Clinical update on pulmonary embolism

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Abstract

Pulmonary embolism (PE) is a major cause of cardiovascular mortality and financial burden that affects the community. The diagnosis of PE can be difficult because of the nonspecific symptoms, which include cough, dyspnea, hemoptysis and pleuritic chest pain. Hereditary and acquired risk factors are associated with PE. Incidence of PE is increasing, associated with the development in the diagnostic methods. Evidence-based algorithms can help clinicians diagnose PE. Serum D-dimer level, computed tomography pulmonary angiogram (CTPA), ventilation-perfusion scintigraphy or echocardiography help to establish clinical probability and the severity of PE. Anticoagulation is the standard treatment for PE. However, thrombolytic treatment is a significant alternative in high risk of PE as it provides rapid clot resolution. This article reviews the risk factors, diagnostic algorithms, and methods of treatment in PE in the light of current information.

Key words: pulmonary embolism, thrombosis, update.

Introduction

Pulmonary embolism (PE) is a common illness which requires early diagnosis and treatment due to its association with high mortality and morbidity rates [1-4]. Significant advances have been achieved in the diagnosis and treatment of PE since venous thromboembolism (VTE) and its triad of contributing factors, including vascular endothelial damage, hypercoagulation and venous stasis, were first defined nearly 150 years ago by Rudolph Virchow, a German pathologist [5]. In this review, we aimed to present the current approach to diagnosis, treatment and follow-up of PE. In addition, we aimed to present data about PE in a single article and minimize differences between medical doctors in clinical practice and applications. This review may also contribute to reduction in PE mortality and health-related costs. We searched electronic databases [PUBMED/MEDLINE (1966–2012), EMBASE and SCOPUS (1965–2012), DARE (1966–2012)] and abstracts from the American Thoracic Society (ATS) and European Respiratory Society (ERS) were searched. The main data search terms were: thromboembolism, lung, clinical update.

Epidemiology

About 90% of clinically evident PE originates in the deep veins of the lower extremities [6]. Venous thromboembolism is a clinical entity which encompasses both pulmonary embolism and deep venous thrombosis (DVT); its prevalence is increased by age due to the presence of accom-

panying disorders. Pulmonary embolism is a cardiopulmonary disease, with an estimated prevalence of 108 per 100 000 in the United States.

Venous thromboembolism has a prevalence of 1/10 000 up until the age of 40, after which the prevalence rapidly increases, reaching around 5-6/1000 by the age of 80 [7]. According to the results of epidemiological studies, acute PE accounts for approximately 100 000 annual deaths in the United States [8] and 10–12% of annual deaths in European hospitals. According to British records, 25 000 hospitalized patients are lost annually due to PE [9, 10]. The prevalence of venous thromboembolism in Caucasians has been reported as 1.43 out of every 1000 individuals [11]. Pulmonary embolism was diagnosed in 7864 patients in Japan in 2006 [12]. Due to the lack of a standardized registry in our country, there are insufficient epidemiological data [13].

Table I. Risk factors for pulmonary embolism

Surgery (in the last 3–6 months)	
Fracture (hip or leg)	Hip or knee replacement
Arthroscopic knee surgery	Laparoscopic surgery (cholecystectomy)
Cancer surgery	Major trauma
Spinal cord injury	Major general surgery
Central venous lines	
Genetic diseases	
Factor V Leiden gene mutation	Prothrombin G20210A mutation
Protein C, S, anti-thrombin III deficiency	Increased factor VIII
Hyperhomocysteinemia	Antiphospholipid antibody syndrome
Anticardiolipin antibody syndrome	Congenital dysfibrinogenemia
Additional diseases	
Previous VTE	Congestive heart failure
Congestive respiratory failure	Myocardial infarction (in the last 1 month)
Malignancy	Nephrotic syndrome
Varicose veins	Paralytic stroke
Primary myelofibrosis	Polycythemia vera
Inflammatory bowel disease	
Others	
Chemotherapy	Obesity
Hormone replacement therapy	Bed rest > 3 days
Pregnancy, postpartum	Immobility due to sitting (more than 4 h)
Increasing age	Cigarette smoking

According to 2005 data from the Turkish Statistical Institute, 9714 patients discharged from hospitals had a diagnosis of PE, but no accurate data exist regarding mortality [14].

