

# *Pulmonary vascular disease*

## *Key points*

- Pulmonary embolism is common, difficult to diagnose and potentially very serious, with a fatality rate of 7–11%.
- Several factors predisposing to pulmonary embolism are recognised and prophylactic treatment should be implemented more widely in those at risk.
- Pulmonary hypertension may result from any of a range of causes or may be idiopathic. Although pharmacological treatment has improved, some forms still have a very poor prognosis.
- Awareness of pulmonary hypertension needs to increase and its pathogenesis requires further research.

Pulmonary vascular diseases such as pulmonary embolism (PE) and pulmonary hypertension (PH) and their effects on right heart function contribute markedly to the global burden of chronic respiratory disease. The burden of pulmonary vascular diseases (figures 1 and 2) is certainly underestimated and merits greater attention from the medical community. Better characterisation and management of patients is needed in order to improve disease outcomes.

## *Pulmonary embolism*

### *Introduction*

PE is a common condition that results in the occlusion of the pulmonary arteries by thrombotic material originating from a deep vein thrombosis. It can cause acute life-threatening, but potentially reversible, right heart failure. Nonthrombotic PE (resulting from fat, tumour, amniotic fluid, air, etc.) will not be discussed in this chapter.

### *Epidemiology*

European incidence estimates of PE range from 6–20 cases per 10 000 inhabitants per year.

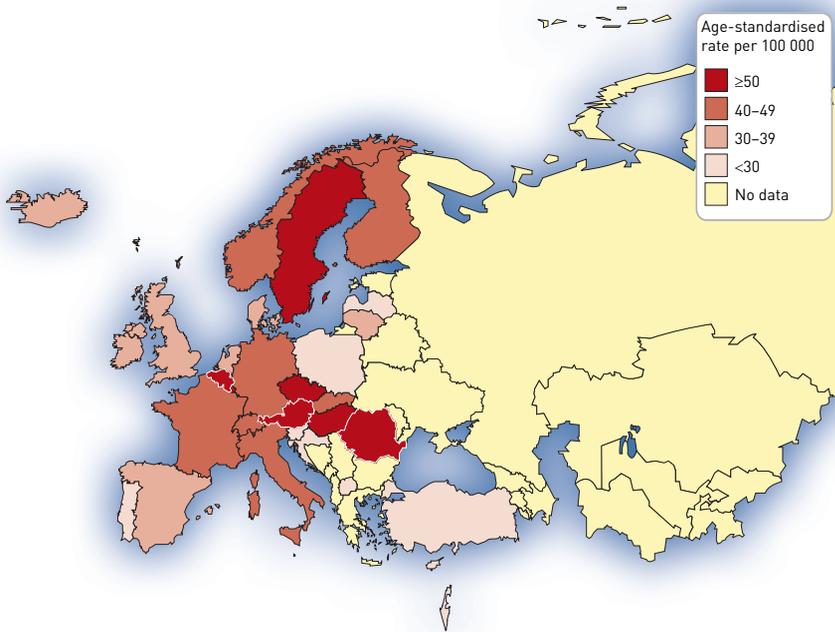
### *Causes/pathogenesis*

PE and deep vein thrombosis are each clinical presentations of venous thromboembolic disease and share the same predisposing factors. PE is usually a consequence of a thrombosis in the veins of the legs or pelvis. Predisposing factors include age, previous venous thromboembolic disease, active malignancy, neurological disease that impairs mobility, medical and surgical events causing prolonged bed rest (such as heart or acute respiratory failure), trauma

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*About 70% of patients with pulmonary embolism have a lower-limb deep vein thrombosis*

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**Figure 1** – Hospital admission rate for pulmonary vascular disease. Data from World Health Organization Hospital Morbidity Database, October 2011 update, and Eurostat, March 2012 update.

