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Management of venous thromboembolism in the intensive care unit

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Abstract Venous thromboembolism, manifested as either deep venous thrombosis or pulmonary embolism (PE), is a major cause of morbidity and mortality in patients admitted to the intensive care unit. Clinically, PE may present as massive thromboembolism associated with cardiogenic shock or may be asymptomatic, as may occur with anatomically small emboli without hemodynamic or respiratory compromise. The management of venous thromboembolism in the critically ill patient can be exceedingly complex. The main treatment objectives are the prevention of recurrent PE and, in case of hemodynamic compromise, definitive therapy for deep venous thrombosis or PE involving removal of thrombus. Prevention of recurrent PE is accomplished with anticoagulation and/or placement of an inferior vena cava filter. Definitive therapy involves thrombolysis and surgical or catheter embolectomy. Fluid and vasoactive therapy with norepinephrine may be indicated for refractory hypotension in patients with massive PE.

1. Introduction

Venous thromboembolism (VTE), manifested as either deep venous thrombosis (DVT) or pulmonary embolism (PE), is a major cause of morbidity and mortality in patients admitted to the intensive care unit (ICU) [1]. The incidence of DVT in ICU patients has ranged from approximately 10% to 100% depending on the specific ICU patient population studied [2-5]. More importantly, unsuspected DVT may be present in patients before ICU admission [6]. Similarly, unsuspected PE may account for acute episodes of hemodynamic instability or hypoxia in many mechanically ventilated patients in the ICU [7] and may also contribute to difficulty weaning from mechanical ventilation [2,5]. In addition, PE is one of the most frequently unsuspected autopsy findings in ICU patients [8]. Finally, patients who survive their first PE remain at risk for long-term complications, including recurrent VTE, post-thrombotic syndrome, and chronic thromboembolic pulmonary hypertension [9].

This brief review focuses on the diagnosis and management of VTE in the critically ill patient with particular emphasis on the treatment of acute PE.

2. Risk factors and diagnostic considerations in the ICU patient with suspected VTE

The major risk factors for VTE in critically ill patients include increasing age (>40 years), serious medical

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illnesses (eg, sepsis, respiratory, or cardiac failure), the presence of central venous catheters, mechanical ventilation, prolonged immobilization, pharmacologic paralysis, recent surgery or trauma, malignancy, and acquired coagulation disorders [1-5]. Almost 75% of upper extremity DVT (subclavian, axillary, or brachial veins) cases are related to direct vascular injuries due to central venous or hemodialysis catheters, pacemakers, or cancer, and the remaining cases are often the result of anatomic predisposition or a hypercoagulable state [10].

The diagnosis of PE may be difficult to confirm in the ICU patient for several reasons [9,11]. First, the typical critically ill patient is unable to complain of the usual symptoms of PE (dyspnea, chest pain, or cough), and physical examination findings are limited except for patients with upper or lower extremity DVT where pain, swelling, warmth, and erythema of the affected limb may be present. Electrocardiographic findings favoring PE may include right bundle-branch block, $S_1Q_3T_3$, and T-wave inversion in leads V_1 through V_4 [9]. Second, the patient may have readily available alternate explanations for hypoxemia, pulmonary infiltrates, respiratory failure, and hemodynamic instability. Third, the patient may be too hemodynamically unstable for transport to the diagnostic imaging suite.

