Pulmonary Embolism in 2017: Increasing Options for Increasing Incidence
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ABSTRACT
Scope of the problem – An increasing burden of disease
Acute pulmonary embolism (PE) is a problem encountered by a majority of medical and surgical specialties in their scope of practice. Acute PE is currently the 3rd leading cause of cardiovascular death in the United States, resulting in 100,000 deaths annually as estimated by the Centers for Disease Control (CDC [1]). There is a paucity of data and a broad range of estimates for both incidence and morbidity due to acute PE. The mortality of all patients presenting with acute PE is estimated between 10-30% at 90 days utilizing current treatment regimens [2]. The incidence of acute symptomatic PE seems to be increasing from 3/100 to more than 6.5/100 in the past 15 years [2]. The increasing burden of disease has led to a period of intense investigation into new therapies and strategies to treat acute PE.

KEYWORDS: pulmonary embolism, pulmonary embolism response team, catheter-directed thrombolysis, RV to LV ratio, PESI

PULMONARY EMBOLISM - MORTALITY RISK
Pulmonary embolism has a wide morbidity range, from the asymptomatic and incidentally discovered where mortality is less than 1%, to massive acute PEs that often lead to progressive shock and death. The difficulty lies in stratifying patients into categories based on risk. Only recently has increased research begun to codify categories of acute PE based on risk. Acute PE in 2017 is currently divided into 3 categories of low, moderate and high risk. The mortality for low-risk patients is approximately 1% and this represents 40% of all presenting pulmonary embolism [4,5]. Another 5-15% of presenting pulmonary embolisms have shock and hemodynamic compromise representing a high-risk cohort. Even with systemic tPA thrombolysis the mortality for these patients exceeds 30%. The third category is the sub-massive or moderate-risk patient population, and makes up the remaining 40-45% of presenting PEs. These patients have a large central thrombus burden and signs of RV failure or compromise without frank shock. These intermediate-risk patients have a high risk of degeneration to shock and death. Depending on the exact definitions, the mortality in this subgroup of patients ranges from 5-20% [4].

STRATEGY FOR RISK STRATIFICATION AND THERAPY SELECTION
Given that PE requires expertise from pulmonology, radiology, non-invasive and interventional cardiology, and cardiothoracic surgery, a multi-disciplinary team approach has been adopted at many institutions to help better serve patients with acute PE. The success of multi-disciplinary teams in the arenas of complicated coronary disease and aortic stenosis have served as a model for PE. PE response teams or PERT are gaining traction at many large medical centers that offer advanced therapies available to patients with acute PE. Engaging specialists from different backgrounds using telemedicine allows timely and efficient discussion of treatment options and provides immediate advice and therapy for patients with massive and sub-massive PE.

Prognostic scoring systems incorporate clinical, laboratory and radiographic parameters. The original and simplified pulmonary embolism severity index (PESI) scores utilize clinical variables that predict mortality [Figure 1]. The modified Miller index uses the CTPA clot burden to predict prognosis. These scores have variable accuracy in predicting morbidity and mortality [6,7,8,9,10]. Laboratory markers of RV dysfunction include BNP or N-terminal-proBNP, which reflect the severity of hemodynamic compromise and RV dysfunction in PE and predict adverse outcome [8,12,13]. They may be an effective tool for triaging patients in the ED for admission to the ICU, step-down or floor units but they do not take into account RV parameters such as RV to LV ratio or RV size and systolic function that are important decision points when considering advances therapies and refining risk stratification.

THE RVS THE PROBLEM
Mortality in acute pulmonary embolism is caused by acute RV failure from acute pressure overload in the setting of a large volume of thrombus. Multiple registries have shown a strong association with RV dysfunction and subsequent death from acute PE [12, 13, 14, 15, 16]. The difficulty lies in which RV parameter seems to best correlate with poor outcomes. Current data suggests that an RV to LV ratio greater than 1 appears to be the best predictor of morbidity and mortality [15, 16]. The RV to LV ratio has been validated both on CT imaging, which is typically the modality through which acute PE is diagnosed, as well as via 2-D
THROMBOEMBOLIC DISEASE

**Emerging Therapies with a Paucity of Data**

The standard therapy for acute pulmonary embolism remains parenteral anticoagulation with the addition of high dose (100 mg) bolus systemic thrombolysis for cases of shock (currently defined as a SBP less than 90 mmHg). These both have level 1 evidence supporting their use in acute PE but are based on decades-old data with small sample sizes. A meta-analysis of trials in patients with massive PE showed a reduction in the composite of recurrent PE and death in systemic lysis patients versus heparin (19). The PEITHO trial demonstrated reduced composite endpoint of death and hemodynamic collapse in intermediate-risk patients (2.6% vs. 5.6%), but no mortality benefit and at the expense of a higher bleeding risk (17,18,19). The MOPPET trial randomized moderate-risk patients to half-dose alteplase (50 mg over 2 hours) anticoagulation with lower pulmonary artery pressure at 28 months and no major bleeding (23). These studies collectively demonstrate that systemic fibrinolysis in patients with massive and sub-massive PE leads to improved hemodynamic stabilization and possibly lower risk of recurrent PE and death but with a higher risk of severe bleeding and intracranial hemorrhage (ICH).

