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Submassive Pulmonary Embolism: Current concepts

Jayakrishnan B[1], Vivek Ravikumar[2], Sami M Bennji[3]

[1]Senior Consultant, [3]Consultant, Division of Pulmonology, Sultan Qaboos Comprehensive Cancer Care and Research Centre, Muscat, Oman.
[2]Senior Resident, Department of Emergency Medicine, Baby Memorial Hospital, Calicut, India

Address for Correspondence: Dr. B Jayakrishnan, MBBS, MD, DTCD, DNB, MRCP(UK), FRCP, FCCP, FICS, Senior Consultant (Pulmonology), Sultan Qaboos Comprehensive Cancer Care and Research Centre, PO Box 566, PC 123, Muscat, Oman. Email: drjayakrish@hotmail.com

Abstract

Submassive pulmonary embolism (PE) represents a subset of patients with disease severity between massive PE and the standard-risk PE. It is characterized by evidence of right ventricular (RV) dysfunction with a normal blood pressure. Risk-stratification in acute PE includes factors related to hemodynamic instability, RV overload, and cardiac biomarkers. The location of the thrombus or the clot burden are not a part of the risk stratification. Patients with confirmed submassive PE should be started on anticoagulation as soon as possible while monitoring closely for deterioration. Thrombolysis or catheter-based therapies may be considered on a case-by-case basis when the benefits outweigh the risk of hemorrhage. Patients who have a large clot burden, severe RV enlargement or dysfunction, high oxygen requirement, or are severely tachycardic needs early multidisciplinary assessment.

Keywords: Pulmonary embolism, Submassive, Thrombolysis

Pulmonary embolism (PE) is one of the leading causes of cardiovascular mortality worldwide. The mortality rates vary depending on the demographics, nature, and severity of PE. Pulmonary embolism is an obstruction in the pulmonary artery due to a clot, tumor, air, or fat [1]. Development of computed tomography pulmonary angiography (CTPA) in late 1990's totally changed the diagnostic approach in PE. The thrombus can occupy any part of the pulmonary circulation. When it is located in the main pulmonary artery at its division and extends into the right and left pulmonary arteries, it is termed saddle pulmonary embolism [2,3]. (**Figure 1**). When clots are located in the branches of the pulmonary artery corresponding to the anatomical lung segments, they are labelled as lobar, segmental, and subsegmental PEs [1].

Classification can be based on the timeframe or severity. Based on the time of onset , they are termed as "acute," "subacute," and "chronic pulmonary embolism" [1]. Severity based classification is not uniform and often leads to documentation errors [4,5]. American Heart Association (AHA), American College of Chest Physicians (ACCP), and European Society of Cardiology (ESC) guidelines uses different terms to classify the same severity [6-8]. (**Table 1**)

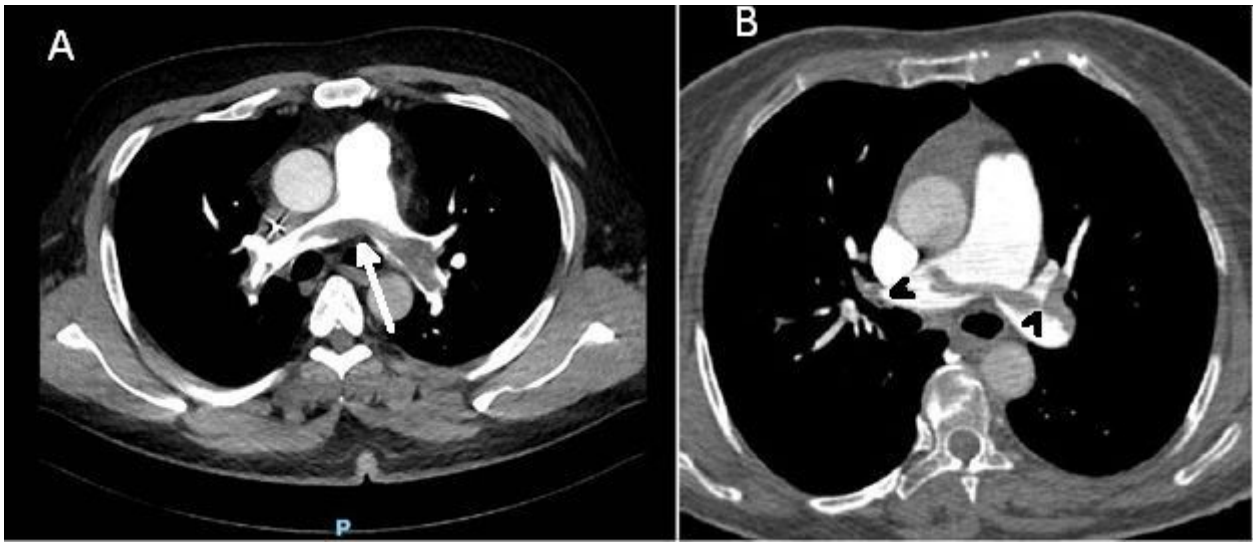

Figure 1: Chest computed tomography angiogram showing a thrombus straddling the bifurcation of the main pulmonary artery (arrow) and extending to the right and left pulmonary arteries (arrowheads) in two different patients (A) and (B).

