise. The number and quality of clinical studies are very different among different diseases. For instance, in myocardial infarction there are several hundred of trials with huge number of patients, more homogenous patients and the quality of treatment is on the very high level with strong evidence strength for recommendations. For pulmonary embolism, the causes of the disease are of extreme importance for the diagnosis, therapy and outcome, with a huge spectrum of possibilities. Hence, it is very difficult to create and carry out randomized studies with sufficient number of homogenous PE cohorts and with sufficient power for firm conclusions regarding management in particular subgroups of PE patients (e.g. PE in elderly, in those with malignant disease, with recent surgery treatment or pregnancy related PE).

The field of PE is an extremely important and complex, demanding a lot of work in the future to establish better guidelines for PE management.

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