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Investigation—echocardiography is a good screening tool for the presence of pulmonary hypertension, but right heart catheteriza- tion is needed to confirm the diagnosis and guide treatment. CT pulmonary angiography and high-resolution CT are important to exclude underlying chronic thomboembolic pulmonary hyperten- sion and parenchymal lung disease. In idiopathic pulmonary arterial hypertension a vasodilator study should be undertaken at the time of right heart catheterization to detect the few (5–10%) patients who will have good long-term survival on calcium channel blockers. Management—treatments for pulmonary arterial hypertension include prostanoids, endothelin receptor antagonists, phospho- diesterase inhibitors, and direct activators of soluble guanylyl cyclase, which improve symptoms of breathlessness, exercise toler- ance, quality of life, and probably survival. Chronic thromboembolic pulmonary hypertension is an important diagnosis to make because selected patients with predominantly proximal disease can be cured by pulmonary endarterectomy. Introduction The normal pulmonary circulation, as described in Chapter 16.15.1, is a low-pressure, high-flow system that delivers the output of the right ventricle to the alveolar capillary network during each cardiac cycle for the purposes of gas exchange. Pulmonary hypertension is defined as a sustained elevation of mean pulmonary arterial pressure to more than 25 mm Hg at rest. Many diseases can lead to an elevation of pulmonary arterial pressure. Therefore, the term ‘pulmonary hypertension’ is not a final diagnosis, but a starting point for further investigation. In general terms, the main causes of pulmonary hypertension are (1) a nar- rowing or obstruction of the precapillary pulmonary arteries, (2) an increase in pulmonary venous pressure, (3) a persistent elevation of pulmonary blood flow, (4) chronic thromboembolic disease, or (5) miscellaneous causes. This simplified approach is worth keeping in mind during the assessment of patients found to have pulmonary hypertension, because it has major consequences for prognosis and management. Classification of pulmonary hypertension Table 16.15.2.1 shows the 5th World Symposium on Pulmonary Hypertension (2013) classification of pulmonary hypertension as determined by an international panel of experts. The grouping of causes in this classification takes into account similarities in aeti- ology, pathology, and haemodynamic assessment at right heart cath- eterization. The classification helps to understand the underlying cause of pulmonary hypertension in a given patient and to plan management, hence it is a useful framework to consider the various causes of pulmonary hypertension, described in more detail next. Pulmonary arterial hypertension The term pulmonary ‘arterial’ hypertension (PAH) refers to con- ditions characterized predominantly by a precapillary obstruction to blood flow through the pulmonary vascular bed, characterized hemodynamically by a mean pulmonary arterial pressure of greater than 25 mm Hg, an end-expiratory pulmonary artery wedge pres- sure (PAWP) 15 mm Hg or less, and a pulmonary vascular resist- ance more than 3 Wood units. This elevation of pulmonary vascular resistance increases the driving pressure required to maintain blood flow through the lungs: pulmonary arterial pressure rises to main- tain adequate left ventricular filling. The normal mean pulmonary arterial pressure (c.17 mm Hg) is about one-fifth of the systemic mean blood pressure. In PAH, mean pulmonary arterial pressure may approach systemic levels. The normally thin-walled right ven- tricle struggles to cope with the increasing pressure. At first it under- goes a degree of hypertrophy, which increases its ability to generate higher pressures, but ultimately it begins to fail and cardiac output

 declines. It is the reduction in cardiac output that generates most of the clinical symptoms in patients, with dyspnoea and fatigue being the most common (Fig. 16.15.2.1). The function of the right heart is the main determinant of prognosis in patients with PAH. Epidemiology and aetiology PAH is broadly divided into idiopathic PAH

