

**МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
Харківський національний медичний університет**

**MODERN PRACTICE
OF INTERNAL MEDICINE
WITH EMERGENCY CONDITIONS**

**Management of the patients
with acute pulmonary embolism**

Guidelines for students and interns

**СУЧАСНА ПРАКТИКА
ВНУТРІШНЬОЇ МЕДИЦИНИ
З НЕВІДКЛАДНИМИ СТАНАМИ**

**Ведення хворих
з гострою тромбоемболією
легеневої артерії**

*Методичні вказівки
для студентів та лікарів-інтернів*

Затверджено вченою радою ХНМУ.
Протокол № 1 від 21.01.16.

**Харків
ХНМУ
2016**

Modern practice of internal medicine with emergency conditions. Management of the patients with acute pulmonary embolism : guidelines for students and interns / comp. O. Yu Babak, I. I. Zelena, A. O. Andrieieva et al. – Kharkiv : KNMU, 2016. – 20 p.

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Сучасна практика внутрішньої медицини з невідкладними станами. Ведення хворих з гострою тромбоемболією легеневої артерії : метод. вказ. для студентів та лікарів-інтернів / упоряд. О. Я. Бабак, І. І. Зелена, А. О. Андрєєва та ін. – Харків : ХНМУ, 2016. – 20 с.

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Management of the patients with acute pulmonary embolism

General Outcome

The students should be able to describe main links of pathogenesis, clinical features, diagnostic and treatment of acute pulmonary embolism.

The aim of this topic is to provide the student with an opportunity to:

- Provide a basic overview of the pathophysiology, diagnosis, and classification of acute pulmonary embolism.
- Evaluate guideline-based management strategies for the treatment of acute pulmonary embolism.
- Develop an individualized pharmacotherapy and monitoring plan for the management of acute pulmonary embolism, when given specific patient information.

Specific Learning Outcomes:

Upon successful completion of this unit, the students should be able to:

1. Describe the acute pulmonary embolism epidemiology.
2. Describe the main mechanism of etiopathogenesis.
3. Describe the main clinical features of acute pulmonary embolism.
4. List and describe the group of drugs that are used in the treatment of acute pulmonary embolism and give specific examples of each.
5. Make a treatment plan of patient with acute pulmonary embolism.

Specification of the theoretical question for training of "Management of the patients with hepatic acute pulmonary embolism"

Student must know:

1. What is the definition of acute pulmonary embolism?
2. What are the main causes of acute pulmonary embolism?
3. What are the main pathogenetic links of acute pulmonary embolism?
4. What are the clinical features of acute pulmonary embolism?
5. What laboratory tests are used in patients with acute pulmonary embolism?
6. What imaging studies are used in patients with acute pulmonary embolism?
7. What treatment methods are used in patients with acute pulmonary embolism?

Acute pulmonary embolism

Definition

Pulmonary embolism (PE) is a blockage of the main artery of the lung or one of its branches by a substance that has travelled from elsewhere in the body through the bloodstream (embolism).

Epidemiology

Venous thromboembolism (VTE) encompasses deep vein thrombosis (DVT) and pulmonary embolism (PE). It is the third most frequent cardio-

vascular disease with an overall annual incidence of 100–200 per 100 000 inhabitants. VTE may be lethal in the acute phase or lead to chronic disease and disability, but it is also often preventable.

Acute PE is the most serious clinical presentation of VTE. Since PE is, in most cases, the consequence of DVT, most of the existing data on its epidemiology, risk factors, and natural history are derived from studies that have examined VTE as a whole.

The epidemiology of PE is difficult to determine because it may remain asymptomatic, or its diagnosis may be an incidental finding; in some cases, the first presentation of PE may be sudden death. Overall, PE is a major cause of mortality, morbidity, and hospitalization in Europe. As estimated on the basis of an epidemiological model, over 317 000 deaths were related to VTE in six countries of the European Union (with a total population of 454.4 million) in 2004. Of these cases, 34 % presented with sudden fatal PE and 59 % were deaths resulting from PE that remained undiagnosed during life; only 7 % of the patients who died early were correctly diagnosed with PE before death. Since patients older than 40 years are at increased risk compared with younger patients and the risk approximately doubles with each subsequent decade, an ever-larger number of patients are expected to be diagnosed with (and perhaps die of) PE in the future.

Pathophysiology

Acute PE interferes with both the circulation and gas exchange. Right ventricular (RV) failure due to pressure overload is considered the primary cause of death in severe PE. Pulmonary artery pressure increases only if more than 30–50 % of the total cross-sectional area of the pulmonary arterial bed is occluded by thromboemboli. PE-induced vasoconstriction, mediated by the release of thromboxane A₂ and serotonin, contributes to the initial increase in pulmonary vascular resistance after PE, an effect that can be reversed by vasodilators. Anatomical obstruction and vasoconstriction lead to an increase in pulmonary vascular resistance and a proportional decrease in arterial compliance.

The abrupt increase in pulmonary vascular resistance results in RV dilation, which alters the contractile properties of the RV myocardium via the Frank-Starling mechanism. The increase in RV pressure and volume leads to an increase in wall tension and myocyte stretch. RV contraction time is prolonged, while neurohumoral activation leads to inotropic and chronotropic stimulation. Together with systemic vasoconstriction, these compensatory mechanisms increase pulmonary artery pressure, improving flow through the obstructed pulmonary vascular bed, and thus temporarily stabilize systemic blood pressure (BP). The extent of immediate adaptation is limited, since a non-preconditioned, thin-walled right ventricle (RV) is unable to generate a mean pulmonary artery pressure above 40 mmHg.

