Pulmonary embolism in the mechanically-ventilated critically ill patient: is it different? 2C03, 3C00

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Pulmonary embolism (PE) confers significant in-hospital morbidity and mortality, and critically ill patients remain at risk for venous thromboembolism despite thromboprophylaxis. Recognition of the clinical manifestations and immediate management of PE are of paramount importance. Despite diagnostic advances, PE is often undiagnosed and untreated in patients receiving mechanical ventilation, as these patients do not exhibit the common clinical features of the condition, making the diagnosis very challenging. Computed tomographic pulmonary angiography is probably the reference standard for the diagnosis of acute PE in the haemodynamically stable, ventilated patient. In the setting of circulatory collapse, bedside echocardiography may be used to risk stratify these patients, based on the presence or absence of right ventricular dysfunction, and guide further management. Treatment options include anticoagulation alone, anticoagulation plus thrombolysis, surgical or catheter embolectomy. Inotropes, vasopressors and pulmonary artery vasodilators may be considered after initial resuscitation of the right ventricle. Few studies have focused on estimating the prevalence of PE among mechanically-ventilated intensive care unit (ICU) patients and there is notable lack of data assessing predictive factors, prevention, diagnostic strategy and management of PE in the ICU setting.

Keywords: *critical illness; mechanical ventilation; pulmonary embolism; echocardiography; venous thromboembolism*

Introduction

Intensive care unit (ICU) patients are at high risk of pulmonary embolus (PE), with its associated morbidity and mortality.[1] Prolonged mechanical ventilation has been associated with high incidence of deep venous thrombosis (DVT) despite thromboprophylaxis.[2,3] In ICU patients, PE has been reported in 7-27% of post-mortem examinations and was thought to have caused or contributed to death in 0-12%, but there was clinical suspicion of PE in only 30% of these patients before death.[4] In sedated and ventilated patients with physiological derangement, PE would produce relatively non-specific signs and minimal or no symptoms, and hence presents a diagnostic challenge.[5]

Natural history

Venous thromboembolism (VTE) includes both DVT and PE and in approximately 90% of cases originates in the deep venous system of the lower limbs.[6] Calf vein DVT itself rarely causes either symptoms or symptomatic PE but when the thrombosis extends to the proximal veins it may then break free and cause major problems. With time, 20-30% of untreated calf DVTs extend proximally into the thigh where they pose 40-50% risk for PE.[8]

Pathophysiology

VTE and mechanical ventilation

Haemostasis is a complex balance of procoagulant and anticoagulant actions that prevent the explosive production of thrombin when the clotting cascade is activated.[9,10] Several preclinical studies and one clinical study in healthy subjects suggest that pulmonary fibrin turnover is altered by mechanical ventilation.[11] Haitsma and colleagues demonstrated that injurious ventilation settings increased pulmonary coagulopathy in an animal model of *Streptococcus pneumoniae* pneumonia, which resulted in a systemic coagulopathy.[12] Coagulation dysfunction with both defective inhibition of coagulation and attenuation of fibrinolysis could potentially contribute to the development of VTE in ventilated patients.[11,12]

Cardiorespiratory response to pulmonary embolism during mechanical ventilation

Acute PE results in increased right ventricular (RV) afterload. If the afterload is severely increased, RV enlargement, hypokinesis, ischaemia and RV failure may ensue.[13,14] The concomitant release of vasoactive and bronchoactive humoral factors such as serotonin from platelets, thrombin from plasma and histamine from tissue, have all been implicated in both pulmonary oedema and the ventilation-perfusion mismatch seen.[15]

Experimental data suggest that the main mechanisms involved in hypoxaemia and the increase in the alveolar-arterial oxygen tension gradient are shunt, low ventilation-perfusion ratio (V/Q), decrease in the mixed venous partial

ICU-acquired risk factors
• Mechanical ventilation
• Immobility
• Femoral venous catheters
• Sedatives
• Paralysing agents
• Vasopressor use
• Platelet transfusion
• Sepsis
Risk factors prior to ICU admission
• Patient specific:
– Age over 60 years
– Personal history or first degree relative with history of VTE
– Obesity (body mass index >30 kg/m^2)
– One or more significant medical comorbidities (cardiopulmonary, metabolic, endocrine disease; acute infectious diseases; inflammatory conditions)
– End-stage kidney disease
– Active cancer or cancer treatment
• Hereditary hypercoagulable states:
– Proteins C, S deficiency
– Antithrombin III deficiency
– Factor V Leiden
– Prothrombin gene mutation
– Plasminogen deficiency
– Activated protein C resistance without factor V Leiden
• Acquired hypercoagulable states:
– Acquired deficiency of antithrombin, protein C or S secondary to consumption (for example, in severe sepsis)
– Lupus anticoagulant
– Heparin-induced thrombocytopaenia
• Setting specific:
– Trauma
– Neurosurgical patients
– Spinal cord injury

Table 1 Risk factors for VTE in ICU.[9,19-24]

pressure of oxygen and possibly, release of mediators such as platelet-activating factor.[15-17]

In patients without pre-existing cardiopulmonary disease who are ventilated to near normal functional residual capacity without significant changes in lung volume and with positive end-expiratory pressure (PEEP) of less than 10 cm H_2O, clinically important changes in RV afterload are uncommon. Acute PE reduces the cross sectional area of the pulmonary vascular bed, resulting in increased pulmonary vascular resistance (PVR).[13,14,18] In mechanically-ventilated patients with limited cardiorespiratory reserve who develop pulmonary emboli, small changes in lung volume can cause acute elevation in PVR which may worsen RV function and result in significant haemodynamic compromise.

