Advances in the Diagnosis and Treatment of Acute Pulmonary Embolism

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Abstract

Over the past two decades, considerable progress in technology and clinical research methods have led to advances in the diagnosis, treatment and prevention of acute venous thromboembolism. Despite this, however, the diagnosis is still often missed and preventive methods are often ignored. Published guidelines are useful, but are limited by the existing evidence base so that controversies remain with regard to topics such as duration of anticoagulation, indications for placement and removal of inferior vena caval filters, and when and how to administer thrombolytic therapy. The morbidity and mortality of this disease remain high, particularly when undiagnosed. While preventive approaches remain crucial, the focus of this review is on the diagnostic and therapeutic approach to acute venous thromboembolism, with an emphasis on acute pulmonary embolism.

Introduction

Venous thromboembolism includes the spectrum of deep venous thrombosis and pulmonary embolism. Acute pulmonary embolism is a worldwide problem responsible for 100,000 to 300,000 deaths per year in the United States alone [1-3], and it is commonly not diagnosed or even suspected until after the patient dies [4,5]. There should be a strong clinical suspicion of pulmonary embolism in settings with compatible symptoms (such as dyspnea and chest pain), particularly when risk factors are present. Unfortunately, in patients who die of acute pulmonary embolism, the clinical presentation is often atypical, making the diagnosis more challenging [5]. Therapy should be initiated and diagnostic testing undertaken when the disease is suspected [1,6]. This review will focus on the diagnostic and therapeutic approach to acute pulmonary embolism.

Pathophysiology of acute pulmonary embolism

The vast majority (95%) of acute pulmonary embolism cases originate from thrombi in the leg or pelvic veins, although emboli may arise from other sources such as the

axillary subclavian system or the renal veins [6]. Death from acute pulmonary embolism is caused by right ventricular failure. When thrombosis propagates from the calf veins to the larger more proximal veins, or originates more proximally, the likelihood of embolization, as well as the impact on the lungs, increases. As the embolic burden increases, right ventricular afterload increases and there is right ventricular dilation and hypokinesia associated with the increased pulmonary vascular resistance. When the clot burden reaches a critical threshold, the right ventricle is unable to generate enough force to achieve an adequate cardiac output and fails, resulting in hypotension and cardiac arrest. A crucial issue in acute pulmonary embolism is how to risk-stratify patients; i.e. how we translate the status of the patient, and particularly the right ventricle, into meaningful treatment decisions.

Risk factors and diagnostic approach

Idiopathic venous thromboembolism occurs, but most patients have one or more underlying risk factors arising from Virchow's triad of stasis, venous injury, or

hypercoagulability (thrombophilia), (Table 1) [6,7]. When suspected, patients should undergo diagnostic testing and if there is a high clinical suspicion and low perceived risk of bleeding, therapy should be initiated during the diagnostic evaluation [1,6,8]. The spectrum of pulmonary embolism presentations ranges from asymptomatic/minimal symptoms to massive emboli causing sudden death or progressing rapidly to death from right-heart failure.

Dyspnea and chest pain are the most common symptoms of acute pulmonary embolism; these and other symptoms and signs are nonspecific (Table 2). While pulmonary embolism commonly presents with symptoms of sudden onset, as many as 25% of patients with proven acute pulmonary embolism relate their onset of their symptoms at more than two weeks prior to the time of diagnosis [9]. Contrary to popular teaching, chest wall tenderness can occur in acute pulmonary embolism because of pulmonary infarction [10]. Patients with acute pulmonary embolism may have no symptoms from the emboli; incidental pulmonary embolism is sometimes documented by computed tomographic angiography (CTA) [6]. It is clear that, with improving technology, multidetector CTA is detecting small, often asymptomatic emboli in patients undergoing CTA for another reason. While it is not clear whether all such patients require therapy, the standard approach at present is to treat [1]. Alarming, however, one recent study suggested that cancer patients diagnosed with and treated for incidental pulmonary embolism have the same high rates of recurrent venous thromboembolism, bleeding complications, and mortality, as those who develop symptomatic pulmonary embolism [11].