The prolongation of RV contraction time into early diastole in the left ventricle leads to leftward bowing of the interventricular septum. The desynchronization of the ventricles may be exacerbated by the development of right bundle-branch block. As a result, left ventricular (LV) filling is impeded in early diastole, and this may lead to a reduction of the cardiac output and contribute to systemic hypotension and haemodynamic instability.

As described above, excessive neurohumoral activation in PE can be the result both of abnormal RV wall tension and of circulatory shock. The finding of massive infiltrates in the RV myocardium of patients who died within 48 hours of acute PE may be explained by high levels of epinephrine released as a result of the PE-induced "myocarditis". This inflammatory response might explain the secondary haemodynamic destabilization which sometimes occurs 24–48 hours after acute PE, although early recurrence of PE may be an alternative explanation in some of these cases.

Finally, the association between elevated circulating levels of biomarkers of myocardial injury and an adverse early outcome indicates that RV ischaemia is of pathophysiological significance in the acute phase of PE. Although RV infarction is uncommon after PE, it is likely that the imbalance between oxygen supply and demand can result in damage to cardiomyocytes and further reduce contractile forces.

Diagnosis

"Confirmed PE" is defined as a probability of PE high enough to indicate the need for PE-specific treatment, and 'excluded PE' as a probability of PE low enough to justify withholding PE-specific treatment with an acceptably low risk.

Clinical presentation

PE may escape prompt diagnosis since the clinical signs and symptoms are non-specific. When the clinical presentation raises the suspicion of PE in an individual patient, it should prompt further objective testing. In most patients, PE is suspected on the basis of dyspnoea, chest pain, pre-syncope or syncope, and/or haemoptysis. Arterial hypotension and shock are rare but important clinical presentations, since they indicate central PE and/or a severely reduced haemodynamic reserve. Syncope is infrequent, but may occur regardless of the presence of haemodynamic instability. Finally, PE may be completely asymptomatic and be discovered incidentally during diagnostic work-up for another disease or at autopsy.

Chest pain is a frequent symptom of PE and is usually caused by pleural irritation due to distal emboli causing pulmonary infarction. In central PE, chest pain may have a typical angina character, possibly reflecting RV ischaemia and requiring differential diagnosis with acute coronary syndrome (ACS) or aortic dissection. Dyspnoea may be acute and severe in central PE; in small peripheral PE, it is often mild and may be transient. In patients with pre-existing heart failure or pulmonary disease, worsening dyspnoea may be the only symptom indicative of PE.

D-dimer testing

D-dimer levels are elevated in plasma in the presence of acute thrombosis because of simultaneous activation of coagulation and fibrinolysis. The negative predictive value of D-dimer testing is high and a normal D-dimer level renders acute PE or DVT unlikely. On the other hand, fibrin is also produced in a wide variety of conditions such as cancer, inflammation, bleeding, trauma, surgery and necrosis. Accordingly, the positive predictive value of elevated D-dimer levels is low and D-dimer testing is not useful for confirmation of PE.

A number of D-dimer assays are available. The quantitative enzyme-linked immunosorbent assay (ELISA) or ELISA-derived assays have a diagnostic sensitivity of 95 % or better and can therefore be used to exclude PE in patients with either a low or a moderate pre-test probability. In the emergency department, a negative ELISA D-dimer, in combination with clinical probability, can exclude the disease without further testing in approximately 30 % of patients with suspected PE.

Computed tomographic pulmonary angiography

Since the introduction of multi-detector computed tomographic (MDCT) angiography with high spatial and temporal resolution and quality of arterial opacification, computed tomographic (CT) angiography has become the method of choice for imaging the pulmonary vasculature in patients with suspected PE. It allows adequate visualization of the pulmonary arteries down to at least the segmental level.

Computed tomographic venography has been advocated as a simple way to diagnose DVT in patients with suspected PE, as it can be combined with chest CT angiography as a single procedure, using only one intravenous injection of contrast dye. CT venography adds a significant amount of irradiation, which may be a concern, especially in younger women.

The incidental discovery of clinically unsuspected PE on CT is an increasingly frequent problem, arising in 1–2 % of all thoracic CT examinations, most often in patients with cancer, but also among those with paroxysmal atrial fibrillation or heart failure and history of atrial fibrillation. There are no robust data to guide the decision on how to manage unsuspected PE with anticoagulants, but most experts agree that patients with cancer and those with clots at the lobar or more proximal level should be treated with anticoagulants.

Lung scintigraphy

Ventilation–perfusion scintigraphy (V/Q scan) is an established diagnostic test for suspected PE. It is safe and few allergic reactions have been described. The test is based on the intravenous injection of technetium (Tc)-99m-labelled macroaggregated albumin particles, which block a small fraction of the pulmonary capillaries and thereby enable scintigraphic assessment of lung perfusion. Perfusion scans are combined with ventilation studies, for

which multiple tracers such as xenon-133 gas, Tc-99m-labelled aerosols, or Tc-99m-labelled carbon microparticles (Technegas) can be used. The purpose of the ventilation scan is to increase specificity: in acute PE, ventilation is expected to be normal in hypoperfused segments (mismatch). According to the International Commission on Radiological Protection (ICRP), the radiation exposure from a lung scan with 100 MBq of Tc-99m macroaggregated albumin particles is 1.1 mSv for an average sized adult, and thus is significantly lower than that of CT angiography (2–6 mSv). Being a radiation- and contrast medium-sparing procedure, the V/Q scan may preferentially be applied in outpatients with low clinical probability and a normal chest X-ray, in young (particularly female) patients, in pregnancy, in patients with history of contrast medium-induced anaphylaxis and strong allergic history, in severe renal failure, and in patients with myeloma and paraproteinaemia.

