Review Article

Pulmonary Embolism: Pathophysiology, Diagnosis, Treatment

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Pulmonary embolism (PE) is the third greatest cause of mortality from cardiovascular disease, after myocardial infarction and cerebrovascular stroke. From hospital epidemiological data it has been calculated that the incidence of PE in the USA is 1 per 1,000 annually.[1] The real number is likely to be larger, since the condition goes unrecognised in many patients. Mortality due to PE has been estimated to exceed 15% in the first three months after diagnosis.[1]

PE is a dramatic and life-threatening complication of deep venous thrombosis (DVT). For this reason, the prevention, diagnosis and treatment of DVT is of special importance, since symptomatic PE occurs in 30% of those affected. If asymptomatic episodes are also included, it is estimated that 50-60% of DVT patients develop PE.[2] DVT and PE are manifestations of the same entity, namely thromboembolic disease.

If we extrapolate the epidemiological data from the USA to Greece, which has a population of about ten million, 20,000 new cases of thromboembolic disease may be expected annually. Of these patients, PE will occur in 10,000, of which 6,000 will have symptoms and 900 will die during the first trimester.

Pathophysiology of pulmonary embolism

The pathophysiology and clinical manifestations of PE depend upon four main factors: a) the extent of occlusion of the vascular tree and the size of the emboli; b) the patient's pre-existing cardiopulmonary condition; c) chemical vasoconstriction due to the release of serotonin and thromboxane from platelets that adhere to the embolus, as well as to fibropeptide B, which is a product of fibrinogen breakdown; and d) the reflex vasoconstriction that is likely to occur as a consequence of pulmonary artery dilatation.[3,4]

Effect of PE on gas exchange

Arterial CO_2 pressure (PCO_2) depends on CO_2 production (VCO_2) in the organism and on minute alveolar ventilation (V_C), via the equation $PCO_2 = k \cdot VCO_2 / V_C$. The sum of V_C and the minute dead space ventilation gives the minute ventilatory gas volume (V_E).

The obstruction of flow in embolised arteries results in the creation of dead space in the corresponding regions of the lung (Figure 1).[5] An increase in dead space has a direct effect on PCO_2 and on end-tidal CO_2 pressure ($ETCO_2$). If V_E does not change—as is the case in patients in the intensive care unit (ICU) under mechanical ventilatory support and pharmaceutical paralysis, where respiration is fully controlled—PCO_2 will increase (provided that CO_2 production is unchanged). However, most patients (with non-mechanical venti-

latory support) increase V_E, and indeed to a greater extent than is required for CO_2 removal (i.e. increase V_C, too), resulting in hypocapnia. Conversely, in patients with extensive PE or respiratory disorders rapid fatigue of the respiratory muscles may ensue, with an increase in PCO_2 (hypercapnia).

In healthy individuals $ETCO_2$ is approximately equal to PCO_2. However, after PE, since the end-tidal air is a mixture of alveolar gas (where PCO_2 is about equal to alveolar CO_2 pressure—$PaCO_2$) and gas from dead space (where the CO_2 pressure in these alveoli is equal to inhaled air pressure, i.e. zero), $ETCO_2$ decreases to a degree commensurate with the extent of the dead space (Figure 1).[5]

A degree of hypoxaemia, albeit small, is seen in most patients with PE. Thus, 63% of patients have partial O_2 pressure in arterial blood (PO_2) <70 mmHg. The remainder have normal PO_2 as a result of hyperventilation, which may reach double or triple the normal V_E. Four mechanisms have been determined to contribute to PE hypoxaemia:[6-8]

a) Arteriovenous communication is created at the levels of both lungs and heart. In the lungs it appears that new vessels "open", bypassing the capillaries, in an attempt to reduce blood pressure in the pulmonary circulation. In the heart, ateriovenous communication from right to left occurs via a patent *foramen ovale*—which transoesophageal echocardiography has demon-strated in 60-70% of healthy individuals—when right atrial pressure increases as a result of PE.

b) Disturbances of ventilation-perfusion (V/Q disturbances) appear to be the main mechanism of hypoxaemia. The local release of histamine causes bronchospasm, while the release of serotonin causes vasospasm, with the result that there are regions with good perfusion and reduced ventilation (functional shunt) and regions with good ventilation and reduced perfusion. Furthermore, the reduced production of surfactant in the affected regions leads to their atelectasis.

c) The fall in cardiac output that accompanies a significant degree of PE leads to a fall in O_2 saturation in mixed venous blood. This decrease in saturation exacerbates any hypoxaemia due to V/Q disturbances.

d) In extensive PE, and especially when the alveolar-arterial membrane is affected, the reduced O_2 perfusion may contribute to hypoxaemia, since an increased amount of blood is forced to pass through the unaffected sections of the lung and thus does not have time to be oxygenated.