Ancillary diagnostic testing

Laboratory testing cannot rule pulmonary embolism in with certainty [6,8]. Leukocytosis is much more common with infection than with pulmonary embolism; in one study, among patients with pulmonary embolism in whom other possible or defined causes for leukocytosis were eliminated, 52 of 266 (20%) had a white blood cell count $> 10,000/\text{mm}^3$ [12]. D-dimer testing is a very sensitive measurement of fibrinolytic activity but not specific enough to be diagnostic of pulmonary embolism [13]. The D-dimer assay is best utilized in patients with low or moderate clinical probability, and clinical probability models of D-dimer levels have been designed and validated. Increasing D-dimer levels do appear to correlate with increasing mortality [14]. Serum troponin may be positive in acute pulmonary embolism, indicating right ventricular ischemia / microinfarction [15] and this is discussed further under "Risk stratification" below. Brain natriuretic peptide (BNP) levels may also be elevated in acute pulmonary embolism because of right ventricular dilation [16]. This may serve as a clue to the diagnosis, but again is nonspecific.

Arterial blood gas analysis may demonstrate hypoxemia and hypocapnia (decreased PCO_2) but may also be normal, particularly in younger patients without cardiopulmonary disease [17]. In the setting of a normal or near-normal chest radiograph and significant unexplained hypoxemia, pulmonary embolism should be considered. The electrocardiogram is nonspecific in acute pulmonary embolism [18]. It may be normal, or may demonstrate sinus tachycardia or an atrial arrhythmia. In particular, new-onset atrial flutter should increase suspicion of acute

Table 1. Risk factors for Venous Thromboembolism*

Hereditary factors**	Acquired factors*	Probable factors
Antithrombin deficiency	Reduced mobility	Elevated homocysteine
Protein C deficiency	Advanced age	Elevated factors VIII, IX, XI
Protein S deficiency	Cancer	Elevated fibrinogen
Factor V Leiden	Acute medical illness	Elevated thrombin-activated fibrinolysis inhibitor
Activated protein C resistance without factor V Leiden	Pregnancy and the postpartum period	Low levels of tissue factor pathway inhibitor
Prothrombin gene mutation	Trauma	
Plasminogen deficiency	Spinal cord injury	
Dysfibrinogenemia	Major surgery	
	Oral contraceptives	
	Hormone replacement therapy	
	Polycythemia vera	
	Antiphospholipid antibody syndrome	
	Heparins	
	Chemotherapy	
	Obesity	
	Central venous catheterization	
	Immobilizer or cast	

*In a compatible clinical setting, acute deep venous thrombosis and/or pulmonary embolism should be considered even in the absence of known risk factors.

**It remains unclear whether some of the disorders listed above are hereditary, acquired, or both.

Table 2. Symptoms and Signs in Patients with Acute Pulmonary Embolism Without Preexisting Cardiopulmonary Disease

Symptoms	Patients (%)	Signs	Patients (%)
Dyspnea	73	Tachypnea (respiratory rate ≥ 20 breaths/min)	70
Pleuritic pain	66	Rales/crackles	51
Cough	37	Tachycardia (heart rate > 100 beats/min)	30
Leg swelling	28	Fourth heart sound	24
Leg pain	26	Increased pulmonary component of second sound	23
Hemoptysis	13	DVT	11
Palpitations	10	Diaphoresis	11
Wheezing	9	Temperature $> 38.5^{\circ}\text{C}$	7
Angina-like pain	4	Wheezes	5
		Homans' sign	4
		Right ventricular lift	4
		Pleural friction rub	3
		Third heart sound	3
		Cyanosis	1

DVT, deep venous thrombosis.

Adapted from Stein PD, Terrin ML, Hales CA, et al. [17].

pulmonary embolism [19]. The S1Q3T3 pattern may be present on the electrocardiogram, but again is nonspecific. With extensive emboli, a right ventricular strain pattern may be present, which can also be considered with regard to determining the level of aggressiveness for therapy in proven pulmonary embolism (also see "Risk stratification in acute pulmonary embolism" below).

The chest radiograph is often abnormal in acute pulmonary embolism, but may be normal or minimally abnormal [20]. Pulmonary infarction may be associated with pleural-based wedge-shaped infiltrates (Hampton's hump), which may be mistaken for pneumonia, and reduced lung markings associated with an ipsilateral prominent proximal pulmonary artery (Westermarck sign) may suggest acute pulmonary embolism. Importantly, echocardiography may identify emboli in-transit in the right atrium and may indicate the diagnosis prior to lung imaging, but this is somewhat unusual, so echocardiography is best used in suspected or proven acute pulmonary embolism to assess the impact of acute pulmonary embolism on right ventricular function. "McConnell's sign" (a regional pattern of right ventricular dysfunction, with akinesia of the mid free wall right ventricular free wall but normal apical contractility) can occur in pulmonary embolism, but acute right ventricular infarction may cause a similar appearance [21].