Pathophysiology

The results of acute PE symptoms are essentially hemodynamic and become significant when greater than 30–50% of the pulmonary artery bed is obstructed by emboli (pulmonary artery pressure > 30–40 mm Hg). Factors affecting the level of hemodynamic dysfunction include thrombus size, diameter of the affected vessels, embolism type, platelet dysfunctions, neurohumoral substances released from the damaged endothelial and mast cells, and the patient's previous cardiopulmonary reserve. Initially, pulmonary vascular resistance increases suddenly, due to the thrombus settling in the pulmonary vascular bed. The thrombus leads to an increase in pulmonary vascular resistance by narrowing the pulmonary vascular bed and vasospasm, and an imbalance in ventilation/perfusion (V/Q), by reducing pulmonary circulation. Increased pulmonary vascular resistance and elevated pulmonary artery pressure may lead to a reduction in right ventricle dilatation and subsequent decrease in blood outflow volume and systemic hypotension [4].

The expected pathological consequences in the lung tissue, depending on the obstructed vessel, include alveolar dead space respiration, hyperventilation caused by hypoxemia, alveolar hypocapnia, bronchoconstriction, alveolar collapse, and atelectasis due to reduction in surfactant production. Therefore, dynamic compliance is reduced and the alveolar-arterial gradient is increased in the lungs [15].

Risk factors of pulmonary embolism

Pulmonary embolism is thought to occur as a result of an interaction between the risk factors related to the patient and conditions. The risk factors of PE include genetic, additional disease and environmental influences.

Idiopathic PE (20%) is sometimes associated with other cardiovascular events, such as myocardial infarction and stroke [16–18]. In recent studies, it was observed that the number of thromboembolic events has been rising in patients with atrial fibrillation after coronary artery bypass graft surgery [19, 20]. A new anti-arrhythmic drug named dronedarone (SR33589) has been used for atrial fibrillation and in this way the risk of thromboembolism has been decreased [21]. In addition it should not be forgotten that millions of women apply hormonal contraception and this situation may lead to PE [22]. Potential predisposing factors for PE are presented in Table I [23].

Clinical presentation of pulmonary embolism

Pulmonary embolism does not have a specific clinical presentation; presentation may range from incidentally diagnosed PE to shock, arterial hypotension (< 90 mm Hg) and sudden death. The number and location of the obstructed vascular beds, and the patient's cardiopulmonary reserve and age may affect the clinical picture. Dyspnea and tachypnea are the most frequent clinical symptoms. Pleuritic chest pain may occur in cases of pulmonary infarction, often accompanied by hemoptysis and alveolar hemorrhage due to the obstruction of distal pulmonary arteries close to the pleura.

In cases of sudden onset isolated dyspnea, a more central PE with more significant hemodynamic problems should be suspected, rather than pulmonary infarction syndrome. A pain resembling retrosternal angina reflecting right ventricle ischemia may occur. Rarely, PE may be diagnosed based on the absence of any other classical causes of progressive dyspnea. Major findings on physical examination include tachycardia (> 100 beats/min) and tachypnea (> 20 breaths/min). Hypotension and shock may occur. Fever (> 38.5°C), cyanosis, gallop rhythm, DVT-related lower limb swelling, and Homan's sign are other findings. Pulmonary embolism was diagnosed in a case with acquired systolic-diastolic murmur and no symptoms in the literature [24]. For this reason, PE should be considered especially in elder patients with positive physical examination findings in cardiac auscultation. Some systemic diseases such as sarcoidosis may lead to pulmonary hypertension or cor pulmonale together with cardiac involvement [25].

Diagnostic tests for pulmonary embolism

There are no clinical or physical examination findings specific for PE. Pulmonary embolism should be suspected in patients with sudden onset dyspnea, chest pain, and tachycardia. Chest X-ray, electrocardiography (ECG), echocardiography (ECHO), and biochemical tests should be performed even if they are not sufficient for definitive diagnosis.