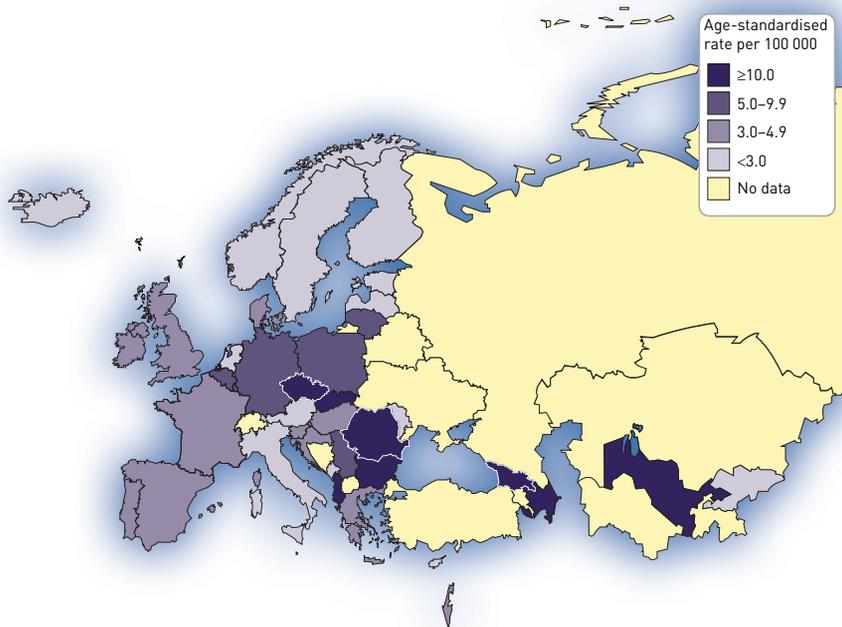
and orthopaedic surgery, congenital or acquired thrombophilia, hormone replacement therapy and oral contraceptive therapy (table 1).

### *Clinical manifestations and consequences*

PE is often difficult to diagnose, and may be missed because of its nonspecific presenting features. Patients may be asymptomatic or present with various signs and symptoms (breathlessness, chest pain, haemoptysis, cough, fever, tachycardia (rapid heart rate), tachypnoea (rapid breathing)). Syncope (fainting), hypotension and shock are signs of severity, indicating reduced haemodynamic reserve. Signs of deep vein thrombosis of the lower or upper limbs may be present.

### *Diagnosis*

When considered in isolation, clinical signs, symptoms and routine tests, such as electrocardiograms, arterial blood gases and chest radiography, do not allow acute



**Figure 2** – Mortality rate for pulmonary vascular disease. Data from World Health Organization World and Europe Mortality Databases, November 2011 update.



PE to be definitively confirmed or excluded, although they do influence the index of suspicion. Despite the limited sensitivity and specificity of individual symptoms, signs and common tests, the combination of these variables, along with clinical judgement or use of a prediction rule, makes it possible to categorise patients with suspected PE in terms of increasing likelihood of PE. A low blood concentration of the fibrin degradation product D-dimer safely excludes PE in patients with a low or moderate clinical probability. Imaging of the proximal deep leg and pelvic veins by ultrasonography may identify a deep vein thrombosis (about 70% of patients with PE have a lower-limb deep vein thrombosis). A normal perfusion lung scan is reliable for excluding PE, while a high-probability ventilation/perfusion lung scan may confirm PE. The value of CT angiography for decision-making in suspected PE has been revolutionised by recent technological improvements and invasive pulmonary angiography is now rarely needed (figure 3). The performance of ventilation/perfusion scanning is poor when there is underlying chronic lung disease; CT angiography is superior in that context. In a patient with suspected PE who is in a critical condition (cardiogenic shock or hypotension), bedside echocardiography is particularly helpful in emergency management decisions (figure 4). In such patients, the absence of echocardiographic signs of right ventricular overload or dysfunction practically excludes PE as the cause of haemodynamic compromise.