When pulmonary embolism is suspected, the history and risk factors, physical exam, and ancillary studies should be integrated to form a differential diagnosis and determine the need for specific testing for acute pulmonary embolism. Formulation of a pretest probability can facilitate the clinician's approach. This can be done simply by gestalt, relying on the clinician's experience, comfort level with the disease, and knowledge of the pulmonary embolism

literature. However, increasing data support the use of clinical prediction models to guide the diagnostic approach. The most widely studied models include the Wells score [13], the PERC score [22], and the series of Geneva scores [23-25] (Tables 3a-c). While these models have clear utility, a strong clinical suspicion of acute pulmonary embolism should not be ignored solely because a clinical predictive model suggests that it can be.

Diagnostic imaging for suspected pulmonary embolism

In patients presenting with suspected acute pulmonary embolism, CTA has become the standard diagnostic test in the United States. Echocardiography may establish the diagnosis in certain settings, such as when emboli in-transit are visualized in the right atrium.

A normal VQ (ventilation/perfusion) scan rules out pulmonary embolism, and a high probability VQ scan in the setting of suspected pulmonary embolism is essentially diagnostic [26]. However, in the majority of patients with acute pulmonary embolism, VQ scans are not diagnostic [26]. Strong clinical suspicion of pulmonary embolism in the setting of a nondiagnostic VQ scan should lead to another imaging study (CTA, pulmonary angiography, or leg imaging). Ideal candidates with suspected pulmonary embolism to consider for VQ scanning would be younger patients, generally under age 40, without underlying cardiopulmonary disease.

A good quality CTA that is negative for acute pulmonary embolism essentially rules out the diagnosis and specificity is excellent [27]. CTA is also very useful in demonstrating other potential causes of dyspnea and chest pain. In addition, CTA may prove that pulmonary embolism is present when another diagnosis initially appears more

Table 3. Criteria for the Wells, PERC and revised Geneva score

Table	Feature	Points
3a. The Wells Score*	PE is most likely diagnosis	Yes = 3 points
	Symptoms and signs of DVT present	Yes = 3 points
	Heart rate > 100/minute	Yes = 1.5 points
	Immobilization at least 3 days, or surgery in previous 4 weeks	Yes = 1.5 points
	Previous, objectively diagnosed DVT or PE	Yes = 1 point
	Hemoptysis	Yes = 1 point
3b. The PERC Score**	Malignancy with treatment within 6 months	Yes = 1 point
	Age < 50 years	
	Pulse < 100/minute	
	Oxygen saturation > 94%	
	Absence of unilateral leg swelling	
	Absence of Hemoptysis	
	Recent surgery	
	Prior DVT/PE	
3c. Revised Geneva score†	Oral contraceptive use	
	Age > 65 years	1
	Previous DVT or PE	3
	Surgery or fracture within 1 month	2
	Active malignancy	2
	Hemoptysis	2
	Heart rate 75 to 94/minute	3
	Heart rate > 95/minute	5
	Unilateral lower limb pain	3
	Pain on deep palpation of lower limb and unilateral edema	4
	0-3 points low probability for acute pulmonary embolism	(8%)
	4-10 points = intermediate probability	(28%)
	>11 points = high probability	(74%)

*In the validation cohort, a score < 4.0 (PE unlikely) combined with a negative Simpli-Red D-dimer assay (not an ELISA-based assay) accurately excluded a diagnosis of acute PE in 98% of patients. As per the first 3 point item in the score, gestalt is part of the method; it is not entirely objective. Furthermore, it has been suggested that, commonly, this subjective 3 point "PE most likely" is what tips the score in favor of PE [13].

**The PERC rule was designed to rule out acute PE in patients presenting to the emergency room without further testing. The 8 variables are listed above. As a diagnostic test, low suspicion and PERC negative status has been shown to have a sensitivity of 97.4% (CI 95.8% to 98.5%) and specificity of 21.9% (CI 21.0% to 22.9%) [22].