Pulmonary angiography

Pulmonary angiography has for decades remained the "gold standard" for the diagnosis or exclusion of PE, but is rarely performed now as less-invasive CT angiography offers similar diagnostic accuracy. Pulmonary angiography is more often used to guide percutaneous catheter-directed treatment of acute PE. Digital subtraction angiography (DSA) requires less contrast medium than conventional cineangiography and has excellent imaging quality for peripheral pulmonary vessels in patients who can hold their breath; it is less useful for imaging of the main pulmonary arteries, due to cardiac motion artefacts.

The diagnosis of acute PE is based on direct evidence of a thrombus in two projections, either as a filling defect or as amputation of a pulmonary arterial branch. Thrombi as small as 1–2 mm within the sub-segmental arteries can be visualized by DSA, but there is substantial inter-observer variability at this level. Indirect signs of PE, such as slow flow of contrast, regional hypoperfusion, and delayed or diminished pulmonary venous flow, are not validated and hence are not diagnostic.

Haemodynamic measurements should always be recorded during pulmonary angiography for estimation of the severity of PE and because they may suggest alternative cardiopulmonary disorders. In patients with haemodynamic compromise, the amount of contrast agent should be reduced and non-selective injections avoided.

Magnetic resonance angiography

Magnetic resonance angiography (MRA) has been evaluated for several years in suspected PE but large-scale studies were published only recently. Their results show that this technique, although promising, is not yet ready for clinical practice due to its low sensitivity, high proportion of inconclusive MRA scans, and low availability in most emergency settings.

Echocardiography

Acute PE may lead to RV pressure overload and dysfunction, which can be detected by echocardiography. Given the peculiar geometry of the RV, there is no individual echocardiographic parameter that provides fast and reliable information on RV size or function. This is why echocardiographic criteria for the diagnosis of PE have differed between studies. Because of the reported negative predictive value of 40–50 %, a negative result cannot exclude PE. On the other hand, signs of RV overload or dysfunction may also be found in the absence of acute PE and be due to concomitant cardiac or respiratory disease. RV dilation is found in at least 25 % of patients with PE, and its detection, either by echocardiography or CT, is useful for risk stratification of the disease.

Compression venous ultrasonography

In the majority of cases, PE originates from DVT in a lower limb. In a study using venography, DVT was found in 70 % of patients with proven PE. Nowadays, lower limb CUS has largely replaced venography for diagnosing DVT. CUS has a sensitivity >90 % and a specificity of approximately 95 % for symptomatic DVT. CUS shows a DVT in 30–50 % of patients with PE, and finding a proximal DVT in patients suspected of having PE is considered sufficient to warrant anticoagulant treatment without further testing.

LABORATORY TESTS AND BIOMARKERS

Markers of right ventricular dysfunction

Right ventricular pressure overload is associated with increased myocardial stretch, which leads to the release of brain natriuretic peptide (BNP) or N-terminal (NT)-proBNP. The plasma levels of natriuretic peptides reflect the severity of haemodynamic compromise and (presumably) RV dysfunction in acute PE. In normotensive patients with PE, the positive predictive value of elevated BNP or NT-proBNP concentrations for early mortality is low. In a prospective, multicentre cohort study that included 688 patients, NT-proBNP plasma concentrations of 600 pg/mL were identified as the optimal cut-off value for the identification of elevated risk. On the other hand, low levels of BNP or NT-proBNP can identify patients with a favourable short-term clinical outcome based on their high negative predictive value. Haemodynamically stable patients with low NT-proBNP levels may be candidates for early discharge and outpatient treatment.

Markers of myocardial injury

Transmural RV infarction despite patent coronary arteries has been found at autopsy of patients who died of massive PE. Elevated plasma troponin concentrations on admission have been reported in connection with PE and were associated with worse prognosis. Heart-type fatty acid-binding protein (H-FABP), an early marker of myocardial injury, was also found to possess prognostic value in acute PE. In normotensive patients, circulating H-FABP

levels ≥ 6 ng/mL had a positive predictive value of 28 % and a negative predictive value of 99% for an adverse 30-day outcome. A simple score, based on the presence of tachycardia, syncope, and a positive bedside test for H-FABP, provided prognostic information similar to that of RV dysfunction on echocardiography.

Other (non-cardiac) laboratory biomarkers

Elevated serum creatinine levels and a decreased (calculated) glomerular filtration rate are related to 30-day all-cause mortality in acute PE. Elevated neutrophil gelatinase-associated lipocalin (NGAL) and cystatin C, both indicating acute kidney injury, have also been found to be of prognostic value. Elevated D-dimer concentrations were associated with increased short-term mortality in some studies, while levels < 1500 ng/mL had a negative predictive value of 99 % for excluding three-month all-cause mortality.