(previously known as primary pulmonary hypertension), and PAH found with other known associated conditions or triggers. Idiopathic PAH is further divided into familial or sporadic disease, with about 10% of patients with idiopathic PAH having an affected relative. Idiopathic PAH is a rare disorder with an estimated incidence of 1 to 2 per million per year. It is more common in women (female:male sex ratio = 2.3:1), can occur at any age, but most commonly occurs between the ages of 40 and 50 years. PAH that is pathologically indistinguishable from the idiopathic form can occur in a range of associated conditions (Table 16.15.2.1). Of the autoimmune rheumatic diseases, the most common asso- ciation is with systemic sclerosis, where PAH can complicate the clinical course in 15–20% of patients in the absence of interstitial lung disease. Other associated conditions include mixed connective tissue disease and systemic lupus erythematosus, and more rarely rheumatoid arthritis, dermatopolymyositis, and primary Sjögren's syndrome. There is a well-recognized association of PAH with congenital heart disease leading to left-to-right shunts. Overall, the preva- lence of PAH is 15–30%, but varies depending on the nature of the underlying cardiac defect. Portal hypertension, usually associated with cirrhosis, is associated with PAH in less than 5% of patients. There is an unusually high prevalence of PAH (c.0.5%) in patients with HIV infection. Epidemiological studies have confirmed the association of PAH with amphetamine-like diet pills: in the 1970s, increased numbers of patients with PAH were found to have been exposed to Aminorex, and in the 1990s further studies confirmed an association of PAH with appetite-suppressant drugs of the fenfluramine and dexfenfluramine group. An epidemic of PAH also occurred in Spain in the 1980s, following the ingestion of contamin- ated rapeseed oil. Other more rarely associated conditions are listed in Table 16.15.2.1. Table 16.15.2.1 Clinical classification of pulmonary hypertension (NICE 2013) 1 Pulmonary arterial hypertension 1.1 Idiopathic PAH 1.2 Heritable PAH 1.2.1 BMPR2 1.2.2 ALK-1, ENG, SMAD9, KCNK3 1.2.3 Unknown 1.3 Drug and toxin induced 1.4 Associated with: 1.4.1 Connective tissue disease 1.4.2 HIV infection 1.4.3 Portal hypertension 1.4.4 Congenital heart diseases 1.4.5 Schistosomiasis 1′ Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis 1″ Persistent pulmonary hypertension of the newborn (PPHN) 2 Pulmonary hypertension due to left heart disease 2.1 Left ventricular systolic dysfunction 2.2 Left ventricular diastolic dysfunction 2.3 Valvular disease 2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies 3 Pulmonary hypertension 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 lung diseases 4 Chronic thromboembolic pulmonary hypertension (CTEPH) 5 Pulmonary hypertension with unclear multifactorial mechanisms 5.1 Haematologic disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy 5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders 5.4 Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH Main modifications to the previous Dana Point classification are in bold. BMPR2, bone morphogenic protein receptor type II; ENG, endoglin; PAH, pulmonary arterial hypertension. Reprinted from J Am Coll Cardiol, vol. 62 (25 Suppl), Simonneau G, et al., Updated Clinical Classification of Pulmonary Hypertension, pp. D34–41, Copyright 2013, with permission from the American College of Cardiology Foundation. Increasing PVR Preclinical Symptomatic / stable Progressive / declining Cardiac output at rest Pulmonary pressure Cardiac output at peak exercise Fig. 16.15.2.1 Relationship between pulmonary hypertension, right ventricular function, and symptoms in pulmonary hypertension. Pulmonary arterial hypertension (PAH) is characterized by progressively

increasing pulmonary vascular resistance. In the early stages, the disease is asymptomatic and only manifests during exercise or during unusually demanding activities, but over time there is a progressive reduction in cardiac output and increasing pulmonary vascular resistance (PVR), eventually progressing to cardiac failure and death.