Although gas disturbances are of particular interest in the pathophysiology of PE and can be of significant assistance in its diagnosis, hypoxaemia usually responds easily to the enrichment of ventilated air with O_2. Therefore, the severity of PE arises mainly from its effect on both the pulmonary and the systemic circulation and not on gas exchange. With few exceptions (e.g. certain patients with chronic obstructive lung disease), the morbidity and mortality of PE are due to cardiovascular and not respiratory failure.
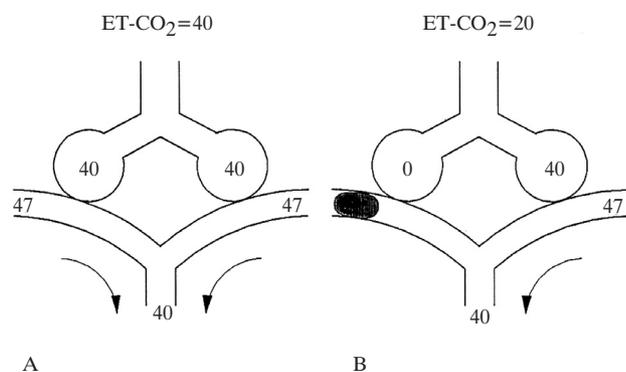
Effect of PE on pulmonary circulation

Emboli impede the pulmonary circulation both mechanically, and through the release of hormonal substances (serotonin), as well as through other mechanisms (e.g. hypoxaemia) related to the vasospasm they cause.[7] This increase in afterload, in combination with the usual tachycardia, increases O_2 consumption by the right ventricle. The right ventricle dilates and thins, its wall stress increases, and coronary perfusion is reduced. At the same time, cardiac output decreases, further exacerbating the hypoxaemia. The increased O_2 demand by the myocardium and the simultaneous reduction in supply place the right ventricle at direct risk of ischaemia, which may lead to cardiac failure (Figure 2).[9] Haemodynamically, there is an increase in right ventricular and right atrial pressure. The right atrial pressure increase may lead to paradoxical embolism in the systemic circulation, via

ET-CO_2=40   ET-CO_2=20

A   B

Figure 1. The increase in dead space and reduction in end-tidal CO_2 ($ETCO_2$) in pulmonary embolism. In A the alveoli and their capillaries have normal ventilation and perfusion, respectively. $ETCO_2$ has a normal value (40 mmHg), which is equal to arterial CO_2 (PCO_2) and alveolar CO_2 ($PaCO_2$). In B we see the effect of obstruction of the blood flow to half the alveoli. The dead space increases, while $ETCO_2$ is reduced to a level proportional to the alveoli that maintain their ventilation but not their perfusion (here one half). The minute ventilatory gas volume (V_E) has been doubled in order to maintain stable PCO_2 (40 mmHg).
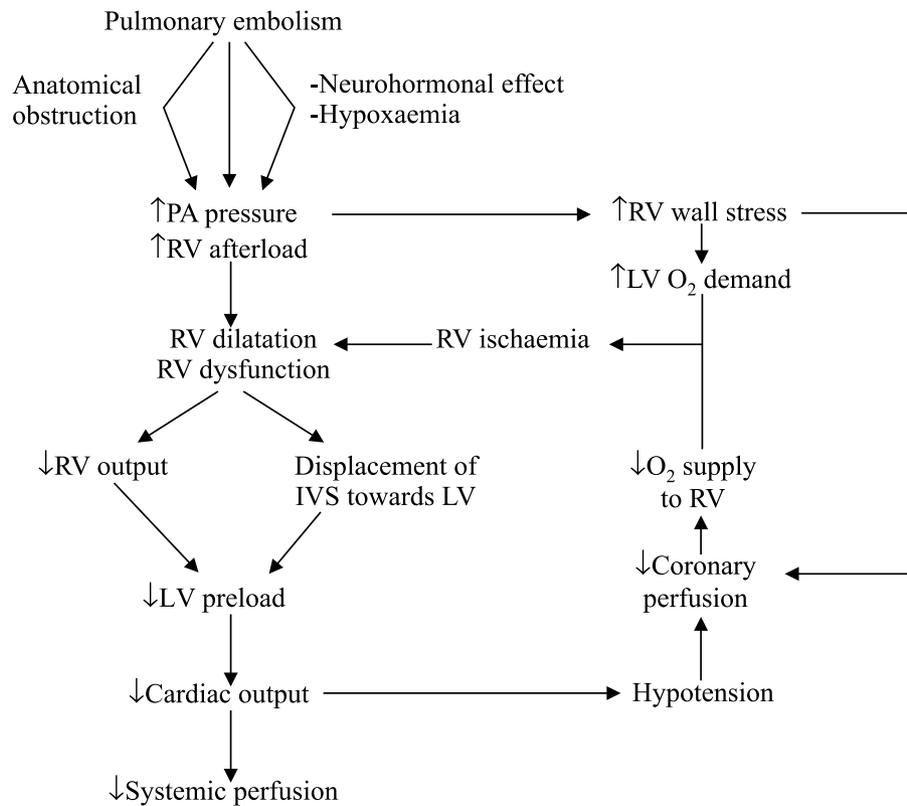
Figure 2. Pathophysiology of the effect of pulmonary embolism on the pulmonary and systemic circulation (modified from reference 9). IVS – interventricular septum; LV – left ventricle; PA – pulmonary artery; RV-right ventricle.

a patent *foramen ovale*. In addition, the increase in pressure and volume in the right ventricle also affects the left ventricle. The displacement of the interventricular septum from right to left changes the characteristics of the left ventricular pressure-volume curve, worsening its distensibility and diastolic filling. The left ventricular preload is therefore reduced, further decreasing cardiac output (Figure 2). The sudden pericardial tension may explain the high values of left ventricular end-diastolic pressure and wedge pressure, while the filling pressure, which reflects preload, is essentially reduced.[10,11]

If the PE is extensive enough for the mean pulmonary pressure to exceed 40 mmHg, the right ventricle will exhibit acute failure. This is the usual cause of death in PE patients.[5] Conversely, PE of small extent is unlikely to affect the patient haemodynamically. This can only happen in patients who already have elevated pulmonary vascular resistances before the occurrence of embolism, because of pre-existing cardiac or pulmonary disease.

Risk factors

The classical triad of risk factors for the occurrence of

thromboembolic disease proposed by Virchow in 1856—local injury to the vascular wall, increased coagulability, and circulatory stasis—can explain most cases of DVT and PE.