TREATMENT IN THE ACUTE PHASE

Haemodynamic and respiratory support

Acute RV failure with resulting low systemic output is the leading cause of death in patients with high-risk PE. Therefore, supportive treatment is vital in patients with PE and RV failure. Experimental studies indicate that aggressive volume expansion is of no benefit and may even worsen RV function by causing mechanical overstretch, or by reflex mechanisms that depress contractility. On the other hand, modest (500 mL) fluid challenge may help to increase cardiac index in patients with PE, low cardiac index, and normal BP. Use of vasopressors is often necessary, in parallel with (or while waiting for) pharmacological, surgical, or interventional reperfusion treatment. Norepinephrine appears to improve RV function via a direct positive inotropic effect, while also improving RV coronary perfusion by peripheral vascular alpha-receptor stimulation and the increase in systemic BP. Its use should probably be limited to hypotensive patients. Based on the results of small series, the use of dobutamine and/or dopamine may be considered for patients with PE, low cardiac index, and normal BP; however, raising the cardiac index above physiological values may aggravate the ventilation-perfusion mismatch by further redistributing flow from (partly) obstructed to unobstructed vessels. Epinephrine combines the beneficial properties of norepinephrine and dobutamine, without the systemic vasodilatory effects of the latter. It may therefore exert beneficial effects in patients with PE and shock. Vasodilators decrease pulmonary arterial pressure and pulmonary vascular resistance, but the main concern is the lack of specificity of these drugs for the pulmonary vasculature after systemic (intravenous) administration. According to data from small clinical studies, inhalation of nitric oxide may improve the haemodynamic status and gas exchange of patients with PE. Preliminary data suggest that levosimendan may restore right ven-

tricular–pulmonary arterial coupling in acute PE by combining pulmonary vasodilation with an increase in RV contractility. Hypoxaemia and hypocapnia are frequently encountered in patients with PE, but they are of moderate severity in most cases. A patent foramen ovale may aggravate hypoxaemia due to shunting when right atrial- exceeds left atrial pressure. Hypoxaemia is usually reversed with administration of oxygen. When mechanical ventilation is required, care should be taken to limit its adverse haemodynamic effects. In particular, the positive intrathoracic pressure induced by mechanical ventilation may reduce venous return and worsen RV failure in patients with massive PE; therefore, positive end-expiratory pressure should be applied with caution. Low tidal volumes (approximately 6 mL/kg lean body weight) should be used in an attempt to keep the end-inspiratory plateau pressure <30 cm H₂O.

Anticoagulation

In patients with acute PE, anticoagulation is recommended, with the objective of preventing both early death and recurrent symptomatic or fatal VTE. The standard duration of anticoagulation should cover at least 3 months. Within this period, acute-phase treatment consists of administering parenteral anticoagulation [unfractionated heparin (UFH), low molecular weight heparin (LMWH), or fondaparinux] over the first 5–10 days. Parenteral heparin should overlap with the initiation of a vitamin K antagonist (VKA); alternatively, it can be followed by administration of one of the new oral anticoagulants: dabigatran or edoxaban. If rivaroxaban or apixaban is given instead, oral treatment with one of these agents should be started directly or after a 1–2 day administration of UFH, LMWH or fondaparinux. In this latter case, acute-phase treatment consists of an increased dose of the oral anticoagulant over the first 3 weeks (for rivaroxaban), or over the first 7 days (for apixaban). In some cases, extended anticoagulation beyond the first 3 months, or even indefinitely, may be necessary for secondary prevention, after weighing the individual patient's risk of recurrence vs. bleeding risk.

Parenteral anticoagulation

In patients with high or intermediate clinical probability for PE, parenteral anticoagulation should be initiated whilst awaiting the results of diagnostic tests. Immediate anticoagulation can be achieved with parenteral anticoagulants such as intravenous UFH, subcutaneous LMWH, or subcutaneous fondaparinux. LMWH or fondaparinux are preferred over UFH for initial anticoagulation in PE, as they carry a lower risk of inducing major bleeding and heparin-induced thrombocytopenia (HIT). On the other hand, UFH is recommended for patients in whom primary reperfusion is considered, as well as for those with serious renal impairment (creatinine clearance <30 mL/min), or severe obesity. LMWH needs no routine monitoring, but periodic measurement of anti-factor Xa activity (anti-Xa levels) may be considered during pregnancy. Peak values of anti-factor Xa activity should be measured 4 hours

after the last injection and trough values just before the next dose of LMWH would be due; the target range is 0.6–1.0 IU/mL for twice-daily administration, and 1.0–2.0 IU/mL for once-daily administration.

Vitamin K antagonists

Oral anticoagulants should be initiated as soon as possible, and preferably on the same day as the parenteral anticoagulant. VKAs have been the "gold standard" in oral anticoagulation for more than 50 years and warfarin, acenocoumarol, phenprocoumon, phenindione and flunidione remain the predominant anticoagulants prescribed for PE. Anticoagulation with UFH, LMWH, or fondaparinux should be continued for at least 5 days and until the international normalized ratio (INR) has been 2.0–3.0 for two consecutive days.