Risk factors

Thrombus formation needs the three components described as Virchow's triad: abnormal flow, endothelial damage and altered blood composition.[19]

The well-known major predisposing factors for PE (relative risk 5-20) include major abdominal and orthopaedic surgery, malignancy, reduced mobility, old age and previous proven VTE. At particular risk are trauma patients, neurosurgical patients and patients with spinal cord injury.[21] Specific risk factors for VTE in the ICU include mechanical ventilation, the presence of femoral venous catheters, sedatives and paralytic drugs, end-stage renal failure, platelet transfusion and the use of vasopressors (**Table 1**).[3,20]

The incidence following trauma varies from 5-63% depending upon patients' risk factors and the nature of the injuries, the methods used to detect asymptomatic VTE (eg surveillance imaging versus clinical detection) as well as the modality and timing of VTE prophylaxis being used.[22] Endothelial damage and blood compositional changes due to inflammatory and stress responses are the reasons for the high risk in trauma patients.[21,22] Factors leading to VTE are likely to develop immediately after the injury, before the administration of prophylaxis. Contraindications arising from associated injuries often limit the potential options for thomboprophylaxis.[23]

Mechanical ventilation has been identified as an independent ICU-acquired VTE risk factor.[20] Both ventilation and PEEP tend to decrease right and left ventricular preload, increase right ventricular afterload and decrease left ventricular afterload. The sum of these effects is that the cardiac output may fall, especially in the presence of hypovolaemia or in those with impaired cardiovascular reflexes.[24] Consequent exacerbation of venous stasis will increase VTE risk.

Diagnosis

Clinical features

The clinical features of PE, including pleuritic chest pain, acute onset shortness of breath and haemoptysis are non-specific and very difficult to identify in the sedated, critically ill patient.[25] Increased oxygen requirements, hypocarbia or sudden cardiovascular collapse may be the main clinical manifestations of PE in the mechanically-ventilated patient.[26] Other prominent clinical findings include: small volume arterial pulse, tachycardia, clinical RV failure with raised jugular venous pressure, a gallop rhythm at the left sternal edge and accentuated second heart sound (often difficult to ascertain on ventilated patients).[27]

It is important to consider PE in the following:

- Weaning failure – PE leads to an imbalance between ventilatory needs and cardiorespiratory capacity.[28]
- Persistent pyrexia without evident source of infection – potential causes of PE-related pyrexia include infarction and tissue necrosis, haemorrhage, local vascular irritation or inflammation, and atelectasis.[29,30]

Several scoring systems (eg Wells prediction rule, revised Geneva scoring system) are available to determine PE probability in the non-ICU population. However, none of these

clinical prediction rules have been validated in the ICU population.[31] The poor sensitivity and specificity (85% and 51% respectively) of clinical impression alone highlights the need for additional diagnostic tools when PE is suspected.[32]

Bedside studies

Readily available bedside diagnostic studies include chest X-ray (CXR), electrocardiography (ECG), arterial blood gas (ABG) analysis, late pulmonary dead space fraction (Fd_{late}) and echocardiography.[33]

Chest X-ray

CXR cannot be used to confirm the diagnosis of PE and should only contribute to the diagnostic approach by ruling out conditions that mimic PE in ICU, such as atelectasis, pulmonary oedema, pleural effusions, pneumonia and pneumothorax.[26]

ECG

ECG is usually abnormal in massive PE due to acute RV failure, possibly in combination with hypoxaemia, but findings are neither sensitive nor specific.[26,30,34-36]

Blood gas analysis

In the ventilated ICU patients, acute episodes of hypoxaemia may be due to PE.[25] In patients with massive PE, grossly impaired gas exchange and impaired cardiac output may result in respiratory acidosis and metabolic lactic acidosis (due to tissue hypoperfusion).[27]

Late dead space fraction

A promising but as yet unproven bedside test for acute PE is the Fd_{late}. To calculate this variable, end-tidal carbon dioxide is determined at a point on the volumetric capnogram equal to 15% of the total lung capacity, by extending the regression line of phase III of the volumetric capnogram. This graphic method is used to extrapolate the arterial-alveolar pCO_2 gradient to a virtual late expiration.[37] Data from studies on small numbers of patients suggest that Fd_{late} has high specificity and sensitivity as a diagnostic test for PE.[37,38] Fd_{late} may become a good cost-effective bedside screening tool for PE and could also potentially be used as a tool to monitor the efficacy of thrombolytic therapy. However, inadequate data are present to define the 'normal' Fd_{late} in critically ill, mechanically ventilated patients, or the size of the PE required to elevate the Fd_{late} above the normal value.[37,38] Therefore, adequately powered studies to evaluate the utility of Fd_{late} as a diagnostic tool for PE in the ICU are warranted before it is widely used.

Echocardiography

Echocardiography is a rapid bedside diagnostic tool which may be useful if the use of thrombolytic therapy or embolectomy is being urgently considered.[39] Transthoracic echocardiographic (TTE) findings associated with PE include:

- thrombus within the right-sided heart chambers
- RV dilation with hypokinesis and RV apical motion sparing, especially when RV wall thickness is less than 7 mm
- septal displacement
- RV strain
- acute pulmonary hypertension
- a tricuspid regurgitation velocity greater than 2.7 m/sec by colour Doppler flow imaging.[40]

None of the signs of PE on TTE has been shown to have satisfactory sensitivity although high specificities have been reported. Therefore, a negative TTE cannot rule out PE. It is also important to recognise that the mechanically-ventilated patient may have a number of reasons for RV strain on TTE including concomitant cardiorespiratory disease such as chronic obstructive pulmonary disease, pulmonary hypertension and right-sided myocardial infarction.[39,40] However, in patients with circulatory shock and a high clinical suspicion of PE, the absence of RV strain on TTE practically excludes PE as the cause of cardiovascular instability.[39-43]

Limitations of TTE in the mechanically-ventilated patient with high level of PEEP include:

- inadequate imaging due to the interposition of the inflated lung between the heart and the chest wall,[43]
- low diagnostic accuracy in the presence of pre-existing cardiopulmonary disease (eg cor pulmonale secondary to ARDS)[39-44]
- the operator-dependent nature of TTE.[41]

An alternative diagnostic bedside method for the diagnosis of haemodynamically significant PE is transoesophageal echocardiography (TOE). TOE provides better visualisation of the proximal pulmonary arteries and detection of central PE.[44] Vieillard-Baron *et al*[45] demonstrated that TOE has good sensitivity for detecting emboli located in the main or right pulmonary artery and limited sensitivity for left proximal or lobar PEs.