16.15.2 Pulmonary hypertension 3697 The classification of PAH includes another rare pulmonary vas- cular disease, pulmonary veno-occlusive disease (PVOD) and pul- monary capillary haemangiomatosis (PCH), which are the same entity. PVOD/PCH is rarer than idiopathic PAH, but its true preva- lence is unknown. Persistent pulmonary hypertension of the new- born is a disorder characterized by a failure of vascular transition from fetal to a neonatal circulation and estimated to affect 0.2% of liveborn term infants. Genetics Familial or heritable PAH is a rare autosomal dominant condi- tion, with reduced penetrance. It is indistinguishable on clinical or pathological grounds from idiopathic PAH. Linkage studies local- ized the gene to the long arm of chromosome 2 (2q33). In 2000, heterozygous germ-line mutations were identified in the BMPR2 gene encoding the bone morphogenetic protein type II receptor, which is a constitutively active serine-threonine kinase that acts as a receptor for bone morphogenetic proteins (BMPs), these being members of the transforming growth factor β (TGFβ) superfamily. Mutations in BMPR-II have now been identified in over 70% of cases of familial PAH, and similar mutations are also found in 15–26% of patients thought to have sporadic or idiopathic disease. Many of these are unexpected examples of familial disease with low penetrance, although de novo mutations have also been reported. BMPR-II mutations have been identified in most of the 13 exons of the BMPR2 gene, most (c.70%) being nonsense or frameshift mutations predicted to cause haploinsufficiency due to nonsense- mediated mRNA decay of the mutant transcript: only the wild-type allele is expressed in these cases, reducing the amount of BMPR- II protein to about 50% of normal. About 30% of the mutations are mis-sense mutations, which cause retention of mutant protein within the endoplasmic reticulum or affect important functional domains of the receptor, such as the ligand-binding domain or the kinase domain. Mutations in BMPR-II have also been found in a small proportion (c.10%) of patients with PAH associated with ap- petite suppressants, and in children with complicated PAH associ- ated with congenital heart disease. Mutations in another TGFβ receptor, ALK-1, have also been re- ported in association with PAH. These are usually found in fam- ilies with hereditary haemorrhagic telangiectasia, but occasionally some family members develop severe PAH. These findings have highlighted the central role of the TGFβ signalling pathway in the pathogenesis of PAH. The BMPR- II/ALK-1 receptor complex on endothelial cells has been found to be the major signalling com- plex for BMPs 9 and 10, providing major mechanistic insights into the pathobiology of PAH. Mutations in other TGFβ-related genes have also been identified in rare cases of heritable PAH, including endoglin, Smad1, Smad9, and BMP9. In addition, mutations in the potassium channel KCNK3 have been reported in rare cases of her- itable PAH. Mutations in the eukaryotic translation initiation factor 2-α kinase 4 (EIF2AK4) were recently identified in families with autosomal recessive PVOD/PCH, accounting for all familial cases and up to 25% of sporadic cases. Pathology Typical morphological appearances include increased musculari zation of small (<200 μm diameter) arteries and thickening or fibrosis of the intima, referred to as concentric intimal fibrosis (Fig. 16.15.2.2). In severe cases, dilatation of small pulmonary ar- terioles is seen and, sometimes, fibrinoid necrosis. In the larger elastic arteries, aneurysmal dilatation and atherosclerotic change may occur, the latter being otherwise extremely unusual in the normotensive pulmonary artery. The term plexogenic arteriopathy is used to describe the presence of plexiform lesions (200–400 μm), which are tangles of capillary-like channels adjacent to small pul- monary arteries. Plexiform