Table 1. Classification of severity based on three different international guidelines

ACCP	AHA	ESC
Low risk	Low risk	Low risk
Intermediate risk	Submassive	Intermediate- low risk
		Intermediate- high risk
High risk	Massive	High risk

Submassive PE represents a subset of patients with disease severity between massive PE, characterized by hemodynamic instability, and the standard-risk PE. The guidelines are clear on the classification of low and high-risk PE, but differ in the defining intermediate risk. Submassive acute PE is characterized by evidence of right ventricular dysfunction with a normal blood pressure [9,10]. Moreover, there is a wide spectrum of clinical severity within all these definitions [4].

Risk-stratification in acute PE utilizes parameters linked to hemodynamic instability, RV overload, and cardiac biomarkers. Clinical Risk Prediction Scores like Pulmonary Embolism Severity Index (PESI) or simplified Pulmonary Embolism Severity Index (sPESI) have been validated for predicting 30-day mortality in patients with acute PE [8]. The PESI scores 11 risk factors while the simplified one, sPESI, uses only six. Elevation of some biomarkers carries an independent risk of short-term mortality and RV dysfunction. Brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) are markers of RV pressure overload while troponin I and troponin T are indicators of myocardial ischemia. Heart-type fatty acid binding protein (h-FABP), plasma cystatin C, growth differentiation factor 15 are a few among the new biomarkers that are being used in in risk stratification for therapeutic interventions in PE [5]. However, using these biomarkers alone to judge severity is not advisable.

Interestingly, the location of the thrombus nor the clot burden seen on CTPA are a part of the risk stratification. Saddle PE, a visible thrombus that straddles the bifurcation of the main pulmonary

artery trunk, represents a large thrombotic burden [2,11]. Though, the visual impact is fearsome, it is not always related to the severity and maybe relatively asymptomatic, hemodynamically stable and can be successfully managed with conventional treatment without the need for aggressive measures [12]. Though 31% of patients with saddle PE were asymptomatic in a study from Spain, compared with patients with non-saddle PE they were more symptomatic and presented with altered vital signs [2]. Similarly, Meinel et al found that the degree of thrombus load and central thrombus location were not predictive for all-cause mortality, though they were associated with adverse clinical outcomes [13]. Even in hemodynamically stable acute pulmonary embolism, patients with thrombi lodged in the main pulmonary arteries were found to have a higher overall mortality and lower survival than patients with segmental or subsegmental pulmonary embolism [14]. Measuring total embolus burden seems to be logical as more obstructed vessels can lead to higher resistance and therefore to right ventricular dysfunction. Four of the most commonly used pulmonary obstruction indices for PE are Mastora, Qanadli, Ghanima and Kirchner scores [15]. Qanadil score cut-off of 18 points was shown to be a strong independent predictor of RV dysfunction in PE [16,17]. In addition to the clot burden indices, other signs in CTPA can also quantify PE severity with a good accuracy, almost immediately at the time of diagnosis [18]. Nevertheless, the role of quantitative clot burden indices in immediate risk stratification is limited. So, clinical, radiological, laboratory, and other comorbid illnesses have to be evaluated together for making a therapeutic decision.

Demonstration of RV strain on CTPA or echocardiograms is a better predictor of an adverse outcome. In clinical evaluation, the right ventricle to left ventricle (LV) diameter-ratio was identified to be the strongest and most robust value to predict clinical outcomes in patients with acute PE [15]. Combining left ventricular outflow tract velocity-time integral (LVOT VTI) of $\leq$ 15 cm with a RV/LV ratio $\geq$ 1, can identify PE patients with impending risk of clinical deterioration, with increased specificity and positive predictive value [19].

In the acute phase, the normotensive patient with confirmed PE and RV dilatation presents a significant dilemma to clinicians. The management of patients with submassive PE is best done by a multidisciplinary approach [5]. Patients with confirmed PE or high pretest probability should be started on anticoagulation as soon as possible unless contraindicated. Even in patients with saddle PE thrombolytics are not needed as most of them are hemodynamically stable with hypotension, if present, being transient [12]. Bleeding risk should be evaluated simultaneously especially when advanced treatment options are considered. The International Society on Thrombosis and Hemostasis defines major bleeding as a decrease in hemoglobin greater than 2.0 gm/dl; a transfusion of more than 2 units of packed red blood cells; or a critical bleeding site such as intracranial, intraarticular, retroperitoneal, intraspinal, pericardial, or intramuscular with compartment syndrome [20].