†The Geneva score was originally designed as a somewhat complex clinical prediction rule which required arterial blood gas analysis. It was ultimately revised, only including clinical data. It was more recently simplified. There are similarities to the Wells score and a recent study suggests that the Wells rule may be more accurate among inpatients and patients presenting to the emergency department, while the revised Geneva score can be used in the emergency department with high reliability.

The simplified Geneva score includes the same parameters as the revised score but the score for each parameter is uniformly 1 point, and if heart rate is > 95/minute an additional point was added. It is suggested that the likelihood of patients having PE with a simplified Geneva score < 2 and a normal D-dimer is 3% [23-25]. Abbreviations: PE, pulmonary embolism; DVT, deep vein thrombosis

likely. For example, Tillie-Leblond and colleagues found that there was a 25% prevalence of pulmonary embolism in patients with COPD (chronic obstructive pulmonary disorder) hospitalized for what was felt to be a COPD exacerbation [28]. Multidetector CTA is quite sensitive, but small, subsegmental emboli are still sometimes difficult to visualize. If a study is suboptimal or if there is doubt, additional lung or leg imaging should be considered.

Imaging of the leg veins by computed tomographic venography can be performed to establish the diagnosis of concomitant deep venous thrombosis, or to look for deep venous thrombosis when the chest CTA is negative, but of course this increases radiation exposure for the patient [29]. Recent data suggest that mortality due to acute pulmonary embolism is higher in the setting of residual

deep venous thrombosis, so that evaluating the legs in acute pulmonary embolism may become more common [30].

While pulmonary angiography has been the gold-standard for establishing the diagnosis of acute pulmonary embolism for decades, it is rarely done nowadays [31]. However, an advantage of this technique is the ability to also consider more aggressive catheter-directed techniques in the setting of extensive emboli (see section on treatment below).

Magnetic resonance angiography takes more time to complete than CTA and the diagnostic yield for pulmonary embolism has been shown to be institution dependent [30]. With nephrogenic fibrosing dermopathy in the setting of renal insufficiency, enthusiasm has

waned. MRA is very sensitive for acute deep venous thrombosis. However, ultrasound is simpler, faster, and adequate in the majority of cases of suspected acute deep venous thrombosis. If chest imaging cannot be performed, ultrasound of the legs can be performed. If deep venous thrombosis is ruled in, the need for therapy is established. [6,32].

In summary, the diagnosis of acute pulmonary embolism requires an integrated approach, often involving more than one test and at least one imaging modality. Prediction rules continue to evolve.

Treatment of acute pulmonary embolism

The primary goal of treatment in venous thromboembolism is the prevention of thrombus extension and pulmonary embolism. The therapeutic approach is generally the same for deep venous thrombosis and pulmonary embolism [1].

Initial therapy – anticoagulation

Pulmonary embolism patients with stable hemodynamics appear to have a low death rate when anticoagulated, provided they have no major underlying disease. Thus, such individuals are treated with either low molecular weight heparin or unfractionated heparin [1]. Importantly, anticoagulation should be considered even prior to the diagnosis of pulmonary embolism if the clinical suspicion is high and the risk of bleeding deemed low [1]. The American College of Chest Physicians (ACCP) consensus statement on venous thromboembolism recommends subcutaneous low molecular weight heparin over standard, unfractionated heparin [1]. If unfractionated heparin is used, the bolus and intravenous drip should be weight-based. Table 4 lists advantages of low molecular weight heparin. Once-daily, subcutaneous fondaparinux without monitoring is at least as effective and as safe as intravenous unfractionated heparin in the initial treatment of patients with stable acute pulmonary embolism [33], and has similar advantages over unfractionated heparin as

low molecular weight heparin, though renal insufficiency (creatinine clearance < 30 mL/min) is a contraindication. While long-term therapy is beyond our scope, recommendations on duration of anticoagulation are outlined in the ACCP statement [1].

The development of new oral agents for both initial and long-term treatment is likely to ultimately simplify therapy [34]. Direct factor Xa inhibitors, such as rivaroxaban and apixaban target an upstream protease in the clotting cascade, and represent a promising approach in anticoagulation [35-37]. Rivaroxaban and apixaban have recently been approved (in the USA and the E.U. respectively), both are approved for venous thromboembolism prophylaxis in total hip and knee replacement but not for therapy of established acute venous thromboembolism. The results of the EINSTEIN deep venous thrombosis and EINSTEIN EXT studies indicate that rivaroxaban offers an improved risk-benefit profile for acute deep venous thrombosis and is a promising alternative to enoxaparin or oral warfarin [38], and the latter study is ongoing [39]. Dabigatran is a direct thrombin inhibitor that is approved by the FDA for prevention of stroke and blood clots in patients with nonvalvular atrial fibrillation [40,41]. Clinical trials (RE-COVER, RE-MEDY) suggest a favorable risk-benefit profile for dabigatran for the treatment of established venous thromboembolism [42,43] and additional studies are ongoing [44,45].