Warfarin can be started at a dose of 10 mg in younger (e.g. <60 years of age), otherwise healthy outpatients, and at a dose of 5 mg in older patients and in those who are hospitalized. The daily dose is adjusted according to the INR over the next 5–7 days, aiming for an INR level of 2.0–3.0. Rapid-turnaround pharmacogenetic testing may increase the precision of warfarin dosing. In particular, variations in two genes may account for more than one-third of the dosing variability of warfarin. One gene determines the activity of cytochrome CYP2C9, the hepatic isoenzyme that metabolizes the S-enantiomer of warfarin into its inactive form, while the other determines the activity of vitamin K epoxide reductase, the enzyme that produces the active form of vitamin K. Pharmacogenetic algorithms incorporate genotype and clinical information and recommend warfarin doses according to integration of these data. In summary, the results of recent trials appear to indicate that pharmacogenetic testing, used on top of clinical parameters, does not improve the quality of anticoagulation. They also suggest that dosing based on the patient's clinical data is possibly superior to fixed loading regimens, and they point out the need to place emphasis on improving the infrastructure of anticoagulation management by optimizing the procedures that link INR measurement with provision of feedback to the patient and individually tailoring dose adjustments.

Thrombolytic treatment

Thrombolytic treatment of acute PE restores pulmonary perfusion more rapidly than anticoagulation with UFH alone. The early resolution of pulmonary obstruction leads to a prompt reduction in pulmonary artery pressure and resistance, with a concomitant improvement in RV function. The haemodynamic benefits of thrombolysis are confined to the first few days; in survivors, differences are no longer apparent at one week after treatment. Accelerated regimens administered over 2 hours are preferable to prolonged infusions of first-generation thrombolytic agents over 12–24 hours. Unfractionated heparin infusion should be stopped during administration of streptokinase or urokinase; it can be continued during rtPA infusion. In patients receiving LMWH

or fondaparinux at the time that thrombolysis is initiated, infusion of UFH should be delayed until 12 hours after the last LMWH injection (given twice daily), or until 24 hours after the last LMWH or fondaparinux injection (given once daily). Given the bleeding risks associated with thrombolysis and the possibility that it may become necessary to immediately discontinue or reverse the anticoagulant effect of heparin, it appears reasonable to continue anticoagulation with UFH for several hours after the end of thrombolytic treatment before switching to LMWH or fondaparinux.

Overall, >90 % of patients appear to respond favourably to thrombolysis, as judged by clinical and echocardiographic improvement within 36 hours. The greatest benefit is observed when treatment is initiated within 48 hours of symptom onset, but thrombolysis can still be useful in patients who have had symptoms for 6–14 days. Thrombolytic treatment carries a risk of major bleeding, including intracranial haemorrhage. Analysis of pooled data from trials using various thrombolytic agents and regimens reported intracranial bleeding rates between 1.9 and 2.2 %. Increasing age and the presence of comorbidities have been associated with a higher risk of bleeding complications.

Surgical embolectomy

The first successful surgical pulmonary embolectomy was performed in 1924, several decades before the introduction of medical treatment for PE. Multidisciplinary teams enjoying the early and active involvement of cardiac surgeons have recently reintroduced the concept of surgical embolectomy for high-risk PE, and also for selected patients with intermediate-high-risk PE, particularly if thrombolysis is contraindicated or has failed. Surgical embolectomy has also been successfully performed in patients with right heart thrombi straddling the interatrial septum through a patent foramen ovale. Pulmonary embolectomy is technically a relatively simple operation. The site of surgical care does not appear to have a significant effect on operative outcomes, and thus patients need not be transferred to a specialized cardiothoracic centre if on-site embolectomy using extracorporeal circulation is possible. Transportable extracorporeal assistance systems with percutaneous femoral cannulation can be helpful in critical situations, ensuring circulation and oxygenation until definitive diagnosis. Following rapid transfer to the operating room and induction of anaesthesia and median sternotomy, normothermic cardiopulmonary bypass should be instituted. Aortic cross-clamping and cardioplegic cardiac arrest should be avoided. With bilateral PA incisions, clots can be removed from both pulmonary arteries down to the segmental level under direct vision. Prolonged periods of post-operative cardiopulmonary bypass and weaning may be necessary for recovery of RV function. Pre-operative thrombolysis increases the risk of bleeding, but it is not an absolute contraindication to surgical embolectomy. Over the long term, the post-operative survival rate, World Health Organization functional class, and quality of life were favourable in published series. Patients presenting with an epi-

sode of acute PE superimposed on a history of long-lasting dyspnoea and pulmonary hypertension are likely to suffer from chronic thromboembolic pulmonary hypertension. These patients should be transferred to an expert centre for pulmonary endarterectomy.

Percutaneous catheter-directed treatment

The objective of interventional treatment is the removal of obstructing thrombi from the main pulmonary arteries to facilitate RV recovery and improve symptoms and survival. For patients with absolute contraindications to thrombolysis, interventional options include (i) thrombus fragmentation with pigtail or balloon catheter, (ii) rheolytic thrombectomy with hydrodynamic catheter devices, (iii) suction thrombectomy with aspiration catheters and (iv) rotational thrombectomy. On the other hand, for patients without absolute contraindications to thrombolysis, catheter-directed thrombolysis or pharmacomechanical thrombolysis are preferred approaches. While anticoagulation with heparin alone has little effect on improvement of RV size and performance within the first 24–48 hours, the extent of early RV recovery after low-dose catheter-directed thrombolysis appears comparable to that after standard-dose systemic thrombolysis.