It has been suggested that in the presence of significant and otherwise unexplained RV strain without clots present on TTE, TOE should rapidly follow at the bedside, if available.[46] The finding of unequivocal thrombus in the pulmonary arteries by TOE has a very high specificity for PE and it is recommended that treatment can be initiated without delay if there is high clinical suspicion.[46] Therefore, TOE can be used as a powerful component of the diagnostic algorithm for PE, providing there is local availability and expertise.

TOE is technically easier in a ventilated patient but may pose an increased risk of traumatic injury to the gastrointestinal tract compared to an awake patient, as the sedated patient cannot assist with probe insertion by swallowing and will not resist when insertion is difficult.[43] In a conscious, critically ill patient with cardiorespiratory compromise, TOE would be technically difficult and could potentially lead to respiratory compromise due to aspiration, laryngospasm and bronchospasm as well as further cardiovascular deterioration due to the vagal and/or sympathetic response to insertion of the probe.[47]

Additional imaging modalities

Ventilation/perfusion scan

V/Q-scanning is impractical in the intensive care setting as it can only be considered when the CXR is normal and there is no concurrent cardiopulmonary disease.[46,48] Very few ICU patients would fulfil these criteria and the logistics of performing a V/Q scan in a ventilated patient make it less appealing than other diagnostic tests.

Spiral computed tomographic pulmonary angiography (CTPA)

CTPA is being used increasingly as a diagnostic tool in PE, with documented sensitivities of 50-100% and specificities of 81-100%.[49] In a multi-centre prospective study, Van Strijen *et al*[50] demonstrated that the sensitivity and specificity of CTPA when looking at PE in segmental and larger arteries only, were 88% and 85% respectively. The sensitivity for subsegmental thrombi was only 26%. Although the clinical significance of subsegmental PE is not very well known, it may have significant clinical impact in critically ill patients with poor cardiorespiratory reserve. In the intensive care context, CTPA is associated with complications of transportation and poses a risk of contrast-induced nephropathy.[51,52] However, in the majority of the patients without PE, CTPA will provide important information and detect alternative cardiopulmonary abnormalities.[53] CTPA can accurately detect RV dysfunction and the severity of PE, which is useful for risk stratification and enables more aggressive therapy in patients with acute PE and no pre-existing cardiopulmonary disease.[54,55]

Pulmonary angiography

It has been suggested that conventional pulmonary angiography (PA) might be necessary to confirm the presence of PE if CTPA is negative and PE is still highly suspected.[56] However, an ancillary prospective investigation of pulmonary embolism diagnosis (PIOPED) II study showed that CTPA is significantly more sensitive than pulmonary angiography in the detection of PE without the potential complications of pulmonary angiography, supporting the shift in the imaging toward CTPA.[57] In addition, angiography is invasive, time-consuming and not always readily available.[46]

Laboratory tests

The usefulness of measures of D-dimer, troponin and B-type natriuretic peptide as diagnostic tests in critically ill patients with clinically suspected PE is limited.[58,59,60]

In summary, in mechanically-ventilated ICU patients with clinically suspected PE, CTPA is the preferred diagnostic imaging modality. In haemodynamically unstable patients whose risks of transportation are high, a bedside diagnostic test, eg echocardiography, would be ideal. If all the tests are negative and PE still highly suspected, ultrasound of the lower limbs may be needed.[61,62] It has been demonstrated that in patients with high clinical suspicion for PE, negative CTPA and negative lower limb ultrasound, the chance of missing a PE could be as high as 7%.[63] Therefore, further testing may be required to evaluate these patients in order to confidently exclude PE or establish an alternative diagnosis. In any given case, the diagnostic approach will depend upon the expertise and availability of the different imaging modalities.

Treatment

The aim of treatment is to correct haemodynamic instability, relieve pulmonary obstruction and prevent clot extension and recurrence. In the ICU patient with suspected or confirmed thrombotic PE, the management should be guided by the estimated risk of poor outcome.[64] The most important predictor of outcome is the patient's cardiovascular status.[64] Normotensive patients with acute PE and normal RV function have a good prognosis with therapeutic anticoagulation alone. Normotensive patients with acute PE and RV dysfunction are at intermediate risk of poor outcomes and early mortality. Patients with massive PE will develop significant haemodynamic instability, cardiogenic shock or cardiac arrest and have the highest morbidity and mortality.[64,65]

Submassive pulmonary embolism without right ventricular strain

In ICU patients with clinically suspected or confirmed PE and no evidence of RV dysfunction (submassive PE without RV strain), therapeutic anticoagulation should be commenced promptly, provided that there are no absolute contraindications to anticoagulation.[65] Bleeding risk assessment prior to anticoagulation is of vital importance. It has been demonstrated that in non-ICU patients with VTE (and no need for thrombolytic therapy or embolectomy), subcutaneous low-molecular-weight heparin (LMWH) appears to be as effective and safe as intravenous unfractionated heparin (UFH).[66,67]

However, critically ill patients may not have a reliable relationship between LMWH doses and anti-thrombotic response due to potentially impaired absorption following subcutaneous administration, decreased clearance secondary to renal impairment, altered drug distribution following fluid resuscitation and use of vasopressors.[68,69] In the ICU setting, where unplanned invasive procedures are very commonly performed, use of LMWH poses a high risk of bleeding complications.[70] Therefore, it must be used with caution and monitoring of anti-factor Xa activity approximately four hours after administration would be advisable.[70] Large, well-designed studies assessing anti-factor Xa activity, dosage and the mode of administration of LMWH to attain adequate anti-thrombotic response in ICU ventilated patients with PE are needed.

Although current guidelines[71] recommend the use of LMWH over UFH for patients with acute non-massive PE, UFH may be a safer treatment option in the ICU with patients at higher risk of haemorrhage, as it has the advantage of immediate discontinuation and rapid reversal if bleeding complications occur (**Table 2**).

Massive pulmonary embolism

Acute massive PE is defined as sustained hypotension (systolic arterial blood pressure <90 mm Hg for at least 15 minutes or requiring inotropic and/or vasopressor support, not due to a cause other than PE) or persistent profound bradycardia (heart rate <40 beats/minute with signs of shock).[73,74] The true incidence of massive PE in ICU patients receiving MV is unknown. The initial response should be to try to correct oxygenation and cardiovascular instability.