Predisposing factor	Patient-related	Setting-related
<b>Strong predisposing factors (risk increased &gt;10-fold)</b>		
Fracture (hip or leg)		✓
Hip or knee replacement		✓
Major general surgery		✓
Major trauma		✓
Spinal cord injury		✓
<b>Moderate predisposing factors (risk increased 2–9-fold)</b>		
Arthroscopic knee surgery		✓
Central venous lines		✓
Chemotherapy		✓
Chronic heart or respiratory failure	✓	
Hormone replacement therapy	✓	
Malignancy	✓	
Oral contraceptive therapy	✓	
Paralytic stroke	✓	
Pregnancy/postpartum		✓
Previous VTE	✓	
Thrombophilia	✓	
<b>Weak predisposing factors (risk increased &lt;2-fold)</b>		
Bed rest >3 days		✓
Immobility due to sitting (e.g. prolonged car or air travel)		✓
Increasing age	✓	
Laparoscopic surgery (e.g. cholecystectomy)		✓
Obesity	✓	
Pregnancy/antepartum	✓	
Varicose veins	✓	

**Table 1** – Predisposing factors for venous thromboembolism (VTE). Reproduced and modified from ANDERSON and SPENCER, 2003, with permission from the publisher.

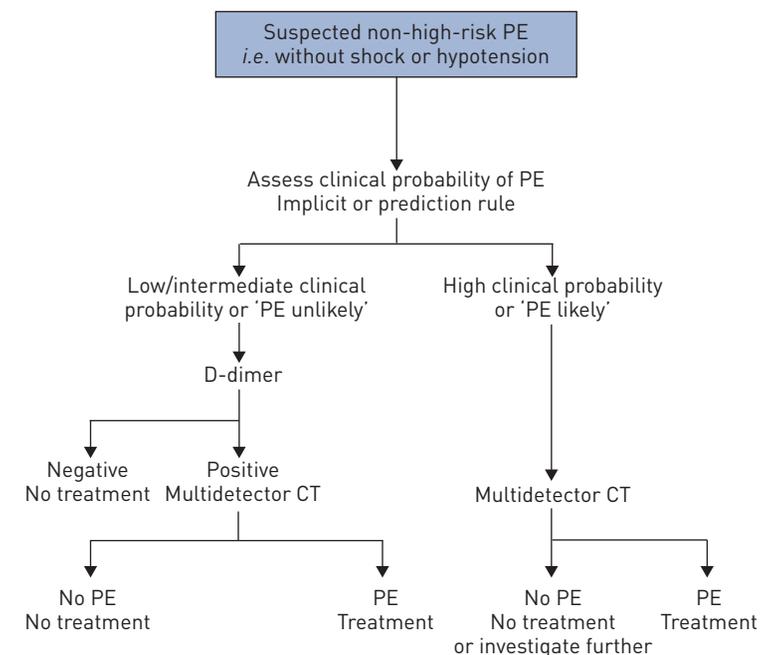
## Prevention

Antithrombotic prophylaxis with low-molecular weight heparin significantly reduces the risk of venous thromboembolic diseases in patients who are at risk. After an acute PE, long-term anticoagulation with anti-vitamin K drugs is necessary. The duration of treatment depends on the clinical circumstances and history of previous thromboembolic disease. In some patients at high risk of recurrent embolism it may be necessary to introduce an inferior vena cava filter.