Computed tomography (CT) angiography has largely supplanted both the ventilation-perfusion lung scan and

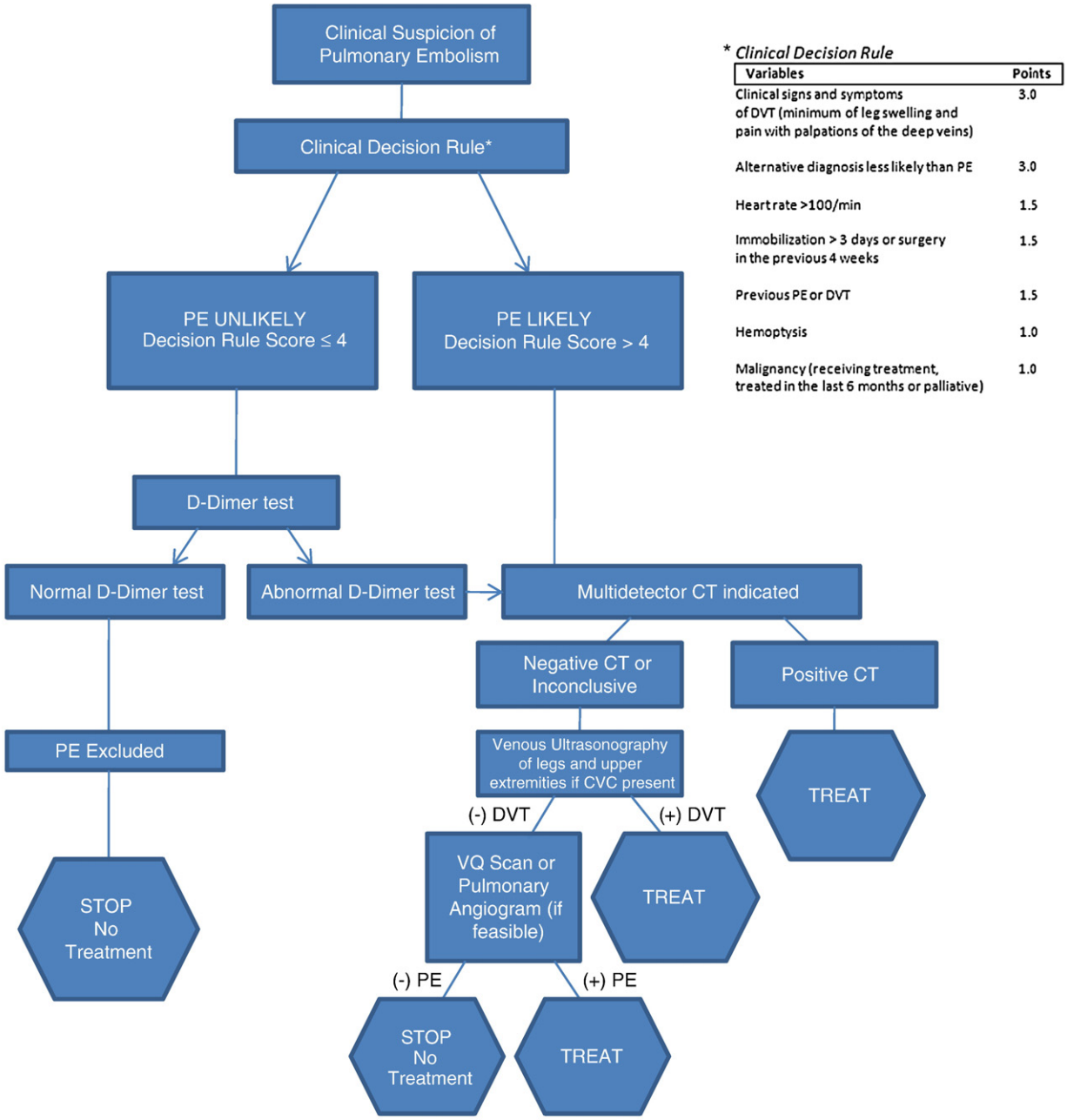

Fig. 1 Diagnostic algorithm for suspected pulmonary embolism.