Resuscitation of the right ventricle

Mercat *et al*[76] showed that in critically ill medical patients with acute massive PE and acute circulatory failure, defined by low cardiac index (<2.5 L/min/m^2), fluid loading with 500 mL of colloid increased the cardiac index significantly and improved haemodynamic status. Although optimisation of RV preload is

	LMWH	UFH
Route of administration	Subcutaneous	Intravenous
Absorption	May be impaired in ICU patients	Bioavailability 100%
Elimination half-life	3-6 hours	Dose-dependent
Monitoring	Anti-factor Xa activity	Activated partial thromboplastin time (aPTT)
Anticoagulant effect	Protamine reverses <40% of anti-factor Xa activity	Reversed by protamine
Heparin-induced thrombocytopaenia	Rare	4% incidence

Table 2 LMWH *vs* UFH for treatment of PE in the critically ill patient.[66-71]

essential, aggressive fluid resuscitation may worsen RV function.[76] Fluid responsiveness in mechanically-ventilated patients with RV dysfunction should be assessed by dynamic parameters of intravascular fluid volume, derived from pulse contour analysis or echocardiography.[77]

Inotropic/vasopressor support

If fluid resuscitation fails to improve the haemodynamic status of the patient, then inotropic and/or vasopressor support should be considered. There are no human randomised controlled trials (RCTs) comparing vasopressor agents in patients with haemodynamically unstable PE.[76,78] In patients with cardiogenic shock, dobutamine may be of benefit, as it increases myocardial contractility and causes vasodilation.[79] Manier *et al*[80] showed that in patients with massive PE requiring ICU admission, administration of dobutamine increased oxygen delivery and tissue oxygenation without changes in the PaO_2. However, the effect of vasodilation can exceed that of increased myocardial contractility, thereby worsening circulatory failure.

Pulmonary vasodilators

Pulmonary vasodilators have been used in massive PE with acute pulmonary hypertension, as they decrease the pulmonary vascular resistance and pulmonary arterial pressure.[81] In a case series of four mechanically-ventilated patients with acute massive PE, Szold *et al*[82] demonstrated that inhaled nitric oxide improved pulmonary and systemic blood pressure and gas exchange. Inhaled aerosolised prostacyclin has been used in severe pulmonary hypertension secondary to massive PE, resulting in transient improvement in pulmonary haemodynamics and gas exchange.[83]

Ventilation strategy in massive pulmonary embolus

In mechanically ventilated patients with massive PE and RV failure, PEEP should be applied with caution as high levels of PEEP may reduce venous return and worsen RV dysfunction due to an increase in RV afterload.[29] It is also recommended that lung protective ventilation strategy (ARDSnet strategy) is employed to reduce plateau pressures.[81]

Indications	• VTE in patients for whom anticoagulation treatment is contraindicated. • VTE in patients who have a complication of anticoagulation therapy. • Failure of anticoagulation therapy. • Free floating iliofemoral or IVC thrombus. • PE prophylaxis in high-risk patients.
Relative contraindications	• Patients on therapeutic anticoagulants. • Severe sepsis. • Patients with thrombus between the venous access site and the deployment site. • Patients undergoing magnetic resonance imaging after IVC filter placement.
Benefits	• Reduce the risk of recurrent PE. • May be safely placed at the ICU bedside under USS guidance. • Cost-effective.
Complications	• Acute complications: – Insertion site bleeding – Arrhythmias – Pneumothorax/Haemothorax (jugular approach) – PE if passage through a – thrombosed vein – IVC trauma – Filter misplacement • Late complications: – Increased risk of subsequent DVT – Filter migration – Filter embolisation – Filter infection – IVC thrombosis

Table 3 Inferior vena cava (IVC) filters.[68,96,97]

Relieving pulmonary artery obstruction

In view of the high mortality associated with massive PE, immediate pharmacological or mechanical recanalisation of the obstructed pulmonary arteries, is required.[84] The 2008 American College of Chest Physicians' evidence-based clinical practice guidelines recommend short-course thrombolytic therapy in patients with haemodynamically unstable PE, unless there are absolute contraindications owing to bleeding risk (grade 1B).[72,74,83] ICU patients with clinically suspected PE and haemodynamic instability should immediately receive a weight-adjusted bolus of UFH (if there are no contraindications to anticoagulation) until diagnostic bedside tests for the assessment of the RV, eg echocardiography, are performed (grade C).[84,85] If transfer of the patient to the radiology department is not feasible due to significant haemodynamic compromise and imminent cardiac arrest, then thrombolysis may be instituted on clinical grounds alone (grade B).[85] A meta-analysis[86] of 11 RCTs comparing thrombolysis with heparin alone for acute PE demonstrated