Venous filters

Venous filters are usually placed in the infrarenal portion of the inferior vena cava (IVC). If a thrombus is identified in the renal veins, suprarenal placement may be indicated. Venous filters are indicated in patients with acute PE who have absolute contraindications to anticoagulant drugs, and in patients with objectively confirmed recurrent PE despite adequate anticoagulation treatment. Observational studies suggest that insertion of a venous filter might reduce PE-related mortality rates in the acute phase, benefit possibly coming at the cost of an increased risk of recurrence of VTE. Complications associated with permanent IVC filters are common, although they are rarely fatal. Overall, early complications – which include insertion site thrombosis – occur in approximately 10 % of patients. Placement of a filter in the superior *vena cava* carries the risk of pericardial tamponade. Late complications are more frequent and include recurrent DVT in approximately 20 % of patients and post-thrombotic syndrome in up to 40 %. Occlusion of the IVC affects approximately 22 % of patients at 5 years and 33 % at 9 years, regardless of the use and duration of anticoagulation. Non-permanent IVC filters are classified as temporary or retrievable devices. Temporary filters must be removed within few days, while retrievable filters can be left in place for longer periods. When non-permanent filters are used, it is recommended that they be removed as soon as it is safe to use anticoagulants. Despite this, they are often left in situ for longer periods, with a late complication rate of at least 10 %; this includes filter migration, tilting or deformation, penetration of the

cava wall by filter limbs, fracturing of the filter and embolization of fragments, and thrombosis of the device.

There are no data to support the routine use of venous filters in patients with free-floating thrombi in the proximal veins; in one series, among PE patients who received adequate anticoagulant treatment alone (without a venous filter), the recurrence rate was low (3.2 %). There is also no evidence to support the use of IVC filters in patients scheduled for systemic thrombolysis, surgical embolectomy, or pulmonary thrombendarterectomy.

THERAPEUTIC STRATEGIES

Pulmonary embolism with shock or hypotension (high risk pulmonary embolism)

Patients with PE presenting with shock or hypotension are at high risk of in-hospital death, particularly during the first few hours after admission. Besides haemodynamic and respiratory support, intravenous UFH should be administered to these patients as the preferred mode of initial anticoagulation, as LMWH or fondaparinux have not been tested in the setting of hypotension and shock. Primary reperfusion treatment, particularly systemic thrombolysis, is the treatment of choice for patients with high-risk PE. In patients with contraindications to thrombolysis – and in those in whom thrombolysis has failed to improve the haemodynamic status – surgical embolectomy is recommended if surgical expertise and resources are available. As an alternative to surgery, percutaneous catheter-directed treatment should be considered if expertise with this method and the appropriate resources are available on site. In these cases, treatment decisions should be made by an interdisciplinary team involving a thoracic surgeon or interventional cardiologist, as appropriate.

Pulmonary embolism without shock or hypotension (intermediate- or low-risk pulmonary embolism)

For most cases of acute PE without haemodynamic compromise, LMWH or fondaparinux, given subcutaneously at weight-adjusted doses without monitoring, is the treatment of choice unless there is severe renal dysfunction. Patients not suffering from shock or hypotension require further risk stratification after the diagnosis of PE has been confirmed. In these patients, risk assessment should begin with a validated clinical score, preferably the PESI or sPESI.

Low-risk patients in the PESI Class I or II, and probably those with sPESI of 0, should be considered for early discharge and outpatient treatment, if this appears feasible based on the patient's anticipated compliance as well as his/her family and social background. For all other patients, assessment of RV function by echocardiography (or CT angiography) and cardiac troponin testing should be considered.

Based on the results of a recently published randomized trial, and as explained in the section on prognostic assessment, patients with acute PE, an echocardiogram or CT scan indicating RV dysfunction, and a positive cardiac troponin test belong to an intermediate-high-risk group. Full-dose systemic thrombolytic therapy, given as primary reperfusion therapy, can prevent potentially life-threatening haemodynamic decompensation or collapse in these patients, but this benefit is counterbalanced by a high risk of haemorrhagic stroke or major non-intracranial bleeding. Accordingly, systemic thrombolysis is not routinely recommended as primary treatment for patients with intermediate-high-risk PE, but should be considered if clinical signs of haemodynamic decompensation appear. Surgical pulmonary embolectomy or percutaneous catheter-directed treatment may be considered as alternative, "rescue" procedures for patients with intermediate-high-risk PE, in whom haemodynamic decompensation appears imminent and the anticipated bleeding risk under systemic thrombolysis is high. Other laboratory markers, such as BNP, NT-proBNP and H-FABP, have also been shown to possess additive prognostic value to clinical and imaging parameters in cohort studies; their potential therapeutic implications have not yet been investigated in prospective trials.

Normotensive patients in the PESI Class III or higher, or sPESI of at least 1, in whom the echocardiogram (or CT angiogram) or the cardiac troponin test – or both – are normal, belong to an intermediate-low-risk group. Anticoagulation is indicated. Existing evidence does not support primary reperfusion treatment. There is no evidence to suggest that bed rest has any beneficial effect on these patients' clinical outcome.