pulmonary angiography as the diagnostic imaging modality of choice in patients with suspected PE [12]. The recent Prospective Investigation of Pulmonary Embolism Diagnosis II (PIOPED II) trial, which only used multirow detector CT, reported sensitivity and specificity rates of 83% and 96%, respectively [13]. In patients with renal insufficiency, prophylactic hydration with sodium bicarbonate before contrast material exposure is recommended [12]. Ventilation-perfusion scans are generally reserved for patients with major renal dysfunction or anaphylaxis to intravenous contrast [12]. In PIOPED II with the exclusion of patients with intermediate or low probability scans, the sensitivity of a high probability (PE present) scan finding was 77.4%, whereas the specificity of very low probability or normal (PE absent) scan finding was 97.7% [12]. Limited studies of contrast-enhanced magnetic resonance angiography have shown that this modality may also be useful in patients with suspected PE in whom radiographic contrast material or ionizing radiation are relatively contraindicated (eg, renal failure, pregnancy). Lower extremity venous ultrasonography revealing DVT may support a clinical diagnosis of PE when other imaging modalities are nondiagnostic [14]. The sensitivity and specificity of lower extremity (venous ultrasonography) for symptomatic proximal DVT range from 93% to 100% and 97% to 100%, respectively [5,6,12]. Finally, although the measurement of D-dimer levels may help guide the need for diagnostic imaging in patients with low clinical probability for PE or if PE is unlikely, its use is limited by comorbid illness (eg, malignancy), advanced age, and the activation of the coagulation system that commonly occurs during critical illness [12]. A diagnostic algorithm (Fig. 1) with a dichotomized version of the Wells clinical decision rule, D-dimer testing, and CT has been shown to be useful in guiding management decisions in almost 98% of patients with clinically suspected PE [15].

Transthoracic or transesophageal echocardiography may be a useful modality for the diagnosis of PE in the ICU where prompt decision making and appropriate triage of critically ill patients can facilitate early institution of therapy for PE while awaiting patient stabilization and further definitive testing [16]. Echocardiographic findings among patients with PE include right ventricular (RV) dilatation and hypokinesis, paradoxical interventricular septal motion toward the left ventricle, tricuspid regurgitation, and pulmonary hypertension [9,16]. The finding of regional RV dysfunction with severe free wall hypokinesis sparing the apex (McConnell sign) is specific for PE [14]. Moderate or severe RV hypokinesis, pulmonary hypertension, a patent foramen ovale, and free-floating RV thrombus are markers for a high risk of death or recurrent PE. In hemodynamically unstable patients, transthoracic echocardiography can be performed rapidly and may reveal evidence of RV failure suggestive of PE, as well as other conditions including myocardial infarction, aortic dissection, and pericardial tamponade [9,16]. Cardiac biomarkers such as troponins and B-type natriuretic peptide may be elevated particularly in patients with massive PE [16]. Although less useful for diagnosing PE, these biomarkers may assist in identifying myocardial dysfunction and injury in patients with submassive PE (normotensive PE patients) who may benefit from intensive monitoring and additional intervention [16-18]. The combination of either elevated cardiac troponins or N-terminal pro–B-type natriuretic peptide and RV dysfunction on echocardiography has been associated with a higher risk of in-hospital complications or death among patients with PE [19,20]. It is important to note that high ventilation pressures may also affect the diagnostic utility of echocardiography and the cardiac biomarkers in mechanically ventilated patients with suspected PE.

3. Venous thromboembolism management in the ICU

Clinically, PE may present as massive thromboembolism associated with cardiogenic shock or may be asymptomatic, as may occur with anatomically small emboli without hemodynamic or respiratory compromise [16,18].

The management of VTE in the critically ill patient admitted to the ICU can be exceedingly complex. The ICU patient may be acutely ill either due to the underlying disease and the superimposed DVT or PE or critically ill due to massive PE. In addition, several factors may affect management issues in the patient with VTE. First, the presence of multisystem organ failure, especially of the liver and kidney, may complicate decisions on anticoagulant therapy. Second, the typical ICU patient is usually on several medications that may cause side effects (eg, heparin-induced thrombocytopenia) that may be attributed to anticoagulation. Third, the critically ill patient is commonly subjected to invasive procedures (eg, central venous catheterization or chest tube placement) or surgery that may necessitate interruption or complicate anticoagulant treatment.