Catheter-based therapies to relieve obstruction quickly and restore pulmonary blood flow and improve RV dysfunction may improve cardiac output and stabilize hemodynamics. Delivery of fibrinolytics directly into the clot may allow for increased clot dissolution, shorter treatment transthoracic echocardiogram [Figure 2]. Combining PE-related risk and patient's clinical status and co-morbidities predicts early outcomes and may be used to guide treatment decision-making [Figure 4].

**Figure 1.** Konstantinides, Eur Heart J. 2014;(35):3033-3080.

<table>
<thead>
<tr>
<th>Early mortality risk</th>
<th>Risk parameters and scores</th>
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<tr>
<td></td>
<td>Shock or hypotension</td>
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<td>High</td>
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PE = pulmonary embolism; PESI = Pulmonary embolism severity index; RV = right ventricular; sPESI = simplified Pulmonary embolism severity index.

The echocardiographic criteria of RV dysfunction involve RV dilatation and/or an increased end-diastolic RV–LV diameter ratio (in most studies, the reported threshold value was 0.9 or 1.0); hypokinesis of the free RV wall; increased velocity of the tricuspid regurgitation jet; or combinations of the above. On computed tomographic (CT) angiography (four-chamber views of the heart), RV dysfunction is defined as an increased end-diastolic RV/LV ratio (left ventricular diameter ratio with a threshold of 0.9 or 1.0).

Markers of myocardial injury (e.g., elevated cardiac troponin I or -T concentrations in plasma), or of heart failure as a result of (right) ventricular dysfunction (elevated natriuretic peptide concentrations in plasma).

Neither calculation of the PESI (or sPESI) nor laboratory testing are considered necessary in patients with hypotension or shock.

Patients in the PESI Class I–II, or with sPESI of 0, and elevated cardiac biomarkers or signs of RV dysfunction on imaging tests, are also be classified into the intermediate-low-risk category. This might apply to situations in which imaging or biomarker results become available before calculation of the clinical severity index.

**Figure 2.** RV to LV ratio from Ultima trial

Instructions for study sites and core laboratory for measurement of sub-annular right ventricular to left ventricular (RV/LV) ratio from the echocardiographic apical 4-chamber view: (1) Obtain an end-diastolic image defined as last available image before onset of tricuspid valve closure. (2) Obtain center line through inter ventricular septum (gray vertical line). (3) Obtain tricuspid annular line (gray horizontal line) at septal insertion point of tricuspid valve (oblique arrow), perpendicular to interventricular septum line. (4) Obtain subannular line 1 cm above and parallel to annular line (vertical arrow). (5) Obtain RV and LV dimensions on subannular line with the use of endocardial borders (red arrows). (6) Calculate RV/LV ratio.
times and reduced risk of bleeding complications. Catheter-directed infusion of tPA plus ultrasound for clot separation is currently the only FDA-approved therapy for PE treatment. The smaller studies supporting EKOS catheter directed thrombolytic therapy include the randomized controlled ULTIMA trial which examined patients with intermediate or sub-massive PE vs traditional anticoagulation therapy or catheter-directed thrombolysis and the single arm Seattle II PE trial.

**ULTIMA AND SEATTLE II PE TRIALS** (20, 21, 22)

The Ultima trial showed rapid improvement of RV function and reduced pulmonary artery pressures within 24 hours when compared to standard anticoagulation in patients with sub-massive acute PE. This benefit was no longer statistically significant at 90 days of follow-up. Bleeding rates were no higher in the treatment arm and led to the approval of catheter-directed thrombolytic therapy for this moderate-risk population. The US based Seattle II PE trial, of which the Miriam Hospital was a site, was a prospective, single arm safety and efficacy trial that confirmed improvement in RV function using catheter directed thrombolytic therapy. (See case example of EKOS CDT, Figure 3.) It also confirmed no major bleeding events as a result of lower dose catheter-directed thrombolytic therapy, [like ULTIMA, a total of 24 mg of tPA]. Although proven safe and effective there has yet to be a randomized controlled trial showing benefit for clinical endpoints in acute pulmonary embolism using catheter-directed therapy (CDT). The pivotal trial for moderate risk PE patients, PE TRACT, hopes to recruit over 500 patients and randomize to anticoagulation with or without catheter-directed thrombolysis. Long-term clinical endpoints should answer this critical clinical equipoise question.

**Figure 3. Sub-massive pulmonary embolism angiogram**
Right and left pulmonary angiograms with sub-massive pulmonary embolism prior to EKOS catheter placement.

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Figure 4. ESC 2014 guidelines

Clinical suspicion of PE

Shock / hypotension?