Chest X-ray

Pulmonary embolism should also be suspected in patients who are found to have hypoxemia through arterial blood gas analysis but have normal chest X-rays and no evidence of airway obstruction. Although there are nonspecific chest X-ray findings associated with PE, chest x-rays are useful in excluding other causes of dyspnea and chest pain.

Subsegmental atelectasis, pleural effusion, pleural-based opacification (Hampton hump), diaphragm elevation, pulmonary artery expansion, sudden blunting of vessels, a prominent right ventricle, a decrease in local vascularization, and/or increased lucency (Westermark sign) may also be observed on chest X-rays.

Electrocardiography and echocardiography

Although ECG changes are not specific to PE, they are associated with right ventricle loading. Electrocardiography findings indicating right ventricle loading may include sinus tachycardia, atrial fibrillation, atrial extrasystoles, T wave inversion in V1-V4 derivations or a QR pattern in a V1 derivation, acute right ventricle dysfunction (classical S1Q3T3 pattern), an S wave deeper than 1.5 mm in DI or aVL derivations, a Q wave in DIII and aVF, voltage reduction in extremity derivations, and an incomplete or complete right bundle branch block. Pulmonary embolism patients often have normal ECGs. Echocardiographic evaluation may be extremely helpful in the assessment of right ventricle functions and response to treatment. The changes, including right ventricle dilatation, paradoxical motion of the septal wall, moderate or severe hypokinesia indicating right ventricle dysfunction, a mobile thrombus within the right ventricle, pulmonary hypertension, a dilated pulmonary artery, inferior vena cava congestion, and the presence of patent foramen ovale, may be observed [16, 26]. A right/left ventricular end-diastolic diameter ratio of ≥ 0.9 on echocardiography has been found to be an independent risk factor for mortality [27]. Echocardiography should be the first evaluation method used on patients admitted to emergency services with shock and suspected PE. Previously, ECHO was found to have a sensitivity of 29-52% and a specificity of 87-96% for diagnosing PE [28].

Findings of computerized tomography pulmonary angiogram

In recent years, computerized tomography pulmonary angiogram (CTPA) has become the preferred diagnostic imaging method for the detection of PE in large and segmental arteries. Computerized tomography pulmonary angiogram has replaced ventilation/perfusion (V/Q) scintigraphy and pulmonary angiography, due to its ability to assess the pulmonary parenchyma and pleural space, as well as to precisely demonstrate the thrombus within the lumen [29, 30]. In the Prospective Investigation of Pulmonary Embolism II (PIOPED II), a multi-center study involving 774 patients, multi-detector CTPA was reported to have a sensitivity of 83% and specificity of 96% [31]. Recent studies have focused on quantifying the thrombus load based on CTPA findings. The computerized tomography severity index has been correlated with blood gas levels and determined to be a good predictor of mortality in patients with PE [32, 33]. Computerized tomography pulmonary

angiogram can be performed on all patients clinically suspected of PE who are able to hold their breath and have no contraindications, such as allergy or renal failure (creatinine clearance < 50 mg/dl) preventing the use of contrast medium. Pulmonary embolism findings that are often noted on CTPA include vascular (intraluminal filling defect), parenchymal (pleural-based wedge-shaped parenchymal consolidation, linear bands, ground-glass, oligemia), and pleural changes (pleural effusion). Computerized tomography pulmonary angiogram has limited value in demonstrating emboli located in subsegmental arteries. According to current guidelines, there is no clear treatment consensus regarding isolated subsegmental emboli. However, subsegmental emboli can be better visualized by pulmonary angiography and their prevalence is around 1-5% [34, 35]. Studies using CTPA have shown that thrombi most commonly occur in the right lower lobe artery [36].

Pulmonary angiography

Today, pulmonary angiography still remains the gold standard for diagnosis of PE by visualizing a filling defect or blunting in a pulmonary arterial branch. Subsegmental arteries of up to 1–2 mm in diameter can be assessed by pulmonary angiography, which is invasive, expensive, not available in every center, and associated with several risks.