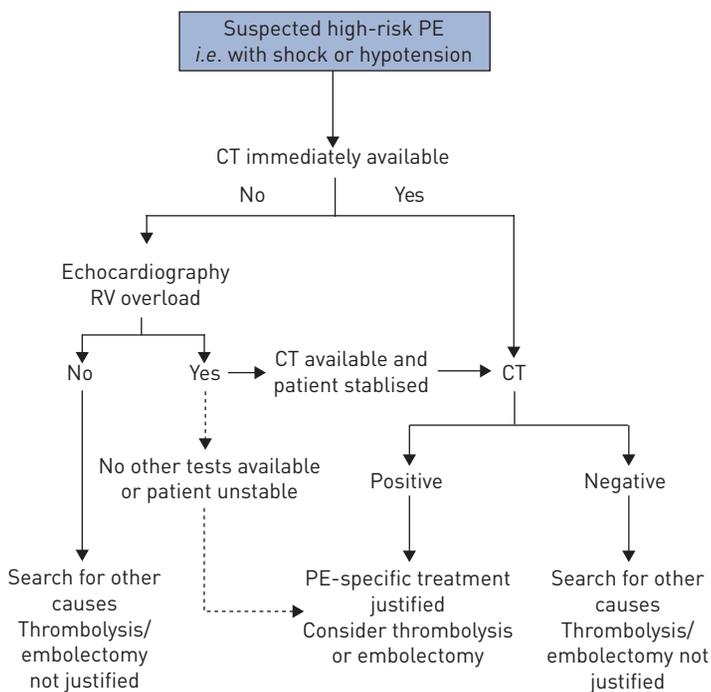
## Management

Initial management includes anticoagulation (unfractionated heparin, low molecular weight heparin or fondaparinux), which should be initiated without delay in patients with confirmed PE and in those with a high or intermediate clinical probability of PE, while

“ It is still widely believed that pulmonary hypertension is a rare condition; this is true for pulmonary arterial hypertension but the global burden as a whole is currently unknown ”



**Figure 3** – Proposed diagnostic algorithm for patients with suspected non-high-risk pulmonary embolism (PE) (i.e. without shock or hypotension). CT: computed tomography. Reproduced and modified from TORVICI *et al.*, 2008, with permission from the publisher.



**Figure 4** – Proposed diagnostic algorithm for patients with suspected high-risk pulmonary embolism (PE) (i.e. presenting with shock or hypotension). CT: computed tomography; RV: right ventricular. Reproduced and modified from TORVICI *et al.*, 2008, with permission from the publisher.

the results of the diagnostic tests are awaited. Supplementary oxygen should be given to hypoxaemic patients. Systemic hypotension or shock should be managed aggressively to prevent progression of right ventricular failure and death. Thrombolytic therapy is the first-line treatment in patients with high-risk PE presenting with cardiogenic shock and/or persistent hypotension. Surgical pulmonary embolectomy is a valuable therapeutic option in patients in whom thrombolysis is absolutely contraindicated or has failed.

## Prognosis

The fatality rate of acute PE is 7–11%. Recurrent episodes are much more likely in individuals who have had a previous PE than after an initial deep vein thrombosis alone (about 60% after PE *versus* 20% after deep vein thrombosis). A small proportion (0.1–4%) of patients will develop chronic thromboembolic PH (CTEPH) after acute PE, even after subclinical PE.

## Future developments

Oral anticoagulants that require neither laboratory monitoring nor dose adjustment are currently in development. Preventive methods should also be implemented more widely.

## Research needs

Better diagnostic methods are still required and the optimal duration of anticoagulation therapy needs to be clarified. The mechanisms of CTEPH are poorly understood and should be identified.

# Pulmonary hypertension

## Introduction

PH is defined as an increase in mean pulmonary arterial pressure (mean PAP) to at least 25 mmHg at rest as assessed by right heart catheterisation. PH is categorised according to measurements of pulmonary capillary wedge pressure (PCWP) as pre-capillary (PCWP at or below 15 mmHg) or post-capillary (PCWP more than 15 mmHg). It is classified into five groups according to pathological, pathophysiological and therapeutic characteristics (table 2). The underlying mechanisms, diagnostic approaches, and prognostic and therapeutic implications are completely different in the different clinical groups.