changes are found in some 50% of cases of idiopathic PAH, but also in other causes of severe pulmonary hypertension, such as that due to congenital heart disease. In some cases of idiopathic PAH, there are pathological changes in the pulmonary venous circulation as well as in the arterial. If these dominate the pathology, the diagnosis is likely to be PVOD/PCH, which has some distinct clinical features. The pathological hallmark of PVOD is the extensive and diffuse occlusion of pulmonary veins by intimal fibrous tissue, which may be loose and oedematous or dense and sclerotic. The intimal thickening is confined usually to the smaller veins. Accompanying arterial changes, particularly mus- cular hypertrophy, often coexist. Pulmonary and pleural lymphatics are dilated, and longstanding venous hypertension may lead to oe- dema and fibrosis. These changes often coexist with PCH, charac- terized by the presence of numerous foci of proliferating, congested, thin-walled capillaries, which invade alveolar tissue, as well as the pleural, bronchial, and vascular tissue. Pathogenesis The process of pulmonary vascular remodelling described earlier in- volves proliferation of smooth muscle cells, fibroblasts, and endothe- lial cells in the vessel wall (Fig. 16.15.2.3). Endothelial dysfunction contributes to the pathogenesis of PAH, manifesting as an increase in the release of vasoconstrictors and a deficiency of endogenous vasodilators. Initially, there is an increased tendency towards endo- thelial cell apoptosis, though clonal survival of endothelial cells may lead to the plexiform lesions seen in severe PAH. The increase in medial and adventitial thickness and cell number may result from increased proliferation, but also from migration of precursor cells from within the vessel wall, the surrounding interstitium, and from circulating progenitor cells. At least in some forms of PAH, increased vasoreactivity may precede the structural changes in the vessels. Certain mediators and growth factors have been shown to be in- volved in driving the cellular changes (Fig. 16.15.2.4). Increased cir- culating and local pulmonary vascular expression of endothelin-1 is observed in patients with PAH. As well as being a potent vaso- constrictor, endothelin stimulates smooth muscle and fibroblast proliferation via the endothelin A (ETA) and/or endothelin B (ETB) receptors, the expression of which is increased in small hypertensive pulmonary arteries—ETB receptors on the endothelium mediating endothelin-1 clearance as well as release of nitric oxide and pros- tacyclin. Circulating levels of serotonin (5HT) are also elevated in PAH, and the known association of severe PAH with appetite- suppressant drugs of the fenfluramine/dexfenfluramine group is thought to be partly due to increased serotonergic signalling by metabolites of these drugs. Serotonin stimulates mitogenesis of vas- cular cells via serotonin receptors, including the 5HT2A, 5HT2B, and 5HT1B receptors. In human pulmonary artery smooth muscle cells, a major proliferative pathway involves activation of mitogen-activated

 protein kinases via the serotonin transporter, increased expression of which is found in hypertensive arteries. A relative deficiency of vasodilator pathways is observed in se- vere PAH, leading to an imbalance that enhances the activity of mitogenic and vasoconstrictor pathways. Patients with PAH pro- duce less endothelial-derived prostacyclin. They also exhibit re- duced expression of nitric oxide synthase in their small pulmonary arteries, and consequently less nitric oxide release. Many of these CD31 α-SMA CD31 α-SMA Plexiform lesion Concentric intimal lesion Fig. 16.15.2.2 Representative images of vascular lesions in idiopathic PAH immunostained for the endothelial marker CD31, or the smooth muscle cell marker α-smooth muscle specific actin (α-SMA). In concentric intimal lesions, a single layer of cells adjacent to the vascular lumen stains for CD31 (upper left panel, open arrow), with concentric layers of cells comprising the vascular wall staining for α-SMA (upper right panel). In plexiform lesions, CD31 stains a single layer of cells lining endothelial channels (lower left panel, arrows), with the

supporting stroma staining for α-SMA (lower right panel). From Atkinson C, et al. (2002). Primary pulmonary hypertension is associated with reduced pulmonary vascular expression of type II bone morphogenetic protein receptor. Circulation, 105, 1672–8. endothelium SMCs Endothelial damage elastic laminae disruption Normal Pulmonary hypertension SMC proliferation, ECM, and elastin proliferation SMC migration, neointima neointima adventitial fibroblasts collagen elastic laminae extracellular matrix narrowed lumen Fig. 16.15.2.3 Cellular mechanisms of pulmonary vascular remodelling. ECM, extracellular matrix; SMC, smooth muscle cell. Reproduced from Hughes, J. B. M. From Pulmonary circulation: Basic mechanisms to clinical practice (2001) with permission of Imperial College Press.