Prolonged immobility, advanced age, postoperative period, post-infarction period, heart failure, obesity, pregnancy, and other factors, predispose for thromboembolic disease via venous stasis. Events such as local trauma, vasculitis and previous thrombosis cause damage to the endothelium of the venous wall. Polycythemia, contraceptive pills, as well as malignant cancers, and especially adenocarcinomas, are associated with coagulability disorders and an increased risk of DVT and PE.[12] A more detailed discussion follows.

Travel

The chance of massive PE during an aeroplane flight is very small (0.4 per million passengers). It usually involves flights of distances greater than 5000 km and passengers over 50 years old, cancer victims, with a history of thromboembolism, thrombophilia, or varicose veins.[13]

Obesity

The degree of correlation between obesity and the occurrence of PE depends on the body mass index (BMI). The relative risk of PE has been found to be 1.7 for BMI 25-28.9 kg/m^2 and 3.2 for BMI 29 kg/m^2 and above.[14]

Contraceptives

Third generation contraceptives, which contain newer progesterones, appear to be free of side effects such as acne and piliation. However, they have been implicated in actions related to the coagulation mechanism, such as resistance to activated protein C; there is thus an increased risk of thromboembolism, indeed even greater than for second generation contraceptives.[15] Advanced age and the smoking habit increase the likelihood of complications among contraceptive users.[16] Despite the increased risk of thromboembolism, the chance of a fatal episode of PE remains small.[17]

Pregnancy

During pregnancy, the risk of thromboembolism increases with the week of gestation. It often occurs during the gestation period, but more rarely after delivery. Advanced age and Caesarean section increase the likelihood of thromboembolic disease.[18]

Hormone therapy

An important meta-analysis of 12 studies determined that the relative risk of thromboembolic disease in women under hormone replacement therapy in the post-menopausal period is 2.1, with higher values (3.5) during the first year of treatment.[19] An interesting randomised, placebo-controlled, prospective study found that the risk of PE in post-menopausal women taking a combination of oestrogen and progesterone was about twice that in the control group.[20]

The incidence of PE has also been investigated in relation to the use of raloxifen and tamoxifen for the prevention and treatment of breast cancer. The rate of occurrence of PE in recently published studies was found to be 2.5 to 3 times higher than in control groups.[21,22]

Cancer

The chance of diagnosing a malignancy is increased for around 2 years after an episode of thromboembolic disease; usually, these are cancers of advanced stage with a consequently poor prognosis.[23,24] Especially in patients with idiopathic thromboembolic disease, the existence of cancer is very probable and should therefore be checked for thoroughly.[25]

Trauma/surgery

Local trauma and orthopaedic operations, especially in the region of the pelvis, hips, thighs and knees, cause damage to the venous wall endothelium. It is believed that surgery predisposes to PE, for an interval of more than a month post operation. It has been found that 25% of cases of PE occur 15-30 days after surgery, and 15% after the 30th day. The 18th postoperative day has the highest degree of risk.[26]

Thrombophilia

In one fifth of cases, genetic predisposition is the main cause of PE, although one of the classical risk factors from Virchow's triad may also be present. The doctor should suspect genetic predisposition when there is: a) a strong family history of thromboembolic disease; b) thrombosis in unusual anatomical sites (upper body or upper limbs, when there is no central line catheter); c) repeated thrombosis with no known risk factors; d) thrombosis occurring at a young age; e) resistance to usual anticoagulant therapy.

It has been known for a long time that a lack of protein C, protein S, and antithrombin III is associated with an extremely high risk of thromboembolic disease. However, these genetic abnormalities are only identified in 5% of patients with DVT.[27] In an even smaller percentage of these patients, insufficiency of the fibrinolytic system (hypoplasminogenaemia, abnormal plasminogen, insufficiency of plasminogen-tPA activator) and insufficiency of factor XII may be encountered. Relatively recently, a mutation of factor V has been found (replacement of arginin with glutamin in position 506 on factor V) which is known as factor V Leiden. This hereditary abnormality is encountered in a high proportion of the general population with heterozygous dominant form (3-4%) and is responsible for 20% of cases of DVT.[27] Factor V Leiden increases coagulability, causing resistance to activated protein C.[28,29] Even though by itself factor V Leiden exerts only a mild thrombogenic effect, increasing coagulability by 2-3 times, the knowledge of its existence is extremely important in circumstances

that increase resistance to activated protein C, such as the use of contraceptive tablets or pregnancy. The use of contraceptives in combination with factor V Leiden increases the likelihood of thromboembolic disease by 35 times.[30] In conditions of increased probability of thromboembolic disease—prolonged immobility, postoperative period, etc.—it is essential to intensify preventive treatment in patients who are carriers of this factor.[31,32]

An elevated titre of antiphospholipid antibodies, especially lupus anticoagulant, is found in around 8.5% of cases of DVT, while being practically nonexistent in the general population.[33] It should be noted that a large number of patients with positive lupus anticoagulant do not suffer from systemic lupus erythematosus.

Hyperhomocysteinaemia is usually an acquired abnormality, which increases the risk of thromboembolic disease by 2-3 times and is due to an insufficient intake of vitamins B_1 and B_6.[34]

The investigation of hypercoagulant states in the acute phase of thromboembolic disease must necessarily include checks for: a) *Factor V Leiden*, because it is the most common anomaly responsible—checked using polymerase chain reaction; b) *Hyperhomocysteinaemia*, because it may usually be treated completely and quickly by the administration of vitamins B_1 and B_6; c) *Lupus anticoagulant*, because if it is present it requires intensive and immediate therapy. In the acute phase it is not necessary to check protein C, protein S, or antithrombin III, firstly because they are rarely deficient, and secondly because their levels in the blood decrease in acute thrombosis. In addition, heparin lowers antithrombin III levels, while coumarin anticoagulants reduce the levels of proteins C and S.