The role of systemic thrombolysis in those with hemodynamically stable disease is not clear. Hence routine use of systemic thrombolysis is not advised in patients with submassive PE. While on anticoagulation, they should be closely monitored for hemodynamic decompensation. Patients with both RV dysfunction and elevated cardiac biomarkers have a greater chance of clinical deterioration. In the case of hemodynamic deterioration, 'rescue thrombolysis' is advised [5]. Thrombolysis can also be considered in normotensive patients, who deteriorate with respiratory failure despite anticoagulation [4]. Alteplase is given as a 100-mg infusion over 2 hours while tenecteplase is given as a bolus injection. The well-known Pulmonary Embolism THrOmbolysis (PEITHO) trial demonstrated a reduction in mortality in the first 7 days from 5.6% in the anticoagulation group to 2.6% in the thrombolysis group but at 30 days there was no significant difference in survival between the two treatment groups [21]. It should be noted that a few from the control group went on to receive rescue thrombolysis thus improving the survival in the anticoagulation group. However, three-year follow-up of the trial showed no long-term mortality benefit in tenecteplase plus heparin treated patients with submassive PE [22]. But, a meta-analysis of 1,775 patients showed a lower rates of all-

cause mortality with thrombolysis at the cost of an increased risk of major bleeding (9.24%) and intra cranial hemorrhage (1.46%) [23]. Igneri et al reviewed seventeen studies on the use of alteplase in patients with submassive PE. Three trials compared 2 different dosing regimens; seven compared alteplase to anticoagulation alone and other thrombolytics were compared in another seven. Studies on tenecteplase plus anticoagulation versus anticoagulation alone were also evaluated. They conclude that without hemodynamic instability at presentation, the short term benefits of thrombolysis in submassive PE may be outweighed by the risk for major bleeding and lack of improvement on long-term functional outcomes compared to those receiving anticoagulation only [24]. The decision of thrombolysis requires careful consideration of the risks and benefits involved and appropriate stratification of risk. The aggressiveness of therapy must match the severity of disease [19,25]. ACCP 2016 guidelines suggest considering systemic thrombolysis in patients with submassive PE with a clinical decline and low bleeding risk. Half-dose thrombolysis with a lower dose (50 mg/2 h or 0.6 mg/kg) of tissue plasminogen activator (tPA) is another option in submassive PE [26]. In a prospective, non-randomized, open-label, single center trial on 76 patients, half-dose tissue-type plasminogen activator (rt-PA) treatment in submassive PE prevented death/hemodynamic decompensation in the first 7-day and 30-day period compared with low molecular weight heparin treatment without increasing the risk of bleeding [27].

Catheter-based treatment (CBT) includes catheter-directed thrombolysis (CDT), mechanical fragmentation, or a combination of both [4]. Catheter-directed thrombolysis involves infusing thrombolytic drugs after positioning catheters unilaterally or bilaterally in the thrombosed pulmonary artery. The risk of intra cranial hemorrhage appears to be as low as 0.5% with CDT. It can be combined with high-frequency ultrasound waves (US-CDT) which alter the structure of polymerized fibrin, thus enhancing the binding and tissue penetration of tPA into the fibrin rich thrombus [4,28,29]. Fixed low-dose US-CDT is the 'halfway house' strategy both for massive PE and submassive PE [29]. In a recent meta-analyses published in 2022, CDT was associated with significantly lower in-hospital, 30-day, and 90- day mortality and a tendency toward lower 1-year mortality with similar bleeding rates compared with systemic anticoagulation in patients with submassive PE [30]. So, patients with a high bleeding risk should be considered for CBT rather than systemic thrombolysis. For those who have contraindications to anticoagulation or have an unacceptably high bleeding risk, placement of an inferior vena cava (IVC) filter should be performed.

Percutaneous mechanical thrombectomy or surgical thrombectomy should be considered if the risk of bleeding under thrombolytic treatment is high. However, surgical embolectomy should be reserved for patients with absolute contraindications to or failed thrombolysis, clot in transit, and clot traversing a patent foramen ovale and should be reserved for special situations in patients with submassive PE [1,28].

There is growing evidence in support of direct oral anticoagulants (DOACs) having a better safety profile for bleeding than Vitamin K antagonists. Patients with submassive PE can be safely transitioned from parenteral heparin to oral anticoagulation after just 72 hours [31]. The aim of long-term treatment (3-6 months after diagnosis) is to complete the treatment of the acute phase as well as to prevent recurrence.

To conclude, hemodynamically stable patients with intermediate-risk/submassive PE who are anticoagulated, should be monitored closely for deterioration. Thrombolysis or catheter-based therapies may be considered on a case-by-case basis when the benefits outweigh the risk of hemorrhage. Patients who have a large clot burden, severe RV enlargement or dysfunction, high oxygen requirement, and/or are severely tachycardic needs early multidisciplinary assessment.

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