The main treatment objectives are the prevention of recurrent PE and, in case of hemodynamic compromise, definitive therapy for DVT or PE involving removal of thrombus [9,16-18,21-23]. Prevention of recurrent PE is accomplished with anticoagulation, placement of an inferior vena cava (IVC) filter, and mechanical thromboprophylaxis (graduated compression stockings or intermittent pneumatic compression devices). Definitive therapy involves thrombolysis and surgical or catheter embolectomy. A treatment algorithm for PE is shown in Fig. 2.

3.1. Anticoagulant therapy

Anticoagulation with intravenous unfractionated heparin (UFH) is the cornerstone of therapy for the critically ill patient with acute PE [22,23]. The ideal dosing regimen consists of administering a loading dose of 80 IU/kg bolus of intravenous

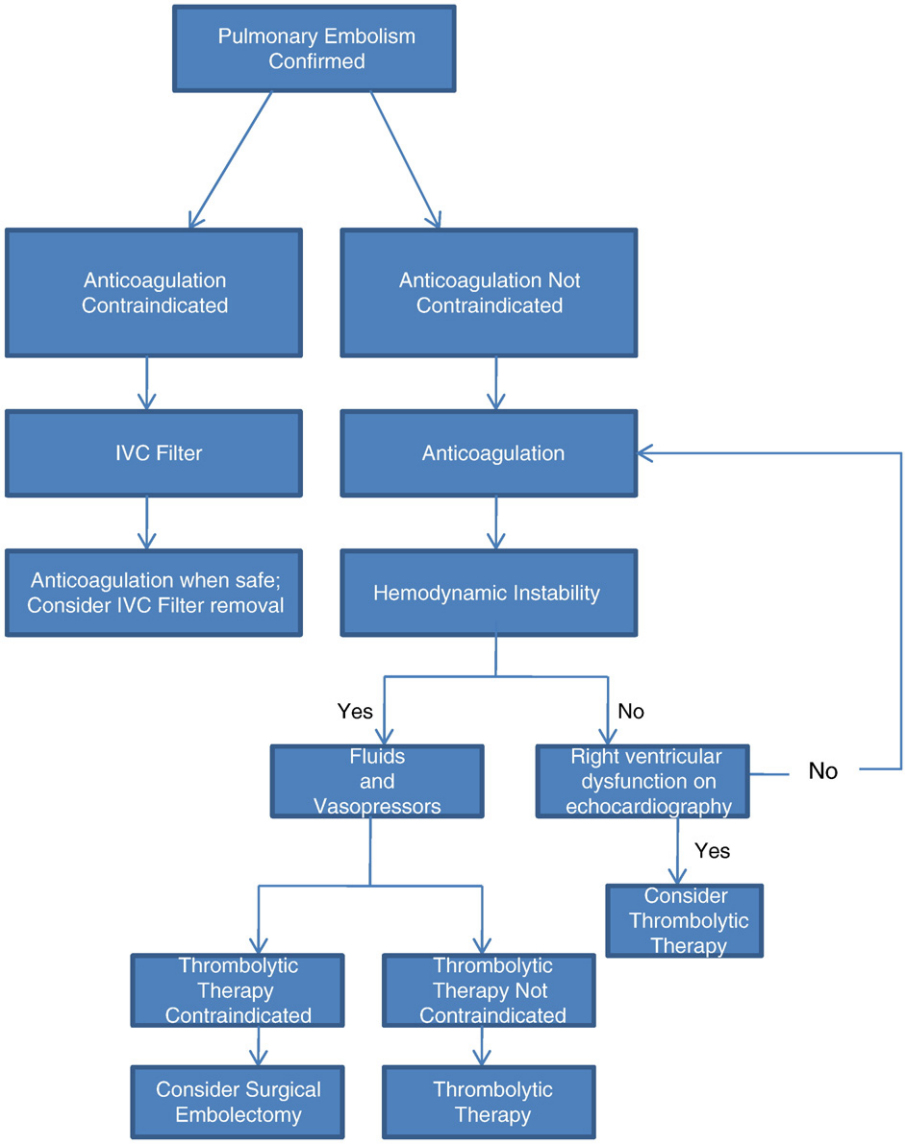

Fig. 2 Treatment algorithm for pulmonary embolism. (Adapted from Tapson VF [17] with the permission of the publisher).

UFH followed by a continuous infusion of 18 IU/kg to maintain a partial thromboplastin time (aPTT) of 1.5 to 2.5 times control values [23]. Early (within 24 hours) therapeutic anticoagulation with heparin has been shown to decrease the risk of recurrent VTE [24]. Limitations of UFH include pharmacokinetic (nonspecific binding to proteins and cells), biophysical (inability to inactivate fibrin-bound thrombin), and biologic (propensity to bind and activate platelets resulting in heparin-induced thrombocytopenia) [23].