Diagnosis

The clinical diagnosis of PE is particularly difficult, since it may easily be confused with other conditions; as a result it is often overlooked (Table 1). Venous thromboembolic disease is often asymptomatic, which adds to the difficulty, while when symptoms of PE are present they tend to be non-specific. Tachycardia, chest pain, cough, unexplained loss of consciousness, and/or haemoptysis, raise the suspicion of PE, while hypoxaemia, haemodynamic instability, syncopal episode and/or cyanosis are characteristic of massive PE.[36-38]

Large series of patients have been studied with a

Table 1. Differential diagnosis of pulmonary embolism.

Pneumonia or bronchitis
Asthma
Exacerbation of chronic obstructive pulmonary disease
Myocardial infarction
Pulmonary oedema
Anxiety-hysteria
Aortic dissection
Lung cancer
Primary pulmonary hypertension
Rib fractures
Pneumothorax
Musculoskeletal pain

view to evaluating the role of clinical signs, findings and symptoms in the diagnosis of PE (Table 2).[36,39]

Pain of pleuritic type is usually associated with peripheral embolism, which causes irritation of the pleura and is associated with pulmonary infiltration on X-ray. Histopathologically, it is associated with alveolar haemorrhage, often with haemoptysis as a symptom.[39,40]

Dyspnoea is mainly associated with central PE, which does not affect the pleura, although the haemodynamic consequences are more serious. It is the most common symptom, while tachypnoea (>20 breaths/minute) is the most frequent sign of acute PE (70-80% of patients with angiographically proven PE exhibit dyspnoea).[36]

On clinical examination tachycardia is usually seen, while there may be signs of right heart failure, such as dilation of the jugulars with a V wave, left parasternal cardiac pulsion, greatly increased pulmonary element of the second heart sound, and a systolic murmur, low left parasternally, increasing during inspiration on auscultation, probably with a third sound in the same region. These symptoms, of course, are often masked by tachypnoea, obesity, pithoid chest, etc.[35]

In arterial blood gases, the coexistence of hypoxaemia and hypocapnia help in the diagnosis of PE. However, these signs are not specific, since PO_2 and PCO_2 may be normal, especially in young people with no prior disease. In addition, PCO_2 may be elevated in patients with massive PE. $ETCO_2$ is always reduced, but lacks specificity.[4-6,38]

The presence or absence of risk factors for venous thromboembolic disease is an essential piece of knowledge for the evaluation of the likelihood of PE. We should be aware that the risk of PE increases with the number of risk factors present, and that PE does

Table 2. Symptoms, clinical signs, and common laboratory findings in suspected pulmonary embolism (PE) in the intensive care unit.[37,40]

	PE (n=219)	No PE (n=546)
Symptoms:		
Dyspnoea	80%	59%
Pleuritic pain	52%	3%
Retrosternal pain	12%	8%
Cough	20%	25%
Haemoptysis	11%	7%
Syncopal episode	19%	11%
Clinical signs:		
Tachypnoea (>20/min)	70%	68%
Tachycardia (>100/min)	26%	23%
Signs of DVT	15%	10%
Fever (>38.5°C)	7%	17%
Cyanosis	11%	9%
Radiological findings:		
Atelectasis	49%	45%
Pleuritic effusion	46%	33%
Peripheral opacification (infarct)	23%	10%
Raised hemidiaphragm	36%	25%
Reduced pulmonary vascularisation	36%	6%
Blood gases:		
Hypoxaemia	75%	81%
Electrocardiogram:		
Right ventricular hypertrophy	50%	12%

DVT – deep venous thrombosis

not usually occur in the absence of any risk factors.[41] Isolated clinical signs and symptoms are not useful, since they have neither good sensitivity nor satisfactory specificity (Table 2). For this reason, Wells et al[42] proposed a prognostic rule (pretest probability) incorporating 7 weighted variables for the diagnosis of PE: existence of clinical signs and symptoms of thromboembolic disease (3 points), absence of alternative diagnosis (3 points), heart rate above 100 (1.5 points), immobility or surgery during the previous 4 weeks (1.5 points), previous thromboembolic disease or PE, (1.5 points), haemoptysis (1 point), and malignancy (1 point). A total score less than 2 means low probability, 2-6 points medium probability, while a score of over 6 points suggests a high probability of PE.

Although the electrocardiogram and chest X-ray are of limited value, often being normal in patients with PE, they should nevertheless be taken into account.[35] The most common electrocardiographic find-ings are tachycardia and T-wave inversion in the precordial leads.[43] A right axis deviation of the form S_I-Q_{III}-T_{III}, first appearance of incomplete or complete right bundle branch block, as well as pulmonary P-waves or atrial fibrillation occur more rarely (<12% for each).[44]

The chest X-ray is mainly of help in ruling out other conditions (e.g. pneumothorax, pulmonary oedema, pneumonia) that have clear radiological findings, and is of less use in the diagnosis of PE. The radiological signs of PE are non-specific (mild pleural effusion, raised diaphragm, atelectasis), or especially difficult to evaluate (protruding pulmonary artery—Knuckle sign, diaphragm-based truncated cone—Hampton's hump sign, local oligaemia—Westermark sign, dilatation of the right superior pulmonary artery—Palla sign). In 25% of cases of PE the chest X-ray is normal. In fact, this is of great assistance, because the coexistence of severe dyspnoea, with a ventilation-perfusion lung scan of even intermediate probability, is practically diagnostic for PE.[4,8,45]