Thrombolytic agents

The ACCP currently carries a Grade 1B level of evidence recommendation in support of thrombolytic administration to hemodynamically unstable patients with massive, acute pulmonary embolism in the absence of absolute contraindications [1], and while most clinicians agree, they are often reluctant to pursue this course [46]. A summary of the ACCP recommendations for administration of thrombolytic therapy is outlined in Table 5. Thrombolytic therapy is generally administered by peripheral intravenous

Table 4. Advantages of low molecular weight heparin over standard, unfractionated heparin*

1. Low molecular weight heparin is at least as effective as standard, unfractionated heparin.
2. In certain prophylactic settings, it is more effective than standard, unfractionated heparin**.
3. No intravenous line needed with low molecular weight heparin.[†]
4. More bioavailable than standard, unfractionated heparin; thus, generally no monitoring with low molecular weight heparin.[†]
5. Low molecular weight heparin facilitates outpatient therapy.
6. Better quality of life, fewer nosocomial complications with low molecular weight heparin.
7. Less heparin-induced thrombocytopenia with low molecular weight heparin.

*Disadvantages include the need to dose adjust low molecular weight heparin for renal insufficiency.

**Examples include total hip/knee replacement, acute stroke with hemiplegia, spinal cord injury.

[†]Monitoring anti-Xa levels while on low molecular weight heparin can be considered if renal function is changing, with long-term use in pregnancy, in extremes of body weight, or any time absorption or therapeutic levels are questioned.

Table 5. A Synopsis of Key Thrombolytic Therapy Recommendations from the 8th ACCP Consensus [1]*

1. All pulmonary embolism patients should undergo rapid risk stratification (Grade 1C).[†]
2. With hemodynamic compromise, thrombolytic therapy is recommended, unless there are major contraindications due to bleeding risk (Grade 1B).[‡]
3. In selected high-risk patients without hypotension, and with a low risk of bleeding, administration of thrombolytic therapy is suggested (Grade 2B).
4. In acute pulmonary embolism, when a thrombolytic agent is used, peripheral vein administration rather than direct pulmonary artery infusion is recommended (Grade 1B).
5. In patients with acute pulmonary embolism, we recommend use of thrombolytic regimens with short infusion times (e.g. a 2-h infusion) over those with prolonged infusion times (e.g. a 24-h infusion) (Grade 1B).

*The decision to use thrombolytics depends on the clinician's assessment of PE severity, prognosis, and bleeding risk.

[†]Grade 1 denotes a strong recommendation, and grade 2 a weak recommendation ("suggestion"). Level A would be based upon high-quality randomized trial data, while B indicates moderate-quality evidence, and C low- or very low-quality evidence.

[‡]Unstable hemodynamics is the clearest indication for thrombolytic therapy. It is controversial as to whether hypotension caused by PE, in the absence of the need for pressors, constitutes a clear indication for thrombolysis. The need for pressors mandates strong consideration for thrombolytics.

infusion. A number of intrapulmonary arterial/intraembolic approaches have been evaluated, including intraembolic thrombolytic delivery, suction, rheolytic and rotational devices, and ultrasound-enhanced thrombolysis [47-55]. As with systemic thrombolysis and surgical embolectomy, clinical trial data for percutaneous catheter intervention (with or without thrombolytics) for acute pulmonary embolism are insufficient to formulate strong recommendations. The potential for an aggressive approach with perhaps a lower bleeding risk than systemic thrombolysis makes these approaches attractive. Overall success rates range from 67% to 100% [47] but studies suffer from significant potential reporting bias. At present, local expertise and familiarity with a particular device should guide the clinician when a catheter-based procedure appears indicated.

Risk stratification in acute pulmonary embolism

In recent years there have been many advances in risk stratification of pulmonary embolism to ensure that the appropriate treatment is given.