Pulmonary angiography should be reserved for cases where noninvasive imaging methods result in equivocal findings.

Magnetic resonance images

Magnetic resonance imaging (MRI) can be used as an alternative to CTPA for patients with renal failure, pregnant women and contraindication to administration of iodinated contrast agents. Magnetic resonance images can be used for confident diagnosis of pulmonary embolism from the main pulmonary artery through the segmental branches of subsegmental pulmonary arteries [37].

Lower extremity ultrasonography

Pulmonary embolism mostly originates in the deep veins of the lower extremities [38]. Positive findings observed during lower extremity ultrasonography in patients suspected of PE facilitate the decision to initiate anticoagulant treatment without further diagnostic evaluation. Although colored Doppler ultrasonography is not the gold standard for diagnosis of DVT, it is commonly used as such. Acquisition of lower extremity sections and visualization of the iliac veins and inferior vena cava, following the acquisition of thoracic sections during CTPA evaluation, increases sensitivity by providing additional information regarding DVT [39].

Ventilation/perfusion scintigraphy (V/Q scintigraphy)

Currently, CTPA undoubtedly plays an increasing role in the diagnosis of PE [40]. Despite being associated with high rates of inconclusive results, V/Q scintigraphy can also be used as a reliable imaging method in centers lacking CTPA, and for patients with high clinical probability of PE but with a contrast medium allergy or renal failure. Anticoagulant treatment can be safely postponed in patients with normal perfusion scintigraphy results [41]. The recent PIOPED II study confirmed the performance of V/Q scintigraphy in diagnosing PE in patients with high probability V/Q scintigraphy results and for excluding PE when diagnosing patients with normal results [42]. Scintigraphic examination should be performed as soon as possible (within 24 h) in cases of PE because a rapid reperfusion occurs in the obstructed vessels due to endogenous thrombolytic activity [6].

Serum D-dimer level

D-dimer, a fibrin degradation product, should be used to exclude PE in patients with low or intermediate probability results. Increased levels of serum D-dimer may be helpful in the diagnosis of PE, but serum D-dimer specificity is rather low since levels can also be elevated in a variety of conditions. The low specificity can be explained given that serum D-dimer level is specific for fibrin, not for PE. The most sensitive methods for measuring serum D-dimer levels are ELISA and the turbidimetric test. Serum D-dimer's specificity for suspected PE is reduced by age and may be decreased to $\leq$ 10% after the age of 80 years [43]. The multicenter Prolong study suggested that serum D-dimer level might be useful in treatment monitorization of patients with definite PE [44].

Cardiac troponins

Cardiac troponins may be elevated when right coronary artery circulation is reduced due to acute right-sided heart failure, and in right ventricle infarction. Several studies have reported that elevated cardiac troponins are associated with poor prognosis for patients with PE [45, 46].

Brain natriuretic peptide

Brain natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP), a right ventricular dysfunction marker, released due to increased myocardial strain, were found to have prognostic significance as indicators of right ventricle dysfunction [47].

Clinical probability in pulmonary embolism

The Wells and Geneva scoring systems are still used together with non-invasive methods to assess

clinical probability [48-50]. Both scoring systems reveal low, intermediate, and high probability PE results. These scores can be used to assess clinical probability for patients suspected of PE in emergency conditions, and a substantial reduction in mortality can be achieved by early diagnosis and treatment initiation in high-risk patients without spending time on imaging methods.

However, it is believed that results from imaging methods should be obtained before initiating treatment in intermediate- and low-risk patients. The low probability category constitutes about 10% of patients, the intermediate probability category about 30%, and the high clinical probability category about 65% [16]. The Wells and Geneva scoring systems are presented in Table II.