The white cell count is usually normal or slightly elevated and is not of help in diagnosis. Also, the classical triad of increased lactate dehydrogenase (LDH), increased bilirubin, in combination with normal levels of transaminases, is seen in only 4% of cases, while the combination of high LDH levels with normal SGOT is found in only 20%. Goldhaber et al[46] found bilirubin >2.0 mg/dl and LDH >400 M/L each in 20% of cases. The only haematological examination that helps in the diagnosis of PE is the measurement of D-dimers with the ELISA method. Although this method is very sensitive (>90%) it is non-specific, since elevated levels of D-dimers are found in many disease conditions that are clinically similar to PE, such as myocardial infarction, pneumonia, heart failure, cancer, post-surgery, trauma, etc. In view of this, the most important contribution of D-dimers is in ruling out PE when their levels are normal (high negative predictive value).[47,48]

The role of cardiac biological indexes as prognostic indexes of PE has already attracted great interest. Elevated troponin levels are associated with high mortality,[49] as are high levels of pro-brain natriuretic peptide (pro-BNP), in contrast to low concentrations of pro-BNP, which as a rule are associated with a good clinical outcome.[50-52]

Perfusion lung scanning is a basic non-invasive examination for the diagnosis of PE. It is based on the embolisation of colloidal radioactive tracer particles in regions of the lung that maintain their perfusion.

Thus, the normal regions opacify, while the regions that have undergone PE do not.[46,53] Despite initial enthusiasm, this examination has not managed to replace angiography, since its specificity is not satisfactory in the diagnosis of PE. Every cause of reduced perfusion in a region of the lung, such as hypoxic vasospasm, or the presence of a West I zone, causes a perfusion defect indistinguishable from those of PE. False positive perfusion scans are seen in patients suffering from asthma, chronic obstructive pulmonary disease, atelectasis, pneumonia, hypovolemia, etc., as well as in patients who are on mechanical ventilation with positive end-expiratory pressure.[3] In contrast to the pathological scan (which is non-specific), a normal scan is particularly useful, essentially ruling out PE, since perfusion scintigraphy has high sensitivity.[46] The specificity of the perfusion scan increases when it can be combined with a ventilation scan. The pulmonary embolus shows a perfusion defect that is not associated with a ventilation defect, or if one exists, the ventilation defect is small. Conversely, a perfusion defect that is due to hypoxic vasospasm is usually of smaller size than the corresponding ventilation defect.[4,46,53]

For ease of evaluation, ventilation-perfusion (V/Q) scanning is classified as high probability, intermediate probability and normal. In order to be classified as high probability for PE, a V/Q scan must have two or more pulmonary regional perfusion defects, with no or very small changes in the ventilation scan and on the chest X-ray. A high probability V/Q scan has 85% specificity in the diagnosis of PE, while for the intermediate probability scan the specificity is low. Unfortunately, however, high probability scans have low sensitivity. In the PIOPED study it was found that only 41% of patients with angiographically proven PE had a high probability V/Q scan.[53] This means that most patients with PE have an intermediate probability or a normal scan. Thus, the V/Q scan is considered particularly useful: a) when it is found to be normal, almost ruling out PE (especially when combined with negative D-dimers), and b) when it is classified as high probability, in which case full treatment is recommended, without the need for angiography. Of course, the presence of another positive examination, or a high clinical suspicion of PE, reinforce the diagnostic conclusion. In the case of an intermediate probability scan further investigation is considered essential.[54]

Spiral computed tomography (CT) of the lung, with intravenous infusion of radiopaque medium, has been widely used in recent years for the diagnosis of PE. Until recently, it had good sensitivity and specificity in the identification of emboli in the large pulmonary arteries (80% and 90%, respectively), but it was less successful in the peripheral vascular tree—beyond the third level of branching in the pulmonary circulation.[55] The new, multi-slice tomographic devices seem to be a great improvement in this respect. In a recent multi-centre study that used multi-slice CT, the sensitivity and specificity were substantially better (83% and 96%, respectively). Furthermore, if CT was combined with imaging of the venous phase, the sensitivity increased significantly (90%) with no reduction in specificity. The positive prognostic value was evaluated as >90% if there was clinical suspicion of PE (96% with high clinical suspicion, 92% with intermediate clinical suspicion).[56] A combination of multi-slice CT and negative D-dimers essentially ruled out PE.[57]

Magnetic resonance pulmonary angiography with gadolinium may prove to be particularly safe and useful in the future,[58] since apart from anatomical characteristics it provides information about right ventricular wall motion.[59]

Transthoracic echocardiography is considered useful in the diagnosis of pressure overload in the right chambers. Thus, it is of particular use in identifying patients with a large PE, in whom the pressure of the pulmonary circulation is elevated (90% sensitivity).[60] In these patients we can see dilatation of the right ventricle and hypokinesis of its free wall, while at the same time the shape of the left ventricle changes, because of the displacement and flattening of the interventricular septum, adopting a D shape on its short axis during both systole and diastole.[61] A characteristic sign is the maintenance of mobility of the apical region of the right ventricle—McConnell sign[62]—in contrast to the hypokinesis of the entire free wall that is observed in chronic pulmonary hypertension.[63] Measurement of systolic pulmonary pressure is feasible in 80-90% of cases with significant PE, via the accompanying tricuspid regurgitation, while diastolic pressure may be measured if there is also pulmonary valve insufficiency (Doppler measurements).[63] However, in a recently published prospective study[64] the echocardiogram was normal and failed to confirm the diagnosis in 50% of patients with angiographically determined PE. The transoesophageal echocardiogram, a bedside examination, is considered especially useful in ICU patients with haemodynamic instability where moving

them away from the unit in order to perform CT, MRI, etc., is difficult. Apart from the aforementioned findings, transoesophageal echocardiography can reveal the existence of thrombus in the main trunk or the pulmonary arteries in 80% of cases with massive PE (Figure 3).[65,66]