There has been increasing interest in identifying low-risk patients with pulmonary embolism who could be potential candidates for outpatient treatment or a brief hospital stay. A clinical score for predicting early mortality in patients with pulmonary embolism has recently been described by Aujesky and associates [56]. The score was derived from a large hospital data base and has been prospectively validated in several independent cohorts [56,57]. Higher scores were associated with advanced age, male sex, number of comorbid conditions and certain clinical abnormalities. However, patients with shock were excluded and the study did not risk stratify for more aggressive approaches.

A challenging dilemma lies with the patient who is not hemodynamically compromised per se, but in whom there appears to be a high risk of decompensation. Stable patients with an abnormal right ventricle and normal

blood pressure ("submassive pulmonary embolism") may fall into this category.

In hemodynamically stable patients with right ventricular dysfunction, Konstantinides and associates [58] demonstrated that patients who received tissue plasminogen activator were significantly less likely to deteriorate clinically than those who received placebo (11% versus 25%) although there was no difference in all-cause mortality. However, treating physicians were allowed to break protocol and administer thrombolytics if they believed that a patient was doing poorly, and there was a high rate of rescue thrombolysis. A number of studies offer compelling arguments that right ventricular dysfunction is an important marker for mortality [59,60]. In the ICOPER registry, the in-hospital mortality of patients with right ventricular dysfunction on echocardiography was 18%, although patients with shock were not analyzed separately [61]. The potential mortality benefit of thrombolytic therapy in pulmonary embolism patients with right ventricular dysfunction and preserved systemic arterial blood pressure should be carefully considered, although large randomized trials have not been completed. As noted subsequently, other factors may aid in the decision to proceed with such aggressive approaches.

It would be ideal to explore the impact of various degrees of right ventricular enlargement and dysfunction in pulmonary embolism. It is unlikely that mild right ventricular dysfunction would result in death in a pulmonary embolism patient in the absence of recurrent emboli – more extreme right ventricular dysfunction is more likely to.

While the electrocardiogram has generally been deemed less useful than echocardiography in risk stratification, it may reveal T-wave inversion or a pseudoinfarction pattern (Qr) in the anterior precordial leads. This suggests right ventricular dilation and dysfunction, which can be integrated into risk stratification decisions [62]. Finally, recent data suggest that mortality due to acute pulmonary

embolism is higher in the setting of residual deep venous thrombosis, so that evaluation of the legs as part of the risk stratification protocol in acute pulmonary embolism should be considered [30]. High levels of BNP, pro-BNP, and cardiac troponins (both T and I) have been associated with a greater risk of death in patients with pulmonary embolism [63,64]. A meta-analysis of 1,985 pulmonary embolism patients from 20 studies showed that any elevation in troponin level confers a five-fold increase in short-term mortality [65]. Troponin levels predict outcome not only for pulmonary embolism patients in shock but also for those who are hemodynamically stable at presentation. Again, lack of randomization and differing definitions for significant elevation of biomarkers prevent firm conclusions. Factors to be considered for risk stratification are shown in Table 6. The American Heart Association Scientific Statement published in March 2011 offers an excellent literature review and presents a compelling rationale for risk stratification of acute pulmonary embolism patients [66].

Risk stratification in massive pulmonary embolism

Patients with pulmonary embolism may present with circulatory collapse or respiratory failure; in such extreme settings, risk stratification may simply consist of proof of pulmonary embolism and documentation of significant hypotension. Treatment combines symptomatic interventions to reverse hemodynamic instability and respiratory failure and treatments designed to decrease pulmonary vascular obstruction rapidly [6,27]. Transfer to the intensive care unit should be considered in any pulmonary embolism patient with unstable vital signs, significant hypoxemia, or evidence of unstable hemodynamics. Oxygen and intubation with mechanical ventilation are instituted as clinically indicated and administered based upon oxygen saturation/arterial blood gas assessment; the potential detrimental effects of mechanical ventilation on right heart function must be realized.

The traditional first-line treatment for hypotension is volume expansion. Evidence from animal experiments suggests that, in cases of pulmonary hypertension, this

may increase myocardial oxygen consumption, resulting in right ventricular ischemia and worsening right ventricular function. Nonetheless, fluid loading may improve the hemodynamic status of patients with massive pulmonary embolism [67].