Diagnostic strategies

Since one third of emergency unit patients suspected of PE are ultimately diagnosed with PE, diagnostic work-ups should be completed before initiating treatment. Echocardiographic examination should primarily be performed on patients highly suspected of PE who present with shock and hypotension in order to detect acute pulmonary hypertension and right ventricle loading. Emergency thoracic tomography should also be performed if available. Pulmonary embolism diagnosis can be confirmed by echocardiography, and treatment of unstable patients can be initiated immediately when other tests cannot be performed.

Serum D-dimer level should be measured for intermediate- and low-risk patients, and diagnosis should be confirmed by thoracic tomography if levels are elevated. Deep venous thrombosis should be assessed in the presence of subsegmental emboli. There is no consensus regarding treatment initiation in isolated subsegmental PE in the absence of DVT. Echo is not a primary diagnostic tool for hemodynamically stable normotensive patients. Pulmonary embolism can be excluded given low or intermediate V/Q scintigraphy results and the absence, in CDUS (color Doppler ultrasonography) images, of a proximal thrombus in the lower extremities. High probability V/Q scintigraphy confirms PE [16]. The diagnostic algorithm for PE is presented in Figure 1 [12].

Treatment

Untreated PE is an important cause of mortality. The mortality rate for untreated PE is approximately 30%, but the rate is reduced to 2-8% by treatment [51]. Figure 2 shows the treatment algorithm for PE [52].

Initial treatment

Studies have shown that unfractionated heparin (UFH), low molecular weight heparin (LMWH), and fondaparinux can be used for treatment of PE. Although PE and DVT appear to be two different manifestations of the same disease, PE is still mostly treated by hospitalization. Since high-risk PE is associated with an early death rate (inpatient or ini-

Table II. Scoring for Wells, revised Geneva and simplified revised Geneva for pulmonary embolism

Clinical characteristics of Well's score	Score	Clinical characteristics	Revised score of Geneva scores	Simplified score of Geneva scores
Hemoptysis	+1	Age > 65 years	+1	+1
Malignant neoplasm (patient receiving treatment, treated in past 6 months or receiving palliative care)	+1	Active malignant condition (solid or hematologic, currently active or considered cured < 1 year)	+2	+1
Previous pulmonary embolism or deep venous thrombosis	+1.5	Surgery or fracture within 1 month	+2	+1
Heart rate > 100/min	+1.5	Hemoptysis	+2	+1
Recent surgery or immobilization	+1.5	Previous deep vein thrombosis or pulmonary embolism	+3	+1
Clinical signs of deep venous thrombosis	+3	Unilateral lower limb pain	+3	+1
Alternative diagnosis less likely than that of pulmonary embolism	+3	Heart rate 75–94 beats/min	+3	+1
		Pain on lower limb deep venous palpation and unilateral edema	+4	+1
		Heart rate > 95 beats /min	+2	+1
Clinical probability				
Low	< 2	Low	0–3	0-1
Intermediate	2–6	Intermediate	4–10	2–4
High	> 6	High	> 10	≥ 5