Pulmonary angiography continues to be the gold standard in the diagnosis of PE, and should be performed when other examinations have failed to solve the problem. If the patient's condition permits, it should be performed during the first week after the start of episodes of PE, since after this period spontaneous revascularisation has been observed in a large number of cases. Angiography is quite a safe examination, with mortality as low as 0.2%.[67] Mortality increases in patients who have a severe degree of pulmonary hypertension (systolic pulmonary pressure >70 mmHg and right ventricular end-diastolic pressure >20 mmHg), but even in such cases it does not exceed 2%.[68]

Lower limb ultrasound, provided it includes compression ultrasonography, is the examination of choice in patients with symptoms of DVT,[69] having a sensitivity and specificity of 73% and 90-100%, respectively.[70,71] Both impedance plethysmography and phlebography (despite still being considered a gold standard) are beginning to become marginalised.[72] Ultrasonography is precise when it is performed in symptomatic patients with a suspicion of DVT, but its sensitivity is much lower when there are no signs of phlebothrombosis.[73] This seems to be because its sensitivity is high in the evaluation of thigh veins, but not in the smaller, branching veins of the shins and the non-compressible veins of the pelvis.[74,75] In these cases magnetic resonance angiography has given good results, while promising even more in the future.[76]

For the successful evaluation of patients in whom PE is suspected, clinical signs and symptoms should be combined with diagnostic laboratory examinations. Thus, for example, patients with a high probability V/Q scan or a positive spiral CT should be treated for PE. For patients with a pathological V/Q scan—not high probability—even with a negative spiral CT examination, there is the likelihood of PE. In such cases compression ultrasonography should be performed. If it is positive, treatment ensues, while if the results are negative the chance of disease is extremely limited. Clinical studies have determined that in suspected PE the combination of negative spiral CT with negative compression ultrasonography safely rules out the disease.[77-79] For patients with a non-high probability V/Q scan and negative spiral CT the disease may be ruled out when the pretest probability[42] is low, or D-dimers are negative. In the remaining patients angiography should be performed, or they should be followed for at least one week with compression ultrasonography, especially if the pretest probability is high. Apart from directing the choice of the most appropriate examination at each stage of diagnosis, diagnostic algorithms can also help to rule out PE early, thus avoiding unnecessary laboratory examinations. Various algorithms have been proposed, depending mainly on the diagnostic methods available and the experience in each centre. In figure 4 a diagnostic algorithm is proposed that could be adopted by most centres.

Figure 3. Transoesophageal echocardiogram, showing a large thrombus in the right main pulmonary artery (RPA) that confirms the diagnosis of massive pulmonary embolism. (From reference 66, reproduced with permission.)

Treatment

The cornerstone of therapy for PE is the prevention of new embolic episodes with anticoagulant treatment or a filter in the inferior *vena cava*, since it has been found that the majority of patients do not die from the embolism that leads to diagnosis, but to the continuing deterioration of their condition due to new emboli.[80-82] However, when the patient is in shock, or the haemodynamic condition is particularly poor, it is necessary to attempt primary lysis of the thrombus/embolus using thrombolysis or some invasive embolectomy technique.

Supportive therapy

The patients often present with hypoxaemia, which

PE suspected

Assess pretest probability[42]

High or moderate probability

Low probability

Scanning V/Q

D-dimers

Low probability

High probability

Non diagnostic

<500 μg/L

≥500 μg/L

Ultrasonography (CUS)

Treatment

Angiography*

PE exclusion

Ultrasonography (CUS)