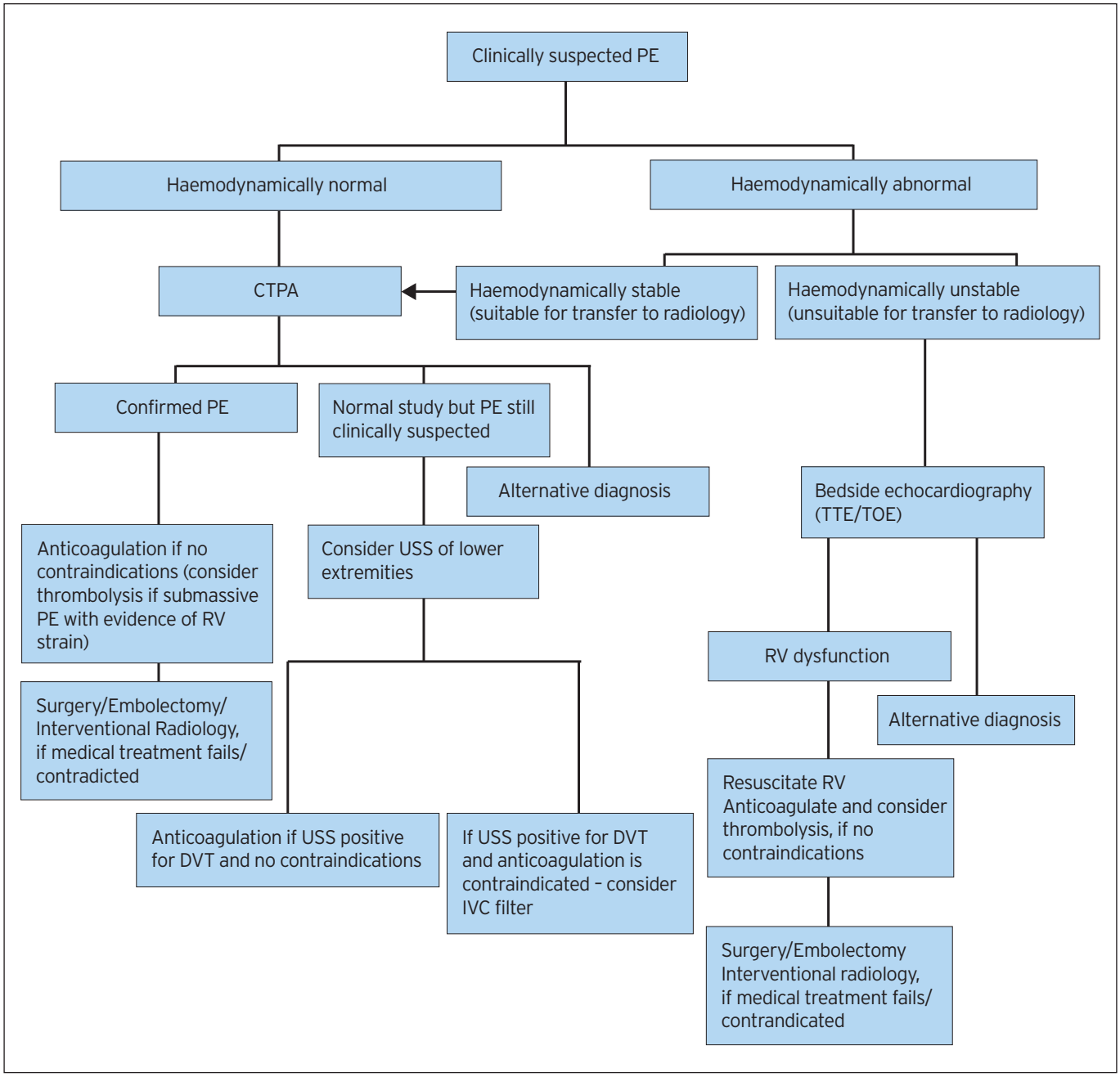

Figure 1 Suggested algorithm for diagnosis and treatment of suspected PE, in the mechanically ventilated critically ill patient. PE indicates pulmonary embolism; CTPA, computed tomographic pulmonary angiography; V/Q scan, ventilation/perfusion scan; TTE, transthoracic echocardiography; TOE, transoesophageal echocardiography; RV, right ventricle; USS, ultrasound scan; DVT, deep venous thrombosis; IVC, inferior vena cava. It is very important to distinguish the haemodynamically stable from the haemodynamically normal patient. A haemodynamically normal patient is one who exhibits no signs of tissue hypoperfusion. In contrast, a haemodynamically stable patient may be persistently tachycardic, tachypnoeic and oliguric, in shock.[95,98]

that thrombolytic therapy was associated with significant reduction in recurrent PE or death in five trials that enrolled patients with massive PE (9.4% *vs* 19.0%; OR 0.45, 95% CI 0.22 to 0.92; number needed to treat=10). Approved thrombolytic regiments for PE include streptokinase, urokinase and recombinant tissue plasminogen activator (rtPA); they seem to be comparable in terms of efficacy.[81] UFH can be given during rtPA administration but it should not be given concurrently with urokinase or streptokinase.[80,84] In the mechanically-ventilated patient the efficacy of thrombolytic therapy can be monitored non-invasively by end-tidal carbon dioxide tension and TTE.[87,88]

There is a paucity of evidence from RCTs for assessing the safety of thrombolytic therapy for PE in the critically ill patient and therefore its use should be individualised and reserved for those who have a low risk of bleeding.

Several studies suggest that catheter embolectomy and fragmentation or surgical embolectomy in expert centres has a role in PE treatment in selected patients with massive PE in whom aggressive medical treatment is contraindicated or has failed.[89-92]

Submassive pulmonary embolism with right ventricular strain

Normotensive patients with acute PE and evidence of RV dysfunction and/or myocardial ischaemia are categorised as having submassive PE with RV strain.[65,93] The largest clinical trial of thrombolysis in submassive PE with RV strain[94] randomised 256 patients to receive rtPA followed by UFH or placebo plus UFH. The study showed that treatment with rtPA when given in conjuction with heparin may improve the clinical course of patients with submassive PE with RV strain and may prevent further clinical or haemodynamic deterioration. In mechanically-ventilated ICU patients with submassive PE and RV dysfunction, resuscitation of the RV and anticoagulation therapy with UFH should be initiated without delay and thrombolysis (if there are no contraindications to anticoagulation) should be considered.

Inferior vena cava filters

To prevent further embolism, if anticoagulation is contra-indicated, an inferior vena cava (IVC) filter may be considered in patients with proximal DVT.[68,74,93,95] The indications, advantages and complications of IVC filters are shown in **Table 3**.

Conclusions

ICU patients receiving mechanical ventilation are at high risk for PE despite thromboprophylaxis. Evaluation of the ventilated critically ill patient and diagnosis of PE can be difficult as the majority of these patients have ongoing physiological derangement, presenting the intensivist with a diagnostic dilemma (**Figure 1**). CTPA is probably the gold standard diagnostic tool if the patient is stable for transfer. Echocardiography is an invaluable non-invasive diagnostic tool in the assessment of the RV at the bedside, which provides a rapid risk stratification and can direct therapeutic strategies.[68] There is a paucity of definitive data regarding the management of PE in the ICU mechanically ventilated patient and therefore some recommendations may rely on lower levels of evidence or expert opinion.[91] Well-designed RCTs are required to estimate the prevalence of PE among critically ill patients receiving mechanical ventilation and evaluate the efficacy and magnitude of clinical benefit of anticoagulation and thrombolytic therapy in the critically ill patient population.