The major complications of UFH are hemorrhage and heparin-induced thrombocytopenia with thrombosis. Between 5% and 20% of patients on intravenous heparin develop identifiable hemorrhage or anemia. Bleeding appears to be correlated with higher intensity of anticoagulation. Protamine sulfate is useful for immediate reversal of bleeding in patients receiving UFH and is dosed at 1 mg IV for every 100 IU of UFH administered [23]. Heparin-induced thrombocytopenia (HIT) occurs in up to 5% of patients on heparin and generally develops 5 to 10 days after heparin exposure, although patients who have received heparin within the previous 100 days can also develop HIT within 24 hours after heparin reexposure [23,25,26]. A useful clinical scoring system called the "4T's" based on the characteristic features of HIT (Thrombocytopenia, Timing, Thrombosis, and the absence of oTher explanations) may be useful to estimate the pretest probability of HIT [27]. Heparin must be discontinued in patients who develop HIT, and a nonheparin alternative anticoagulant (eg, lepirudin or argatroban) should be administered [25,26]. Lepirudin is an irreversible direct thrombin inhibitor with a half-life of approximately 80 minutes and is renally excreted. In critically ill patients with renal failure (creatinine clearance [CrCl] <30 mL/min), lepirudin should be avoided. Furthermore, given the

increased bleeding rates observed among patients treated with higher doses of lepirudin, it is recommended that the initial infusion rate be 0.1 mg/kg per hour and the initial intravenous bolus be omitted. In contrast, argatroban is a reversible direct thrombin inhibitor with a half-life of 45 minutes and is metabolized in the liver. In patients with hepatic insufficiency or failure, the half-life of argatroban is prolonged, and these patients will need dose reduction and increased anticoagulant monitoring to avoid bleeding complications [25].