Positive

Negative

Positive

Negative

Negative

Positive

Treatment

3 months follow up

Treatment

PE exclusion

Spiral CT

Treatment
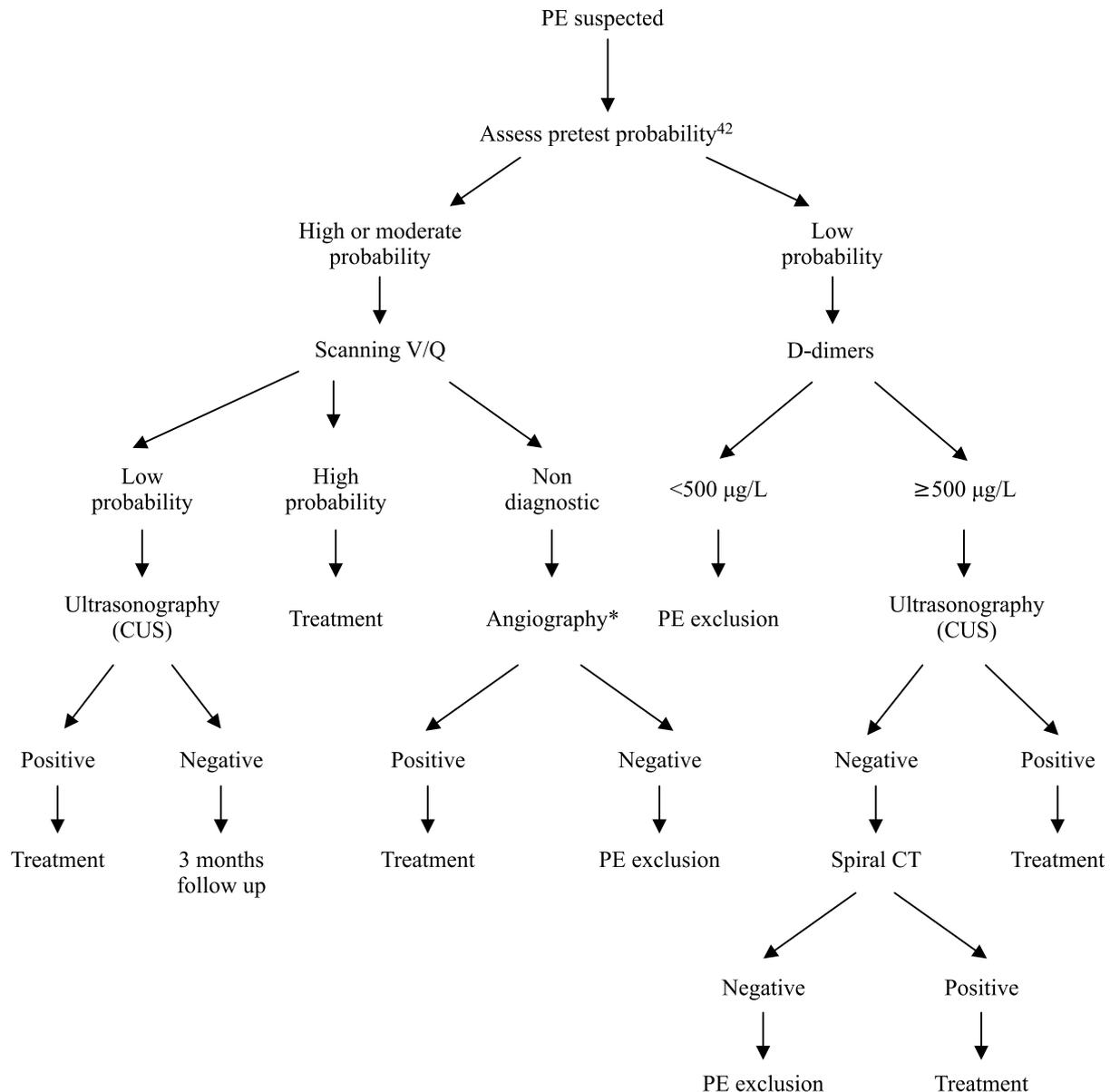
Negative

Positive

PE exclusion

Treatment

Figure 4. Diagnostic algorithm when there is suspicion of pulmonary embolism (PE).
*Alternatively, according to the capabilities of the diagnostic centre, spiral computed tomography (CT) could be performed, or repeated compression ultrasonography (CUS) of the lower limbs, on the 1st, 3rd, 7th and 14th day.

responds to O_2 administration, since the main pathophysiological mechanism is V/Q disturbances. Bed rest appears to help via two mechanisms. First, the restriction of movement reduces the likelihood of thrombus detachment from its peripheral location; second, it reduces O_2 consumption (VO_2) and therefore the need for increased cardiac output. In extreme cases of patients in shock, it may be necessary to instigate pharmaceutical muscle paralysis and mechanical ven-

tilation in the ICU, in order to reduce VO_2 to the minimum.[10]

Noradrenaline may be used in severe cases, since by inducing peripheral vasospasm it can increase the pressure in the aorta and the flow to the coronary vessels (improving right heart ischaemia), without affecting right ventricular afterload.[83] Other inotropic drugs (dopamine, dobutamine, isoproterenol and adrenaline) appear to have no place in PE, since they increase

O_2 consumption without a corresponding improvement in cardiac output.[10]

Fluid administration is contraindicated, as further dilatation of the right ventricle leads to an increase in myocardial O_2 consumption and greater restriction of the left ventricle, because of the displacement of the interventricular septum, and therefore a reduction in cardiac output.[84]

Anticoagulant therapy

Heparin is the basic treatment for PE, preventing the formation of new thrombi and giving time for the endogenous fibrinolysis to take effect, dissolving older thrombi.[80,85] Heparin administration should be started immediately, even before the diagnosis of PE is established, provided that anticoagulant therapy is not contraindicated. The recommended regimen is rapid intravenous administration of 5,000-10,000 IU (80 IU/kg), followed by a continuous drip infusion of 1,000-1,200 IU (18 IU/kg) per hour. The maintenance dose is determined by the activated partial thromboplastin time (aPTT), which should be between 60 and 80 s (aPTT=1.5-2.5 times that before heparin administration). If the aPTT is below the lower limit desired, the maintenance dose is increased by 200 IU, and a rapid bolus infusion is given (for aPTT <35 s, 80 IU/kg; for aPTT 35-40 s, 40 IU/kg).[86,87] In patients who are resistant to heparin—defined as inability to achieve the desired aPTT with drip infusion above 50,000 IU/24 hours—and in patients who exhibit thromboembolic disease with high aPTT prior to heparin administration (patients with lupus anticoagulant or other antibodies against anticardiolipin), the dosage is determined on the basis of serum heparin levels (0.3-0.4 IU/ml).[88] Once the desired aPTT has been achieved, oral coumarin anticoagulants may be given. Coadministration with heparin is required for 5 days, since the full anticoagulant effect of coumarins is achieved within that time.[89] The desired international normalised ratio (INR) in this case is 3, as heparin administration prolongs it somewhat. An INR of around 2.5 is ideal after heparin is discontinued. The duration of anticoagulant therapy after PE has not yet been firmly established. The minimum interval seems to be 6 months.[90] In patients with repeated episodes of PE, lifelong treatment may be required,[91] while in patients deficient in antithrombin III, protein C or S, and those with factor V Leiden and PE, therapy is likely to be needed for many years, but not for the rest of their lives.[92,93]

Relatively recently, low molecular weight heparin has been used in the treatment of haemodynamically stable PE, with similar efficacy and greater safety compared to standard heparin.[81,94,95] It should be noted, though, that treatment with low molecular weight heparin has not been used for massive PE and should not be used until the necessary studies have been reported.