Declaration

The authors declare that they have no conflict of interest and no financial interest in any of the products mentioned in this paper.

References

1. **Hoyt DB, Swegle JR**. Deep venous thrombosis in the surgical intensive care unit. *Surg Clin North Am* 1991;71:811-30.
2. **Ibrahim EH, Iregui M, Prentice D *et al***. Deep vein thrombosis during prolonged mechanical ventilation despite prophylaxis. *Crit Care Med* 2002;30:771-74.
3. **Cook D, Crowther M, Meade M *et al***. Deep venous thrombosis in medical-surgical critically ill patients: prevalence, incidence, and risk. *Crit Care Med* 2005;33:1565-71.
4. **Geerts W, Selby R**. Prevention of venous thromboembolism in the ICU. *Chest* 2003;124:357-63.
5. **Rocha AT, Tapson VF**. Venous thromboembolism in intensive care patients. *Clin Chest Med* 2003;24:103-22.
6. **Saeger W, Genzkow M**. Venous thromboses and pulmonary emboli in post-mortem series: Probable causes by correlations of clinical data and basic diseases. *Pathol Res Pract* 1994;190:394-99.
7. **Kearon C**. Natural history of venous thromboembolism. *Semin Vasc Med* 2001;1:27-37.
8. **Cook D, Meade M, Guyatt G *et al***. Clinically important deep vein thrombosis in the intensive care unit: a survey of intensivists. *Crit Care* 2004;8:145-52.
9. **Williams MT, Aravindan N, Wallace MJ *et al***. Venous thromboembolism in the intensive care unit. *Crit Care Clin* 2003;19:185-207.
10. **Borissoff JI, Spronk HM, Heeneman S *et al***. Is thrombin a key player in the 'coagulation-atherogenesis' maze? *Cardiovasc Res* 2009;82:392-403.
11. **Schultz MJ, Marcel L**. Pulmonary coagulopathy: a potential therapeutic target in different forms of lung injury. *Thorax* 2007;62:563-64.
12. **Haitsma JJ, Schultz MJ, Hofstra JJ *et al***. Ventilator-induced coagulopathy in experimental *Streptococcus pneumoniae* pneumonia. *Eur Respir J* 2008; 32:1599-606.
13. **Tapson VF. Acute Pulmonary Embolism**. *N Engl J Med* 2008;358:1037-52.
14. **Goldhaber SZ, Elliott CG**. Acute pulmonary embolism: part I: epidemiology, pathophysiology, and diagnosis. *Circulation* 2003;108: 2726-29.
15. **Elliott CG**. Pulmonary physiology during pulmonary embolism. *Chest* 1992;101:Suppl:163S-71S.
16. **Manier GY, Castaing Y,Guenard GH**. Determinants of hypoxemia during acute phase of pulmonary embolism in humans. *Am Rev Respir Dis* 1985;132:332-38.
17. **Nakos G, Kitsiouli EI, Lekka ME**. Bronchoalveolar lavage alterations in pulmonary embolism. *Am J Respir Crit Care Med* 1998;158:1504-10.
18. **Shekerdemian L, Bohn D**. Cardiovascular effects of mechanical ventilation. *Arch Dis Child* 1999;80:475-80.
19. **Kitagawa K, Sakoda S**. Mechanism underlying thrombus formation in cerebral infarction. *Rinsho Shinkeigaku* 2009;49:798-800.
20. **Cook D, Attia J, Weaver B *et al***. Venous thromboembolic disease: an observational study in medical-surgical intensive care unit patients. *J Crit Care* 2000;15:127-32.
21. **Attia J, Ray JG, Cook DJ *et al***. Deep vein thrombosis and its prevention in critically ill adults. *Arch Intern Med* 2001;161:1268-79.
22. **Toker S, Hak DJ, Morgan SJ**. Deep vein thrombosis prophylaxis in trauma patients. *Thrombosis* 2011;2011:505373.
23. **Hak DJ**. Prevention of venous thromboembolism in trauma and long bone fractures. *Curr Opin Pulm Med* 2001;7:338-43.
24. **Luce JM**. The cardiovascular effects of mechanical ventilation and positive end-expiratory pressure. *JAMA* 1984;252:807-11.
25. **Merrer J, De Jonghe B, Golliot F *et al***. Complications of femoral and subclavian venous catheterization in critically ill patients: a randomized controlled trial. *JAMA* 2001;286:700-07.
26. **Stein PD, Terrin ML, Hales CA *et al***. Clinical, laboratory, roentgenographic, and electrocardiographic findings in patients with acute pulmonary embolism and no pre-existing cardiac or pulmonary disease. *Chest* 1991;100:598-603.
27. **Miller GA, Sutton GC**. Acute massive pulmonary embolism. Clinical and haemodynamic findings in 23 patients studied by cardiac catheterization and pulmonary arteriography. *Br Heart J* 1970;32:518-23.
28. **Haddad F, Doyle R, Murphy DJ *et al***. Right ventricular function in cardiovascular disease, part II: pathophysiology, clinical importance, and management of right ventricular failure. *Circulation* 2008;117:1717-31.
29. **Vassilakopoulos T, Zakynthinos S, Roussos Ch**. Respiratory muscles and weaning failure. *Eur Respir J* 1996;9:2383-2400.
30. **Marik PE**. Fever in the ICU. *Chest* 2000;117:855-69.
31. **Nucifora G, Badano L, Hysko F *et al***. Pulmonary embolism and fever: when should right-sided infective endocarditis be considered? *Circulation* 2007;115:173-76.
32. **Robert-Ebadi H, Righini M**. Diagnosis of pulmonary embolism. *Rev Mal Respir* 2011;28:790-99.