16.15.2 Pulmonary hypertension 3699 important vasodilator pathways also exert antiproliferative effects on smooth muscle cells and fibroblasts via production of the cyclic nucleotides cAMP and cGMP. Deficiency of these key vasodilator pathways has provided the rationale for many of the new therapies that have emerged over the past two decades (see ‘Newer agents’). Another important pathway involved in the process of pulmonary vascular remodelling includes loss of potassium channel (Kv1.5 and Kv2.1) expression and function, promoting smooth muscle cell con- traction and survival. Activation of vascular elastases within the vessel media and disruption of the elastic laminae is also a key step in disease pathogenesis. Inflammatory cells may also contribute, espe- cially in PAH associated with autoimmune conditions, accompanied by increased expression of inflammatory cytokines and chemokines in small pulmonary arteries. Pathological studies have identified the presence of throm- bosis in small pulmonary arteries of patients with PAH. It is not clear whether this represents in situ thrombosis as a consequence of the reduced blood flow, or embolic phenomena. Platelet dys- function has also been recognized in PAH, and an increased fre- quency of antiphospholipid antibodies associated with an increased thrombotic risk. The identification of mutations in the BMPR-II receptor has high- lighted the important role of the TGFβ superfamily in the patho- genesis of familial PAH. Most mutations lead to a reduction in a critical signalling pathway, the Smad pathway, downstream of BMP receptors. This, in turn, leads to the failure of BMPs to activate tran- scription of important target genes. In smooth muscle cells, BMPR-II mutation leads to a failure of the normal growth suppressive and proapoptotic effects of bone morphogenetic proteins, favouring excessive pulmonary artery smooth muscle cell proliferation and survival (Fig. 16.15.2.5). In endothelial cells, by contrast, BMPR- II mutation promotes endothelial dysfunction and endothelial cell apoptosis. The combination of endothelial cell dysfunction and smooth muscle cell proliferation within the pulmonary circula- tion favours the development of vascular obliterative lesions and pulmonary hypertension. Clonal expansion of apoptosis-resistant endothelial cells may contribute to the formation of plexiform le- sions. However, this simple model does not explain all of the features of heritable PAH. In particular, it does not explain why disease is confined to the lung circulation, although BMPR-II is most highly expressed in the lung vasculature. In addition, it does not explain why the presence of the mutation is not sufficient on its own to cause disease, with gene penetrance as low as 20% in some families. These observations indicate that additional environmental and/or genetic factors are necessary for disease manifestation. This puta- tive ‘second hit’ may further impact on BMP signalling pathways, leading to a critical reduction in bone morphogenetic signalling via Smad proteins and initiation of the process of pulmonary vascular remodelling. Although mutations in BMPR-II are not generally found in most secondary forms of PAH, it is now becoming clear that dysfunction of the BMPR-II pathway is involved in their pathogenesis. Further research is likely to reveal further clues to the involvement of this important pathway in vascular disease. Clinical

features Symptoms The three main presenting symptoms are dyspnoea, chest pain, and syncope. The severity of symptoms is related to prognosis. A modified New York Heart Association (NYHA) score is a useful way to assess symptom severity and follow response to treatment (Box 16.15.2.1). Unexplained breathlessness on exertion should always raise the possibility of PAH, particularly in the setting of conditions known to be associated with pulmonary hypertension (Table 16.15.2.1). The condition may have an insidious onset: frequently, there is a delay of years between the onset of first symptoms and diagnosis. Syncope is an ominous sign, usually reflecting severe right ventricular dysfunc- tion. Other symptoms include lassitude, abdominal swelling from ascites, and ankle swelling. Small haemoptyses may occur at later stages. Clinical signs Tachypnoea may be present, even at rest. Peripheral cyanosis is common due to a low cardiac output. Central cyanosis occurs later as pulmonary gas exchange deteriorates or right-to-left shunting oc- curs through a patent foramen ovale. The jugular venous pulse may be elevated with a prominent ‘a’ wave, reflecting the increased force Endothelin-1 Angiotensin II serotonin NO PGI2 ANP Adrenomedullin Vasoconstrictors = vasodilators Normal Endothelin-1 Angiotensin II serotonin NO PGI2 Vasoconstrictors > vasodilators Pulmonary hypertension ANP Adrenomedullin Minimal resting tone Increased tone Vascular remodelling Fig. 16.15.2.4 An imbalance of pulmonary vascular vasodilators and vasoconstrictors contributes to the vascular constriction and remodelling in pulmonary hypertension. ANP, atrial natriuretic peptide; NO, nitric oxide; PGI2, prostacyclin.