Filter placement in the inferior vena cava

Filter use is indicated in cases of PE where there are contraindications for anticoagulant administration (active haemorrhage, endangered haemorrhage following severe brain injury or craniotomy), or when repeated episodes of PE occur despite full anticoagulant therapy.[85] Filters do not appear to help in cases of proximal DVT with free-floating thrombus,[96] while their combination with anticoagulants does not improve survival in comparison with anticoagulant therapy alone.[97]

Thrombolysis

Thrombolysis should be performed immediately in patients with circulatory shock, or obvious haemodynamic instability (massive PE). The outcome in these patients is clearly better in comparison with anticoagulant therapy alone.[98-101] A recent meta-analysis found a significant reduction in deaths and PE reoccurrence in studies that included haemodynamically unstable patients (9.4% versus 19%).[98]

In patients with stable blood pressure, but signs of right cardiac dysfunction on echocardiography (submassive PE), there is no consensus regarding the use of thrombolysis.[102-110] Konstantinides et al,[108] in a recent large, randomised, blind study in which heparin was administered with either alteplase or placebo, observed a better clinical course in the patients who were given alteplase. Specifically, they found that in the alteplase group (rt-PA) fewer patients needed scaling of therapy, i.e. a need for inotrope administration, secondary thrombolysis because of circulatory shock, intubation and mechanical ventilation, emergency surgical embolectomy, or cardiopulmonary resuscitation (24.6% versus 10.2%, p=0.004). However, the mortality did not differ between the two groups.[108]

Supporters of thrombolysis in patients with submassive PE maintain that it directly improves cardiac function, while at the same time reducing the episodes of reembolisation in these patients.[104,108-110]

Those who argue for heparin treatment alone in patients with submassive PE, base their position on the increased risk of haemorrhage as a result of thrombolysis.[105,106] The recent meta-analysis mentioned above[98] found that thrombolysis was associated with a non-significant increase in major haemorrhages (9.1% versus 6.1%; OR 1.42, 95% CI 0.81-2.46) but with a significant increase in minor haemorrhages (22.7% versus 10.0%; OR 2.63, 95% CI 1.53-4.54).

From the above it appears that the benefit of thrombolysis in this group of patients with submassive PE should be assessed together with the risk of major haemorrhage, which increases with age.[105,106] Reviewing a recent disagreement in the literature between Konstantinides[109] and Dallen,[106] concerning the role of thrombolysis in submassive PE, Goldhaber[107] concluded that thrombolysis would most probably have a place in the subgroup of patients who are haemodynamically stable but at high risk. High risk patients could be defined on the basis of echocardiographic criteria and cardiac biological indexes (troponin, brain natriuretic peptide). This would, of course, need to be evaluated in a randomised, prospective study.

In the case of thrombolysis, rt-PA in a dosage of 100 mg, in continuous drip administration within two hours, seems to be superior to urokinase and streptokinase, which are also used. Thrombolysis is effective (administration window) even 14 days after PE.[111] Newer thrombolytic drugs that are used in cases of infarction (reteplase, tenecteplase, lanoteplase) have not been tested in randomised studies of PE and should not be given. For patients in whom aggressive intervention is necessary, but the risk of haemorrhage is high, the decision for embolectomy is considered mandatory.[112,113]

Embolectomy

In patients with haemodynamic instability, in whom thrombolysis has failed or is contraindicated (intracranial haemorrhage, recent surgery or trauma), transvenous catheter thrombectomy is performed.[112] Various devices have been developed for the aspiration or pulverisation of thrombus in the pulmonary circulation.[114] If such a device is not available, or the procedure fails, surgical thrombus removal is indicated, with open thoracotomy and extracorporeal circulation.[115,116] Although emergency embolectomy has found wide acceptance, the results are not satisfactory, since the condition of patients who are referred for surgery is extremely serious. Meyer et al[112] reported 58% mortality among patients undergoing emergency embolectomy who suffered cardiac arrest. Cardiac arrest and cardiogenic shock are independent additional risk factors.[117,118] Rapid diagnosis and haemodynamic stabilisation play a determining role in the improvement of results.[117,118]

Pulmonary endarterectomy in patients with pulmonary hypertension and evidence of thromboembolic disease on pulmonary angiography has been well-documented in the literature.[119-123] Although the incidence of the disease after an acute episode of PE is hard to determine—many cases remain undiagnosed—it is estimated to be around 3.8% during the two first years after PE.[124] These patients, if left without surgical treatment, have an extremely poor prognosis. The results from centres with experience in these procedures are of great interest. They report a significant reduction in mean pulmonary pressure and pulmonary resistances, and mainly a significant improvement in the patients' World Health Organisation functional class, with high 5-year survival (74-86%).[122,123] The perioperative mortality depends entirely on the experience of the centre. It seems that with greater experience mortality is limited to 4.4-9%.[121-123] Independent factors affecting in-hospital mortality are advanced age (>60 years) and the existence of mainly peripheral, and not central, thrombi in the pulmonary circulation.[123] Persistent pulmonary hypertension and haemorrhage are the usual causes of perioperative death.[122,123]

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