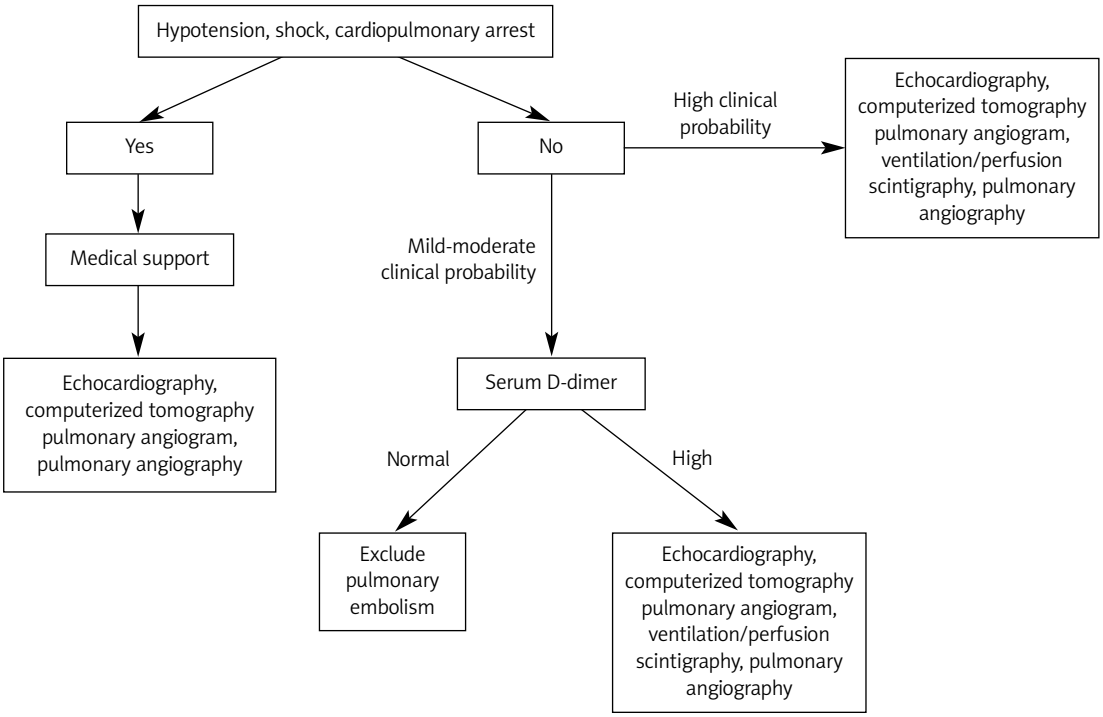

Figure 1. Diagnosis of pulmonary embolism

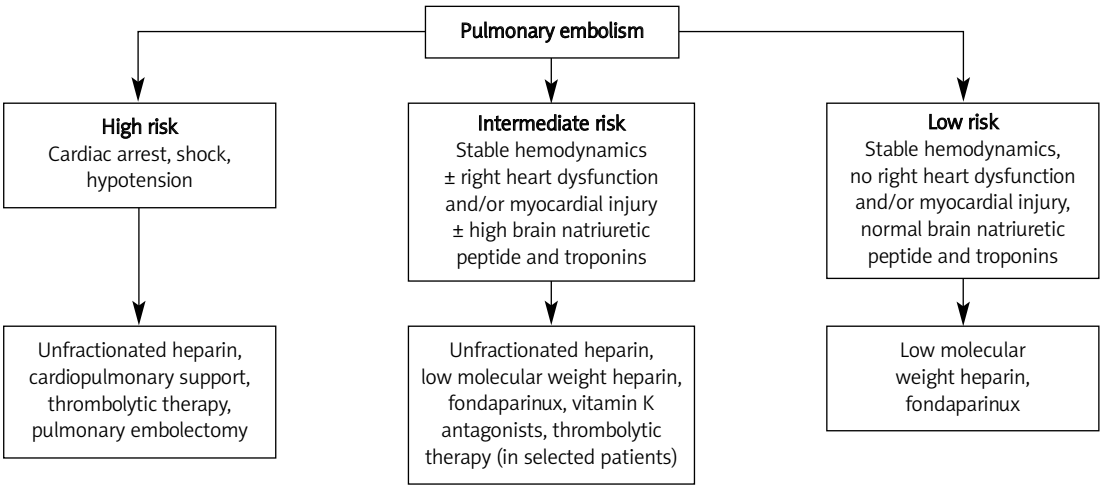

Figure 2. Treatment algorithm of pulmonary embolism

tial 30-day mortality) of > 15%, hospitalization is required.

According to the current guidelines, the mortality rate in the low-risk PE group is < 1%, and hospitalization may not be necessary for all patients in this group [16]. However, due to a lack of consensus, hospitalization is still recommended for treatment initiation.

Primarily, hemodynamic dysfunction should be corrected in high-risk PE patients presenting with shock and hypotension. Oxygen and fluid support should be provided, and UFH should be initiated without delay. Following an initial intravenous dose (40–80 IU/kg or 5000 IU), a continuous infusion should be administered (in 5% dextrose solution at a rate of 14–18 IU/kg/h or 1300 IU/h).