33. **Lucassen W, Geersing GJ, Erkens PM *et al***. Clinical decision rules for excluding pulmonary embolism: a meta-analysis. *Ann Intern Med* 2011; 155:448-60.
34. **National Institute for Health and Clinical Excellence**. NICE Clinical Guideline 92. *Venous Thromboembolism: Reducing the Risk*. 2010;92:1-50.
35. **Stein PD, Dalen JE, McIntyre KM *et al***. The electrocardiogram in acute pulmonary embolism. *Prog Cardiovasc Dis* 1975;17:247-57.
36. **Ahonen A**. Electrocardiographic changes in massive pulmonary embolism. II. Analysis of the changes in ST segment and T wave. *Acta Med Scand*. 1977;201:543-45.
37. **Anderson JT, Owings JT, Goodnight JE**. Bedside noninvasive detection of acute pulmonary embolism in critically ill surgical patients. *Arch Surg* 1999;134:869-74.
38. **Eriksson L, Wollmer P, Olsson CG *et al***. Diagnosis of pulmonary embolism based upon alveolar dead space analysis. *Chest* 1989;96:357-62.
39. **Goldhaber SZ**. Echocardiography in the management of pulmonary embolism. *Ann Intern Med* 2002;136:691-700.
40. **Miniati M, Monti S, Pratali L *et al***. Value of transthoracic echocardiography in the diagnosis of pulmonary embolism: results of a prospective study in unselected patients. *Am J Med* 2001;110:528-35.
41. **Stawicki SP, Seamon MJ, Meredith DM *et al***. Transthoracic echocardiography for suspected pulmonary embolism in the intensive care unit: unjustly underused or rightfully ignored? *J Clin Ultrasound* 2008;36:291-02.
42. **McConnell, MV, Solomon, SD, Rayan ME *et al***. Regional right ventricular dysfunction detected by echocardiography in acute pulmonary embolism. *Am J Cardiol* 1996;78:469-73.
43. **Beaulieu Y, Marik PE**. Bedside ultrasonography in the ICU: part 1. *Chest* 2005;128:881-95.
44. **Pruszczyk P, Torbicki A, Kuch-Wocial A *et al***. Diagnostic value of transoesophageal echocardiography in suspected haemodynamically significant pulmonary embolism. *Heart* 2001;85:628-34.
45. **Vieillard-Baron A, Qanadli SD, Antakly Y *et al***. Transesophageal echocardiography for the diagnosis of pulmonary embolism with acute cor pulmonale: a comparison with radiological procedures. *Intensive Care Med* 1998;24:429-33.
46. **Riedel M**. Emergency diagnosis of pulmonary embolism. *Heart* 2001;85: 607-09.
47. **Mathur S, Singh P**. Transoesophageal echocardiography related complications. *Indian J Anaesth* 2009;53:567-74.
48. **British Thoracic Society Standards of Care Committee Pulmonary Embolism Guideline Development Group**. British Thoracic Society guidelines for the management of suspected acute pulmonary embolism. *Thorax* 2003;58:470-83.
49. **Rathbun SW, Raskob GE, Whitsett TL**. Sensitivity and specificity of helical computed tomography in the diagnosis of pulmonary embolism: a systematic review. *Ann Intern Med* 2000;132:227-32.
50. **Van Strijen MJ, De Monye W, Kieft GJ *et al***. Accuracy of single-detector spiral CT in the diagnosis of pulmonary embolism: a prospective multicenter cohort study of consecutive patients with abnormal perfusion scintigraphy. *J Thromb Haemost*. 2005;3:17-25.
51. **Szem JW, Hydo LJ, Fischer E *et al***. High-risk intrahospital transport of critically ill patients: safety and outcome of the necessary "road trip." *Crit Care Med* 1995;23:1660-66.
52. **Abdelaziz MM, Wali SO, Hamad M *et al***. Pulmonary embolism: A diagnostic approach. *Ann Thorac Med* 2006;1:31-40.
53. **Kim KI, Müller NL, Mayo JR**. Clinically suspected pulmonary embolism: utility of spiral CT. *Radiology* 1999;210:693-97.
54. **Zhao DJ, Ma DQ, He W *et al***. Cardiovascular parameters to assess the severity of acute pulmonary embolism with computed tomography. *Acta Radiol* 2010;51:413-19.
55. **Lim KE, Chan CY, Chu PH *et al***. Right ventricular dysfunction secondary to acute massive pulmonary embolism detected by helical computed tomography pulmonary angiography. *Clin Imaging* 2005;29:16-21.
56. **Stone E, Roach P, Bernard E *et al***. Use of computed tomography pulmonary angiography in the diagnosis of pulmonary embolism in patients with an intermediate probability ventilation/perfusion scan. *Intern Med J* 2003;33:74-78.
57. **Wittram C, Waltman AC, Shepard JA *et al***. Discordance between CT and angiography in the PIOPED II study. *Radiology* 2007;244:883-89.
58. **Stein PD, Hull RD, Patel KC *et al***. D-dimer for the exclusion of acute venous thrombosis and pulmonary embolism: a systematic review. *Ann Intern Med* 2004;140:589-602.
59. **Lim W, Cook DJ, Griffith LE *et al***. Elevated cardiac troponin levels in critically ill patients: prevalence, incidence, and outcomes. *Am J Crit Care* 2006;15:280-88.
60. **Cepkova M, Kapur V, Ren X *et al***. Clinical significance of elevated B-type natriuretic peptide in patients with acute lung injury with or without right ventricular dilatation: an observational cohort study. *Ann Intensive Care*. 2011;1:18.
61. **Fernandez-Canton G, Lopez Vidaur I *et al***. Diagnostic utility of color Doppler ultrasound in lower limb deep vein thrombosis in patients with clinical suspicion of pulmonary thromboembolism. *Eur J Radiol* 1994;19:50-55.
62. **Stein PD, Woodard PK, Weg JG *et al***. Diagnostic pathways in acute pulmonary embolism: recommendations of the PIOPED II Investigators. *Radiology* 2007;242:15-21.
63. **Gottschalk A, Stein PD, Goodman LR *et al***. Overview of prospective investigation of pulmonary embolism diagnosis II. *Sem Nucl Med* 2002;32:173-82.
64. **Marshall PS, Matthews KS, Siegel MD**. Diagnosis and management of life-threatening pulmonary embolism. *J Intensive Care Med* 2011;26: 275-94.
65. **Piazza G, Goldhaber SZ**. Fibrinolysis for acute pulmonary embolism. *Vasc Med* 2010;15:419-28.
66. **Kearon C, Ginsberg JS, Julian JA *et al***. Comparison of fixed-dose weight-adjusted unfractionated heparin and low-molecular-weight heparin for acute treatment of venous thromboembolism. *JAMA* 2006;296:935-42.
67. **Simonneau G, Sors H, Charbonnier B *et al***. A comparison of low-molecular-weight heparin with unfractionated heparin for acute pulmonary embolism. The THESEE Study Group. Tinzaparine ou Heparine Standard: Evaluations dans l'Embolie Pulmonaire. *N Engl J Med* 1997;337:663-69.
68. **Carlbom DJ, Davidson BL**. Pulmonary embolism in the critically ill. *Chest* 2007;132:313-24.
69. **Clark NP**. Low-molecular-weight heparin use in the obese, elderly, and in renal insufficiency. *Thromb Res* 2008;123:58-61
70. **Dörffler-Melly J, de Jonge E, Pont AC *et al***. Bioavailability of subcutaneous low-molecular-weight heparin to patients on vasopressors. *Lancet* 2002;359:849-50.
71. **Hirsh J, Raschke R**. Heparin and low-molecular-weight heparin: the seventh ACCP conference on antithrombotic and thrombolytic therapy. *Chest* 2004;126:188-203.
72. **Kearon C, Kahn SR, Agnelli G *et al***. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians evidence-based clinical practice guidelines (8th Edition). *Chest* 2008;133:454-545.
73. **Kucher N, Goldhaber SZ**. Management of massive pulmonary embolism. *Circulation* 2005;112:28-32.
74. **Jaff MR, McMurtry MS, Archer SL *et al***. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. *Circulation* 2011;123:1788-830.
75. **Mercat A, Diehl JL, Meyer G *et al***. Hemodynamic effects of fluid loading in acute massive pulmonary embolism. *Crit Care Med* 1999;27:540-44.
76. **Ghignone M, Girling L, Prewitt RM**. Volume expansion versus norepinephrine in treatment of a low cardiac output complicating an acute increase in right ventricular afterload in dogs. *Anesthesiology* 1984; 60:132-35.
77. **Marik PE, Cavallazzi R, Vasu T *et al***. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. *Crit Care Med* 2009;37:2642-47.