Low-molecular-weight heparins (LMWHs) have several advantages over UFH, including improved bioavailability, more predictable dose response, and lesser incidence of HIT. Currently approved LMWH agents in the United States are enoxaparin, dalteparin, and tinzaparin. However, in ICU patients who are morbidly obese or develop renal failure, dosing of LMWHs may be unpredictable and may lead to serious adverse consequences such as prolonged bleeding [26]. In addition, ICU patients often have significant edema that may impair the absorption of LMWHs administered subcutaneously [28]. Thus, monitoring of anti-Xa levels 4 hours after injection of the LMWH should be considered in these settings. Target therapeutic range for anti-Xa is 0.5 to 1.0 U/mL for patients on twice daily LMWH dosing and 1.0 to 2.0 U/mL for patients dosed once daily [23]. Although LMWHs have been demonstrated to be as effective and safe as UFH in clinical trials of acute PE [29,30], these trials excluded patients with hemodynamically significant PE and patients who developed PE in the ICU. Protamine sulfate is less efficacious in reversing LMWH-related bleeding, and because of the longer half-life of LMWH, a second dose of protamine may be required. The dose is 1 mg protamine per 1 mg of enoxaparin or 100 U of dalteparin or tinzaparin [23]. Fondaparinux, a novel anti–factor Xa inhibitor, has also been recently shown to be as effective and safe as intravenous UFH in hemodynamically stable patients with PE and may also be used in patients with HIT [31]. This agent, however, is limited in its use for ICU patients because of its long half-life (~17 hours) and renal elimination precludes its use in patients with severe renal failure (CrCl <30 mL/min). Danaparoid is another approved agent for thromboprophylaxis and treatment of HIT in Canada, Europe, Japan, and other countries but is not currently available in the United States. Promising new oral direct thrombin inhibitors (eg, dabigatran) and factor Xa inhibitors (idraparinux, rivaroxaban, apixaban) are currently in clinical thromboprophylaxis trials. Table 1 lists the recommended doses of the various anticoagulants that may be used for PE in critically ill patients [16,23].

Table 1 Recommended doses of anticoagulants for PE in the critically ill

Unfractionated heparin: 80 U/kg actual body weight intravenous bolus followed by infusion of 18 U/kg per hour [a]
Enoxaparin: 1 mg/kg SC every 12 h [b]
Dalteparin: 100 IU/kg body weight subcutaneously every 12 h
Tinzaparin: 175 IU/kg body weight subcutaneously once daily
Lepirudin: 0.1 mg/kg per hour IV infusion with the goal of maintaining aPTT 1.5-2.5× above patient's baseline
Argatroban: 0.5-1 μg/kg per minute IV infusion with the goal of maintaining aPTT 1.5 to 3.0× above patient's baseline (not to exceed 100 s)
Fondaparinux: 7.5 mg SC once daily (5.0 and 10 mg in patients weighing <50 or >100 kg, respectively) [c]

[a] Subsequent doses should be adjusted using a standard nomogram to rapidly reach and maintain an aPTT at levels corresponding to therapeutic heparin level (0.3 to 0.7 IU/mL anti–factor Xa activity).

[b] In patients with renal failure, the dose of LMWH should be reduced by half and anti-Xa levels should be monitored.

[c] Contraindicated in patients with renal failure (CrCl <30 mL/min).

Table 2 Major contraindications to thrombolysis

Active internal or intracranial hemorrhage
Uncontrolled hypertension at presentation
Recent major trauma or surgery within the preceding 7 days (6 months for craniocerebral trauma or neurologic surgery)

3.2. Inferior vena cava filters

Inferior vena cava filters are indicated for patients with PE who are at high bleeding risk from anticoagulants and in those patients in whom PE has recurred despite adequate anticoagulation therapy [23]. However, the risk and benefits of insertion of an IVC filter as an adjunct to anticoagulant and thrombolytic therapy in patients with massive PE remain uncertain [23]. Potential long-term complications of IVC filters include recurrent DVT and post-thrombotic syndrome. In high-risk patients with proximal DVT, the initial beneficial effect of IVC filters for the prevention of PE was counterbalanced by an excess of recurrent DVT, without any difference in mortality [32]. Retrievable IVC filters are attractive for patients with transient contraindications to anticoagulation such as trauma recent major surgery. However, to date, there have been no randomized controlled trials comparing the safety and efficacy of retrievable vs conventional IVC filters in patients with VTE.