## Epidemiology

It is still widely believed that PH is a rare condition; this is true for pulmonary arterial hypertension (PAH) (group 1) but the global burden of PH as a whole is currently unknown. Worldwide, its two most common causes are PH complicating the course of left heart disease (group 2) and PH complicating the course of chronic respiratory disease and/or hypoxia (group 3). CTEPH (group 4) complicates the course of 0.1–4% of patients with acute PE. Better awareness of this complication may result in an increase in detected cases. The burden of PH is certainly underestimated, both in developing and developed countries, and further well-designed studies are essential if we are to better understand and manage the disease in populations exposed to various risk factors.

Approximately half of patients with group 1 PH (PAH) have an associated disease (connective tissue diseases such as systemic sclerosis, congenital heart disease,

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- 1 PAH**
    - 1.1 Idiopathic PAH
    - 1.2 Heritable
      - 1.2.1 BMPR2
      - 1.2.2 ALK1, endoglin (with or without hereditary haemorrhagic telangiectasia)
      - 1.2.3 Unknown
    - 1.3 Drug- and toxin-induced
    - 1.4 Associated with (APAH)
      - 1.4.1 Connective tissue diseases
      - 1.4.2 HIV infection
      - 1.4.3 Portal hypertension
      - 1.4.4 Congenital heart disease
      - 1.4.5 Schistosomiasis
      - 1.4.6 Chronic haemolytic anaemia
    - 1.5 Persistent pulmonary hypertension of the newborn
  - 1\* Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis**
  - 2 PH due to left heart diseases**
    - 2.1 Systolic dysfunction
    - 2.2 Diastolic dysfunction
    - 2.3 Valvular disease
  - 3 PH due to lung diseases and/or hypoxia**
    - 3.1 Chronic obstructive pulmonary disease
    - 3.2 Interstitial lung disease
    - 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
    - 3.4 Sleep-disordered breathing
    - 3.5 Alveolar hypoventilation disorders
    - 3.6 Chronic exposure to high altitude
    - 3.7 Developmental abnormalities
  - 4 Chronic thromboembolic pulmonary hypertension**
  - 5 PH with unclear and/or multifactorial mechanisms**
    - 5.1 Haematological disorders: myeloproliferative disorders, splenectomy
    - 5.2 Systemic disorders, sarcoidosis, pulmonary Langerhans' cell histiocytosis, lymphangioliomyomatosis, neurofibromatosis, vasculitis
    - 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
    - 5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis
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**Table 2** – Clinical classification of pulmonary hypertension. PAH: pulmonary arterial hypertension; BMPR2: bone morphogenetic protein receptor, type II; ALK1: activin receptor-like kinase 1 gene; APAH: associated pulmonary arterial hypertension. Reproduced and modified from SIMONNEAU *et al.*, 2009, with permission from the publisher.

portal hypertension and HIV infection), while the other half include idiopathic, heritable and appetite suppressant drug- (anorexigen-) induced PAH. The prevalence of PAH in Europe ranges between 1.5–5.2 cases per 100 000 people, with a predominance in women (female:male ratio 2:1). PAH can develop at any age (the mean age at diagnosis is 50 years). In some developing countries such as Brazil, prevalent diseases like schistosomiasis are associated with a high risk of PAH.

## *Causes/pathogenesis*

PAH results from chronic remodelling of the small pulmonary arteries leading to progressive vascular obstruction. CTEPH results from obstruction of the pulmonary vascular bed by nonresolving thromboemboli. PH due to heart disease is a consequence of chronically elevated post-capillary pressure. PH due to chronic lung diseases and/or hypoxaemia is due to persistent hypoxic pulmonary vasoconstriction and remodelling as well as loss of lung vessels due to underlying pulmonary emphysema or fibrosis.

## *Clinical manifestations and consequences*

PH causes breathlessness, fatigue, reduced exercise capacity, chest pain, haemoptysis and hoarseness (left recurrent laryngeal nerve palsy). In the modern management era, PH is still a progressive and fatal disease, which often presents with signs of right heart failure, such as lower limb oedema, ascites, hypotension, presyncope and syncope.