Vasopressor therapy is still used in the setting of massive pulmonary embolism. However, in experimental animal models with massive pulmonary embolism and severe hypotension, the vasopressor isoproterenol did not prove beneficial and may in fact be detrimental [68,69]. In contrast, norepinephrine improved right ventricular function in animal experiments, increasing systemic arterial pressure over a wide range of blood pressure and right ventricular afterloads, suggesting that its effects were not limited to the subset of animals with profound hypotension [70]. This suggests that norepinephrine may be worth considering in patients with massive pulmonary embolism. Evidence relating to the effects of epinephrine in patients with massive pulmonary embolism and shock arises from small case series or single case reports in which patients also received thrombolytic therapy and other vasopressors [71].

Embolectomy and vena caval filter placement

No clear guidelines can be offered for pulmonary embolectomy. It is reasonable to consider it in patients with proven massive pulmonary embolism and hemodynamic instability, particularly when thrombolytic therapy has failed or is contraindicated [1,72,73]. Because these patients are very compromised, the risk of death may be high with this approach. A surgical approach is sometimes considered when there are right heart thrombi, with or without paradoxical embolism, but no data from randomized trials are available; thrombolysis is also commonly considered in such cases.

The primary indications for inferior vena caval filter placement include contraindications to anticoagulation, major bleeding complications during anticoagulation, and recurrent embolism while on therapeutic anticoagulation [1]. Filters are sometimes placed, in the case of massive pulmonary embolism, when it is believed that additional emboli might be lethal, either with or without

Table 6. Factors to consider when risk-stratifying patients with acute pulmonary embolism

1. Vital signs (excessive tachycardia/tachypnea, hypotension – unstable hemodynamics is the clearest indication for thrombolytic therapy).
2. Echocardiography (right ventricle enlargement/hypokinesis).
3. Biomarkers (troponin/brain natriuretic peptide).
4. Oxygenation.
5. Clot burden (lung and legs).
6. Comorbid disease/cardiopulmonary reserve.
7. Bleeding risk.

Table 7. Key points in diagnosis/treatment of pulmonary embolism

1. Therapy for acute pulmonary embolism should be initiated if the clinical suspicion is high and the perceived bleeding risk is low.
2. As anticoagulation is initiated and pulmonary embolism is diagnosed, risk stratification should be considered.
3. Depending on the scenario, more aggressive treatment with thrombolytic therapy or embolectomy can be considered.
4. There is now a large body of evidence from large randomized comparisons that unfractionated heparin, low molecular weight heparin and fondaparinux are all safe and effective approaches to initial anticoagulation.
5. Low molecular weight heparin and fondaparinux are easier to administer, do not require monitoring, and are backed by a substantial evidencebase in the modern era.
6. Documented venous thromboembolism in patients with transient risk factors should be treated for 3 to 6 months, but more extended treatment is appropriate when significant risk factors persist, when venous thromboembolism is idiopathic, or when venous thromboembolism is recurrent.
7. Bleeding risk should also be considered.
8. Inferior vena caval filter placement should be undertaken if anticoagulation is contraindicated due to bleeding.
9. Evidence-based guidelines continue to be refined based upon new clinical trial data. New anticoagulants are on the horizon.

thrombolytic therapy. However, this indication is not based on clinical trial data and more data should be acquired. While filters are effective in reducing the incidence of pulmonary embolism, they have been shown to increase the incidence of deep venous thrombosis and have not been shown to increase overall survival [74]. Retrieval is feasible after many months and removal approximately one year after placement has been reported [75,76] but more data are needed to guide this practice. Recommendations for the use of vena caval filters have recently been published [76].

Conclusions

In summary, acute pulmonary embolism is a potentially fatal disease, and clinicians should be aware of potential risk factors, and the typical and more unusual presentations. Anticoagulation is the standard care for stable patients and should be considered even prior to diagnosis of pulmonary embolism if there is a strong suspicion of pulmonary embolism and the risk of bleeding is deemed low. The presence of unstable hemodynamics is a strong indication for thrombolytic therapy. When anticoagulation is contraindicated, an inferior vena caval filter should be placed. Patients should be risk-stratified and, when appropriate, considered for more aggressive therapy. Given this complexity, risk stratification has become a crucial cornerstone in approaching therapy, but it is still evolving and more data are needed.

Abbreviations

BNP, brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; CTA, computed tomographic angiography; VQ, ventilation/perfusion.

Competing interests

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