78. **Marik PE, Cavallazzi R, Vasu T *et al***. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. *Crit Care Med* 2009;37:2642-47.
79. **Jardin F, Genevray B, Brun-Ney D *et al***. Dobutamine: a hemodynamic evaluation in pulmonary embolism shock. *Crit Care Med* 1985;13:1009-12.
80. **Manier G, Castaing Y**. Influence of cardiac output on oxygen exchange in acute pulmonary embolism. *Am Rev Respir Dis* 1992;145:130-36.
81. **Torbicki A, Perrier A, Konstantinides S *et al***. Guidelines on the diagnosis and management of acute pulmonary embolism: the task force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). *Eur Heart J* 2008;29:2276-315.
82. **Szold O, Khoury W, Biderman P *et al***. Inhaled nitric oxide improves pulmonary functions following massive pulmonary embolism: a report of four patients and review of the literature. *Lung* 2006;184:1-5.
83. **Webb SA, Stott S, van Heerden PV**. The use of inhaled aerosolized prostacyclin (IAP) in the treatment of pulmonary hypertension secondary to pulmonary embolism. *Intensive Care Med* 1996;22:353-55.
84. **Lankeit M, Konstantinides S**. Thrombolysis for pulmonary embolism: Past, present and future. *Thromb Haemost* 2010;103:877-83.
85. **British Thoracic Society Standards of Care Committee Pulmonary Embolism Guideline Development Group**. British Thoracic Society guidelines for the management of suspected acute pulmonary embolism. *Thorax* 2003;58:470-484.
86. **Wan S, Quinlan DJ, Agnelli G *et al***. Thrombolysis compared with heparin for the initial treatment of pulmonary embolism: a meta-analysis of the randomized controlled trials. *Circulation* 2004;110:744-49.
87. **Wiegand UK, Kurowski V, Giannitsis E *et al***. Effectiveness of end-tidal carbon dioxide tension for monitoring thrombolytic therapy in acute pulmonary embolism. *Crit Care Med* 2000;28:3588-92.
88. **Zhu L, Wang C, Yang Y *et al***. Value of transthoracic echocardiography in therapy regimens evaluation in pulmonary embolism. *J Thromb Thrombolysis* 2008;26:251-56.
89. **Aklog, L, Williams, CS, Byrne, JG *et al***. Acute pulmonary embolectomy: a contemporary approach. *Circulation* 2002;105:1416-19.
90. **Yalamanchili, K, Fleisher, AG, Lehrman, SG *et al***. Open pulmonary embolectomy for treatment of major pulmonary embolism. *Ann Thorac Surg* 2004;77:819-23.
91. **Meneveau, N, Seronde, MF, Blonde, MC *et al***. Management of unsuccessful thrombolysis in acute massive pulmonary embolism. Chest 2006;129:1043-50.
92. **Davidson, B, Karmy-Jones, R**. When pulmonary embolism treatment isn't working. *Chest* 2006;129: 839-40.
93. **Piazza G, Goldhaber SZ**. Management of submassive pulmonary embolism. *Circulation* 2010;122:1124-29.
94. **Konstantinides S, Geibel A, Heusel G *et al***. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. *N Engl J Med* 2002;347:1143-50.
95. **Stavropoulos SW**. Inferior vena cava filters. *Tech Vasc Interv Radiol* 2004; 7:91-95.
96. **Streiff MB**. Vena caval filters: a review for intensive care specialists. *J Intensive Care Med* 2003;18:59-79.
97. **Sahni A, Lem V**. Inferior vena cava filters: a concise review. *Hosp Pract* 2011;39:71-78.
98. American College of Surgeons Committee on Trauma. Shock. In: *Advanced Trauma Life Support for Doctors*. Student course manual. 7th edition. Chicago: USA; 2004. p 78.

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