## *Diagnosis*

PAH is notoriously difficult to recognise clinically. In the early stages of disease, patients are generally asymptomatic or mildly symptomatic. Indeed, initial symptoms are often rather unspectacular, and may lead patients, relatives and physicians to assume that they are simply unfit. Later, the symptoms are often attributed to a more common cardiorespiratory disease. As a result, there is commonly a substantial delay of 2 or more years before diagnosis and initiation of PAH treatment.

Clinical signs, symptoms and routine tests, such as electrocardiogram, arterial blood gases, chest radiography and pulmonary function, do not allow the physician to exclude or confirm PH. Doppler echocardiography is used to evaluate the right heart chambers and to estimate PAP. When PH is suspected, invasive right heart catheterisation is mandatory to confirm PH, define whether it is pre- or post-capillary and evaluate its severity.

Because of the progressive and nonspecific nature of PH symptoms, early PH detection is still a challenge. The implementation of screening programmes targeting high-risk patient groups should help to identify patients earlier. Recent screening programmes (based on Doppler echocardiography followed by right heart catheterisation if PH is suspected) have demonstrated that early diagnosis of PH is possible in patients with predisposing conditions, such as HIV infection, systemic sclerosis and sickle cell disease. Such screening programmes allow diagnosis of patients with markedly lower PAP, compared with those diagnosed in routine clinical practice. Similarly, after an acute episode of PE, persistent symptoms, as well as perfusion scan defects or elevation of PAP, may enable early detection of CTEPH.

## *Prevention*

There is no known method of preventing PAH; however, in patients at risk, early diagnosis allows earlier treatment. Appropriate treatment of chronic heart disease

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may prevent the development of post-capillary PH. Chronic respiratory disease and hypoxaemia should be treated with long-term oxygen therapy or assisted ventilation in order to prevent PH. Treatment and follow-up of acute PE is recommended to limit the risk of CTEPH.

### ***Management***

Basic therapies include oral anticoagulation, diuretics and oxygen, if needed. PAH can be treated with drugs such as prostacyclin derivatives, endothelin receptor antagonists and type 5 phosphodiesterase inhibitors. Severe PAH is a well-recognised indication for lung transplantation. CTEPH can be cured with surgical pulmonary endarterectomy in eligible patients. PH due to chronic left heart disease and PH due to chronic lung disease and/or hypoxia should not be treated with PAH drugs. Treatment of the underlying heart or lung condition is recommended to prevent or treat PH complicating left heart or respiratory disease.

### ***Prognosis***

The natural history of PAH was described in the USA in the 1980s, when a cohort of patients with idiopathic/familial PAH were described and followed for up to 5 years. The study confirmed that PAH had a dismal prognosis, with a median survival of 2.8 years. Recent years have witnessed the approval of three classes of drugs for PAH and survival analyses have been performed in US and European registries. In a mixed cohort of incident and prevalent French PAH patients, 1-, 2-, and 3-year survival rates were 87%, 76%, and 67%, respectively. Better survival was observed in congenital heart disease when compared to idiopathic, familial and anorexigen-associated PAH or connective tissue diseases. In patients with idiopathic, familial and anorexigen-induced PAH, mortality is most closely associated with male sex, right ventricular haemodynamic function and exercise limitation. Thus, PAH remains a progressive, fatal disease even in the modern era of management. CTEPH can sometimes be cured by surgical pulmonary endarterectomy; however, in inoperable patients or if significant PH persists after surgery, the prognosis remains poor. PH due to chronic heart or lung disease usually reflects the severity of the underlying cardiopulmonary condition and this impacts adversely on the patient's prognosis.

### ***Future developments***

There is no cure for PAH and novel therapies are required. Prevention measures or early intervention in patients at risk of PH are needed.

## Research needs

A simple noninvasive PH diagnostic method is eagerly required. Better awareness of PH is essential for earlier diagnosis and management. The exact pathogenesis of PAH and CTEPH need further study in order for new preventative and/or curative tools to be developed for these severe conditions.

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