SPECIFIC PROBLEMS

Pregnancy

Pulmonary embolism is the leading cause of pregnancy-related maternal death in developed countries. The risk of PE is higher in the post-partum period, particularly after a caesarean section. Exposure of the foetus to ionizing radiation is a concern when investigating suspected PE during pregnancy; although this concern is largely overruled by the hazards of missing a potentially fatal diagnosis. This is particularly true for pregnant patients with suspected high-risk PE. Moreover, erroneously assigning a diagnosis of PE to a pregnant woman is also fraught with risks, since it unnecessarily exposes the mother and foetus to the risks of anticoagulant treatment and will impact on delivery plans, future contraception, and thromboprophylaxis during future pregnancies. Therefore, investigations should aim at diagnostic certainty. The usefulness of D-dimer in pregnancy is controversial. A normal D-dimer value has the same exclusion value for PE in pregnant women as

for other patients with suspected PE but is found more rarely, because plasma D-dimer levels physiologically increase throughout pregnancy. The treatment of PE in pregnancy is based on heparin anticoagulation, because heparin does not cross the placenta and is not found in breast milk in significant amounts. Increasing experience suggests that LMWHs are safe in pregnancy, and their use is endorsed in several reports. Treatment should consist of a weight-adjusted dose of LMWH. Adaptation according to anti-Xa monitoring may be considered in women at extremes of body weight or with renal disease, but routine monitoring is generally not justified. Unfractionated heparin is not contraindicated in pregnancy, although it requires aPTT monitoring and is probably more likely to cause osteoporosis if used for longer periods. Fondaparinux should not be used in pregnancy due to the lack of data. VKAs cross the placenta and are associated with a well-defined embryopathy during the first trimester. Administration of VKAs in the third trimester can result in foetal and neonatal haemorrhage, as well as placental abruption. Warfarin may be associated with central nervous system anomalies throughout pregnancy. New oral anticoagulants are contraindicated in pregnant patients. The management of labour and delivery require particular attention. Epidural analgesia cannot be used unless LMWH has been discontinued at least 12 hours before delivery. Treatment can be resumed 12–24 hours after removal of the epidural catheter. Close collaboration between the obstetrician, the anaesthesiologist, and the attending physician is recommended. After delivery, heparin treatment may be replaced by anticoagulation with VKA. Anticoagulant treatment should be administered for at least 6 weeks after delivery and with a minimum overall treatment duration of 3 months. VKAs can be given to breast-feeding mothers.

Pulmonary embolism and cancer

The overall risk of venous thromboembolism in cancer patients is four times as great as in the general population. Although the largest absolute numbers of VTE episodes occur in patients with lung, colon, and prostate cancer, the relative risk for VTE is highest in multiple myeloma, brain, and pancreatic cancer (46-, 20-, and 16-fold increased vs. healthy controls, respectively). In the metastatic stage, stomach, bladder, uterine, renal, and lung cancer are also associated with a high incidence of VTE. Patients receiving chemotherapy have a six-fold increase in the adjusted risk ratio for VTE compared with a healthy population. Nevertheless, prophylactic anticoagulation is not routinely recommended during ambulatory anti-cancer chemotherapy, with the exception of thalidomide- or lenalidomide-based regimens in multiple myeloma. LMWH or VKA are not effective in preventing thrombosis related to the use of permanent central venous lines in cancer patients. The risk of VTE increases over 90-fold in the first 6 weeks after cancer surgery,

compared with that in healthy controls, and is second only to the risk of VTE after hip or knee replacement surgery. Notably, the risk of VTE after cancer surgery remains elevated (up to 30-fold) between the fourth and twelfth post-operative month. Continued vigilance is therefore necessary, as currently recommended prophylactic anticoagulation covers only the first 30 days after cancer surgery.

A negative D-dimer test has the same diagnostic value as in non-cancer patients. On the other hand, D-dimer levels are non-specifically increased in many patients with cancer. In one study, raising the D-dimer cut-off level to 700 µg/L, or using age-dependent cut-off levels, increased the proportion of cancer patients in whom PE could be ruled out from 8.4 to 13 % and 12 %, respectively; the corresponding false-negative rates appeared acceptable. This strategy needs further validation.

The widespread use of CT scanners has resulted in an increasing number of incidentally diagnosed, asymptomatic PEs in cancer patients. Their significance, particularly if limited to segmental or sub-segmental arteries, is unclear; however, in view of the high risk of an adverse outcome reported by uncontrolled studies, the treatment strategies recommended for symptomatic PE should be also considered for incidental PE found in patients with malignancy.

When selecting the mode of anticoagulation in patients with cancer and acute PE, LMWH administered in the acute phase (except for high-risk PE) and continued over the first 3–6 months should be considered as first-line therapy. However, this strategy is based largely on the results of a single trial with an observed 50% reduction in the rate of recurrence of VTE without increased bleeding risk, as compared with the early transition from heparin to VKA. Evidence regarding treatment of cancer-related PE with fondaparinux and the new oral anticoagulants is limited.

Chronic anticoagulation may consist of continuation of LMWH, transition to VKA, or discontinuation of anticoagulation. The decisions should be made on a case-by-case basis after considering the success of anti-cancer therapy, the estimated risk of recurrence of VTE, the bleeding risk, and the preference of the patient. Periodic reassessment of the risk-benefit ratio of chronic anticoagulant treatment is a reasonable strategy.