3.3. Thrombolytic therapy

Thrombolytic therapy is indicated only in hemodynamically unstable (defined as systolic blood pressure <90 mm Hg) patients with PE as these patients have mortality rates ranging from 30% to more than 75% if cardiopulmonary resuscitation is required [16-18,21-23]. Currently used thrombolytic agents include recombinant tissue plasminogen activator (alteplase), streptokinase, and urokinase. Thrombolytic regimens with a short infusion time are favored over those with a prolonged infusion time. For PE, streptokinase is recommended in a 250 000-IU loading dose over 30 minutes followed by 100 000 IU/h for 24 hours. Urokinase is

recommended in a 4400 IU/kg body weight loading dose over 10 minutes followed by 2200 IU/kg for 12 hours. Alteplase is recommended as a 10-mg IV bolus followed by a 90-mg infusion over 2 hours. Of note, intravenous heparin is begun after the infusion of thrombolytic agent is completed and aPTT is less than 2 times the control value [19]. Catheter-directed intrapulmonary arterial thrombolysis may facilitate earlier reperfusion but has not been shown to offer any major advantages over systemic intravenous thrombolysis [23,33].

Although thrombolysis has been associated with more rapid resolution of radiographic and hemodynamic abnormalities than anticoagulant therapy, no mortality benefit has been reported with thrombolytic agents. The use of thrombolytic agents in PE patients with RV dysfunction without hypotension or shock remains controversial. One trial demonstrated reduced need for escalation of treatment (with measures such as mechanical ventilation, vasopressors, or thrombolysis) in PE patients with RV dysfunction without shock who received alteplase plus heparin vs heparin alone, although no mortality benefit was demonstrated [34]. Tenecteplase, a new thrombolytic agent with relatively long half-life enabling bolus administration, is currently being evaluated in an ongoing clinical trial of hemodynamically stable patients with submassive PE. The contraindications to the use of thrombolytic agents are listed in Table 2.

3.4. Catheter or surgical embolectomy

Catheter or surgical embolectomy is indicated only in patients with massive PE who are unable to receive thrombolytic therapy or whose critical status does not allow enough time for infusion of thrombolytic agent [16,23]. Interventional catheterization techniques include transvenous insertion of a catheter followed by mechanical disruption of thrombus, clot pulverization with a rotating basket catheter, percutaneous rheolytic thrombectomy, or pigtail rotational catheter embolectomy [23,35,36]. However, there are no randomized trials that have evaluated interventional catheterization techniques for massive PE. A recent study reported a 1-year survival rate of 86% in 47 patients who underwent emergency surgical embolectomy for massive central PE [37]. Complications of surgical embolectomy include acute respiratory distress syndrome, renal failure, and neurologic sequelae.

3.5. Extracorporeal membrane oxygenation for massive PE

Several case reports and case series have demonstrated the utility of extracorporeal membrane oxygenation (ECMO) in the management of massive PE [38,39]. Maggio et al [39] reported an overall survival rate of 62% in 21 patients with massive PE who received ECMO, all of whom were on vasoactive agents, acidemic, and hypoxic at the time of institution of ECMO.

3.6. Fluid and vasoactive therapy for massive PE

Experimental studies have shown either no benefit or modest deterioration with fluid therapy for massive PE. The risk of excessive fluid administration is RV overload with shift of the interventricular septum and worsening of diastolic interdependence, resulting in decreased cardiac output and increased RV ischemia. Limited studies in humans, however, indicate that fluid loading may augment cardiac output as long as frank RV overload or ischemia is not present [16,40]. Although studies in humans are limited, norepinephrine has been the preferred vasoactive agent for refractory hypotension in patients with massive PE [41]. Dobutamine may be used in combination with norepinephrine to increase myocardial contractility while minimizing vasodilation and the risk of hypotension [42].

3.7. Key messages

- Critically ill patient with VTE mandates additional unique management considerations.
- The goal is to achieve optimal risk-benefit ratio for each individual patient.
- Anticoagulation is appropriate for most patients with VTE.
- Inferior vena cava filter placement should be considered for patients with PE who are at high bleeding risk from anticoagulants and in patients in whom PE has recurred despite adequate anticoagulation therapy.
- Thrombolytic therapy, catheter or surgical embolectomy, and pharmacologic support with vasoactive agents may be indicated in massive PE.

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