Yes

No

Diagnostic algorithm as in Figure 3

PE confirmed

Diagnostic algorithm as in Figure 4

PE confirmed

Assess clinical risk (PESI or sPESI)

PESI class III-IV or sPESI ≥1

PE class I-II or sPESI = 0

Intermediate risk

Consider further risk stratification

RV function (echo or CT)

Laboratory testing

Both positive

Intermediate-high risk

A/C; monitoring; consider rescue reperfusion

One positive or both negative

Intermediate-low risk

Hospitalization; A/C

Low risk

Primary reperfusion

Consider early discharge and home treatment, if feasible

A/C = anticoagulation; CT = computed tomographic pulmonary angiography; PE = pulmonary embolism; PESI = pulmonary embolism severity index; RV = right ventricular; sPESI = simplified pulmonary embolism severity index.

If echocardiography has already been performed during diagnostic work-up for PE and detected RV dysfunction, or if the CT already performed for diagnostic work-up has shown RV enlargement (RV/LV (left ventricular) ratio ≥ 0.9), a cardiac troponin test should be performed except for cases in which primary reperfusion is not a therapeutic option (e.g., due to severe comorbidity or limited life expectancy of the patient).

Markers of myocardial injury (e.g., elevated cardiac troponin I or T concentrations in plasma), or of heart failure as a result of (right) ventricular dysfunction (elevated natriuretic peptide concentrations in plasma) If a laboratory test for a cardiac biomarker has already been performed during initial diagnostic work-up (e.g., in the chest pain unit) and was positive, then an echocardiogram should be considered to assess RV function, or RV size should be (re)assessed on CT.

Patients in the PESI Class I-II, or with sPESI of 0, and elevated cardiac biomarkers or signs of RV dysfunction on imaging tests, are also to be classified into the intermediate-low risk category. This might apply to situations in which imaging or biomarker results become available before calculation of the clinical severity index. These patients are probably not candidates for home treatment.

Thrombolysis, if (and as soon as) clinical signs of haemodynamic decompensation appear; surgical pulmonary embolectomy or percutaneous catheter-directed treatment may be considered as alternative options to systemic thrombolysis, particularly if the bleeding risk is high.

Monitoring should be considered for patients with confirmed PE and a positive troponin test, even if there is no evidence of RV dysfunction on echocardiography or CT.

The simplified version of the PESI has not been validated in prospective home treatment trials; inclusion criteria other than the PESI were used in two single-arm (non-randomized) management studies.
The AngioVac thrombectomy device utilizes a 22F venous catheter that can remove large volume thrombus using a centrifugal pump and venous reinfusion, and is designed to remove thrombus from iliac veins, IVC, RA and PA. The need for a 26F sheath and a perfusionist limits its use. The Inari FlowTriever device is a 22F venous sheath aspiration system that utilizes an aspiration guide catheter and a catheter composed of three self-expanding nitinol disks to entrap and remove thrombi. Limitations include the large access sheath and difficulty manipulating the guide catheter into the pulmonary artery. The Penumbra thrombectomy device provides 29 mmHg vacuum aspiration with an 8F device that uses a separator wire to clear the system of thrombus.

**OTHER PE THERAPIES**

In high-risk patients with shock from acute PE who fail or have a contraindication to systemic thrombolytic therapy, several options remain. Extracorporeal membrane oxygenation (ECMO) therapy can unload the RV and provide oxygenation to allow for recovery. It is being used more frequently for critically ill patients with high expected mortality but vascular complications from large bore sheaths remain the current limitation to this promising therapy. Data is only available through small registry and single-center data with regards to the efficacy of ECMO in the acute PE patient. Surgical embolectomy remains an important option for critically ill patients for whom high dose thrombolytics have failed or are contraindicated, and they must have proximal disease that is accessible through a median sternotomy. IVC filter use has fallen out of favor due to its high complication rate and low efficacy rate, and is only indicated in patients with an absolute contraindication to anticoagulation. Both the American and European guidelines do not recommend routine use of IVC filters in patients with PE.

Due to the complexities of assigning risk and choosing therapy for acute PE patients in a rapid manner, we’ve taken the burden of PE head-on in an effort to improve outcomes for patients. At Rhode Island and The Miriam Hospitals we offer advanced therapy for intermediate- and high-risk PE that include percutaneous catheter-directed thrombolyis, aspiration thrombectomy, surgical embolectomy and ECMO therapies. In order to rapidly triage patients to the appropriate therapy, we have created a pulmonary embolism response team to provide a multi-disciplinary approach to the management of acute PE. A call placed from the pulmonary fellow rapidly assembles a team including pulmonary critical care, interventional and non-invasive cardiology, interventional radiology and a cardiothoracic surgeon. The case is presented by the pulmonary critical care fellow, including access to all relevant imaging data and a discussion is held to determine the best care for the patient. We are currently collecting clinical data to compare our efforts pre- and post-initiation of the PERT team in a prospective trial dubbed Providence PE.

**MORE WORK TO BE DONE**

Definitive randomized controlled trials are currently in the early phases of approval so 3-5 years will lapse before any decisive data is available to guide treatment of acute PE patients. In the interim we are using guideline-based therapies and the PERT in an effort to maximize benefit for this common and highly morbid condition. Until appropriate studies fill knowledge gaps, we suggest utilization of multi-disciplinary PERTs and collection of data both locally and nationally through the PERT Consortium. (Figure 4. Suggested PE Treatment Algorithm, adapted from the ESC 2015 Guidelines)

**References**

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