Unfractionated heparin monitorization should be performed to keep the target aPTT of the patient 1.5–2.5 times higher than the baseline aPTT. Hemorrhage, transient benign thrombocytopenia in the first 2–5 days, heparin-related immune thrombocytopenia between 5 and 15 days, hypersensitivity reactions including urticaria, angioedema, anaphylaxis hyperkalemia due to reduction of aldosterone, or osteoporosis after use for 1 month or longer may be observed due to UFH treatment. Unfractionated heparin can be used safely during pregnancy and lactation. In cases of heparin resistance, where the

aPTT remains below the therapeutic level despite a treatment dosage of > 35 000 IU/day, anti-factor Xa activity should be investigated, and LMWH treatment should be administered.

If thrombolytic treatment is considered, UFH can be stopped and streptokinase (loading dose of 250 000 IU in 30 min, and maintenance dose of 100 000 IU/h within 12–24 h, rapid treatment 1.5 million IU/2 h), urokinase (loading dose of 4400 IU/kg in 10 min, and maintenance dose of 4400 IU/kg/h within 12–24 h, rapid treatment 3 million IU/2 h) or recombinant tissue plasminogen activator (100 mg every 2 h) can be administered [53]. Thrombolytic treatment should not be administered to patients who had a tumor or experienced bleeding, hemorrhagic stroke, or ischemic central nervous system injury within the last 6 months. Patients who experienced trauma or underwent a surgical procedure within the last 3 months should be similarly excluded.

Currently, a new generation of thrombolytic agents, such as reteplase and tenecteplase, are also being used in the management of PE [54]. Surgical pulmonary embolectomy is recommended for high-risk PE patients when there is an absolute contraindication for thrombolytic treatment or the treatment is not successful.

Anticoagulation should be initiated immediately for patients in the normotensive intermediate-risk PE group with right ventricle dysfunction and myocardial damage, as well as for patients in the hemodynamically stable low-risk PE group. For this purpose, intravenous UFH (5000 IU in 2–3 doses daily), subcutaneous LMWH (enoxaparin 1.5 mg/kg/day, dalteparin 200 IU/kg/day, nadroparin 3400 IU/day, tinzaparin 175 U/kg/day), or parenteral anticoagulants such as fondaparinux (5–7.5 mg/day) can be administered. Vitamin K antagonists (warfarin, initial dose of 5–10 mg/day) should also be added as oral anticoagulants to the treatment within 24 h. When the target of the international normalized ratio (INR, between 2.0 and 3.0) is achieved for at least 2 consecutive days, treatment should be continued with vitamin K antagonists only. The purpose of long-term anticoagulation is to reduce the risk for recurrent PE. However, there is always a recurrence risk for PE after discontinuation of vitamin K antagonists.

Maintenance treatment

The risk of thrombosis recurrence is especially high in patients in whom the initial venous thrombosis was unprovoked [55]. The recurrence rate of PE is 25% within 5 years [56, 57]. Several high-risk factors exist for recurrent PE, including a previous history of PE, male gender, proven protein S and C deficiencies, factor V and prothrombin G20210A homozygosity, the presence of lupus anticoagulant, ongoing thrombosis in proximal veins, and active cancer. These patients are candidates for treatment of indefinite duration after the first unprovoked PE attack. In patients undergoing secondary prophylaxis the risk of hemorrhage should not be forgotten.

Three months of anticoagulant treatment is sufficient for patients with provoked PE, as long as underlying reversible risk factors, such as surgical intervention, trauma, medical disease, estrogen treatment, and pregnancy are eliminated [16]. Routine use of venous filters in treatment of PE is not suggested, and venous filters should be reserved for patients with absolute contraindications to anticoagulant use or those at high risk for recurrent PE (bilateral or massive DVT, prolonged immobility, chronic heart or renal failure, or active cancer).

Conclusions

Pulmonary embolism continues to be associated with high mortality rates and, therefore, requires prompt diagnosis and treatment. Risk factors should be carefully investigated after the initial PE attack, and management should be planned accordingly. We believe that this review will provide physicians with guidance on best clinical practice.

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