Non-thrombotic pulmonary embolism

Different cell types can cause non-thrombotic embolization, including adipocytes, haematopoietic, amniotic, trophoblastic, and tumour cells. In addition, bacteria, fungi, parasites, foreign materials, and gas can lead to PE. Symptoms are similar to those of acute VTE and include dyspnoea, tachycardia, chest pain, cough, and occasionally haemoptysis, cyanosis, and syncope. Diagnosis of non-thrombotic PE can be a challenge. In the case of small particles,

microemboli cannot be detected on CT images. An overview of typical imaging findings for the various types of non-thrombotic PE has been provided. Given the rarity of this disease, clinical evidence is limited and mainly based on small case series.

Septic embolism

Septic embolism to the pulmonary circulation is a relatively rare clinical event and is commonly associated with right-sided endocarditis. Risk factors include intravenous drug abuse and infected indwelling catheters or pacemaker wires. Other causes include septic thrombophlebitis from the tonsils and the jugular, dental, and pelvic regions. The diagnosis is based on identifying the source of septic emboli, positive blood culture tests, and chest X-ray or CT after considering the clinical context. Although *Staphylococcus aureus* is the most common bacterial pathogen, the increasing number of immunocompromised patients – and those with indwelling catheters and vascular prostheses – leads to a rise in the incidence of anaerobic gram positive and -negative bacteria, bacterioides species, and fungi. Specific treatment of the responsible bacterial or fungal micro-organism is necessary.

Foreign-material pulmonary embolism

The increasing use of interventional techniques in modern medicine has drastically increased the incidence of foreign-material PE. Examples of foreign material include silicone, broken catheters, guide wires, *vena cava* filters, coils for embolization, and endovascular stent components. If possible, intravascular foreign objects should be removed, since the material may cause further thrombosis and sepsis.

Fat embolism

Embolization of fat occurs in almost all patients with pelvic or long-bone fractures and in those undergoing endomedullary nailing or placement of knee and hip prostheses, but also during lipid and propofol infusion, intraosseous infusion and bone marrow harvest, and in sickle cell disease, fatty liver disease, pancreatitis, and after liposuction. Pulmonary involvement is not only due to vascular obstruction but also to the release of substances triggering an inflammatory cascade, thus explaining why some patients with fat embolism develop acute respiratory distress syndrome. The classical triad of fat embolization is characterized by altered mental status, respiratory distress, and petechial rash occurring typically 12–36 hours after injury. Fat globules can be found in blood, urine, sputum, broncho-alveolar lavage, and cerebrospinal fluid. In most cases the condition is self-limiting. Treatment should be supportive. Although the successful use of high doses of methyl prednisolone has been reported in humans, along with the positive effects of phorbol myristate acetate and sivelestat in animals, there is no evidence that these drugs alter the course of the disease.

Air embolism

Although air embolism can occur in both the venous and arterial systems, venous emboli are more common. Venous air embolization is often an iatrogenic complication of the manipulation of central venous and haemodialysis catheters. The lethal volume of air after injection in humans is estimated to range from 100 to 500 mL. The major effect of venous air embolism is the obstruction of the right ventricular outflow tract, or of the pulmonary arterioles, by a mixture of air bubbles and fibrin. Although the diagnosis can be made by X-ray or echocardiography, CT scanning may be the most sensitive diagnostic test, showing a unique picture of round or mirror-shaped densities localized ventrally in the supine patient. Treatment includes maintenance of the circulation, prevention of further entry of gas, and volume expansion. The patient should be placed in the left lateral decubitus position to prevent right ventricular outflow obstruction by airlock. In the case of large amounts of central air, aspiration with the use of a central venous catheter might be an option. Administration of up to 100 % oxygen can decrease bubble size by establishing a diffusion gradient that favours elimination of the gas.

Amniotic fluid embolism

Amniotic fluid embolism is a rare but catastrophic complication unique to pregnancy. Estimated incidences, obtained through validated case identification, range between 1.9 and 2.5 cases per 100 000 maternities. The most likely mechanism is that amniotic fluid is forced into the uterine veins during normal labour or when the placenta is disrupted by surgery or trauma. As a consequence, pulmonary vessels are obstructed by cell groups and meconium, and an inflammatory reaction occurs due to the release of active metabolites. The majority of patients develop seizures. Some patients are diagnosed with pulmonary oedema and acute respiratory distress syndrome later in the course of the event. Mortality is high – up to 21 %, even in recent cohort studies. Management should be supportive.

Tumour embolism

Pulmonary intravascular tumour emboli are seen in up to 26 % of autopsies of patients with solid malignancies, although the diagnosis is rarely made before death. Carcinoma of the prostate gland, digestive system, liver, and breast is most commonly implicated. Radiologically, tumour microembolism may mimic many lung conditions, including pneumonia, tuberculosis, and interstitial lung disease, whereas tumour macroembolism is indistinguishable from VTE. Treatment should target the underlying malignant disease.

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Навчальне видання

СУЧАСНА ПРАКТИКА ВНУТРІШНЬОЇ МЕДИЦИНИ З НЕВІДКЛАДНИМИ СТАНАМИ

Ведення хворих з гострою тромбоемболією легеневої артерії

Методичні вказівки для студентів та лікарів-інтернів

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Комп'ютерний набір І. І. Зелена
Комп'ютерна верстка Н. І. Дубська

Формат 60×84/16. Умов. друк. арк. 1,25. Зам. №16-33135.

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Свідоцтво про внесення суб'єкта видавничої справи до Державного реєстру видавництва, виготовників і розповсюджувачів видавничої продукції серії ДК № 3242 від 18.07.2008 р.

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with acute pulmonary embolism

Guidelines for students and interns