section 16 Cardiovascular disorders 3700 of atrial contraction, or—if tricuspid regurgitation is present—there may be a large ‘V’ wave. There may be a right ventricular heave and a pulsatile liver. On auscultation, forceful closure of the pulmonary valve leads to an accentuated pulmonary arterial component of the second heart sound. There are often a third and fourth right heart sound. The murmurs of tricuspid regurgitation (systolic) or pul- monary regurgitation (diastolic) may be heard. Jaundice, ascites, and peripheral oedema may be present at advanced stages of the disease. Differential diagnosis If the symptoms and clinical signs suggest pulmonary hypertension, the differential diagnosis should be considered with reference to the classification in Table 16.15.2.1. Most importantly, the presence of left heart disease, parenchymal lung disease, or congenital heart dis- ease should be excluded. Pulmonary hypertension due to chronic thromboembolic disease is important to detect because specific sur- gical treatment is available. Idiopathic PAH remains a diagnosis of exclusion. Clinical investigation The investigation of a patient with suspected pulmonary hyper- tension involves (1) the exclusion of other underlying causes and (2) an assessment of severity of pulmonary hypertension and right heart failure for prognosis and treatment. The investigations that are useful in identifying the aetiology of newly diagnosed, unexplained pulmonary hypertension are listed in Box 16.15.2.2. Blood tests A thrombophilia screen, including antithrombin III, proteins C and S, factor V Leiden, anticardiolipin antibodies, and lupus anticoagu- lant should be performed, and may reveal clotting abnormalities predisposing to chronic thromboembolic pulmonary hypertension (CTEPH). Thyroid function should be checked since both hypo- and especially hyperthyroidism are commonly reported associations. An autoantibody screen should be performed to exclude underlying autoimmune rheumatic or vasculitic disease: positive antinuclear antibodies (ANA) can be found in 30–40% of patients with idio- pathic PAH, but a positive test for antineutrophil cytoplasmic anti- bodies (ANCA) would be uncommon. Since there is an increased incidence of unexplained pulmonary hypertension in HIV-positive patients, this diagnosis should always be considered. MUTANT WILD TYPE cell membrane R - smad Normal pulmonary artery Primary pulmonary hypertension Co-smad P P P P R-smad BMP–2, –4, –7 GDF–5, –6 heterodimeric complex BMPR-II Type 1 receptor cell proliferation clonal expansion

growth inhibition cell differentiation DNA binding partner gene transcription Fig. 16.15.2.5 The potential role of mutations in the bone morphogenetic protein type II receptor (BMPR-II) in familial PAH. The wild-type receptor signals in response to ligands by activating receptor-regulated Smad proteins (R-Smads), which dimerize with common partner Smads (Co-Smads) to regulate gene expression in the vascular cell. Mutation in BMPR-II disrupts Smad signalling and leads to abnormal vascular cell proliferation. BMP, bone morphogenetic protein; GDF, growth differentiation factors. By Hughes, J. B. M. From Pulmonary circulation: Basic mechanisms to clinical practice (2001). With permission of Imperial College Press. Box 16.15.2.1 Modified New York Heart Association functional classification of pulmonary hypertension • Class I—pulmonary hypertension without resultant limitation of phys- ical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain, or near syncope • Class II—pulmonary hypertension resulting in slight limitation of phys- ical activity. The patient is comfortable at rest. Ordinary physical ac- tivity causes undue dyspnoea or fatigue, chest pain, or near syncope • Class III—pulmonary hypertension resulting in marked limitation of physical activity. The patient is comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain, or near syncope • Class IV—Pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnoea and/or fatigue may be present at rest. Discomfort is increased by any physical activity

16.15.2 Pulmonary hypertension 3701 Imaging The plain chest radiograph shows enlargement of the proximal pul- monary arteries, which may be dramatic, with peripheral pruning of the pulmonary vascular pattern, giving rise to increased peripheral radiolucency. If heart failure is present the heart may be enlarged, with particular enlargement of the right atrium (Fig. 16.15.2.6). The chest radiograph may also give clues to underlying diagnoses such as interstitial lung disease. Spiral contrast-enhanced CT will detect proximal pulmonary arterial obstruction suggestive of acute or chronic thrombo- embolic disease (Fig. 16.15.2.7). A pattern of mosaic perfusion of the lung parenchyma is also a feature of CTEPH, and may be the only sign in predominantly distal disease (Fig. 16.15.2.8). A high- resolution CT scan will pick up unsuspected parenchymal abnor- malities, such as fibrosis. CT scanning is also useful to indicate more uncommon forms of PAH, such as PVOD, when there may be a degree of mediastinal lymphadenopathy and septal lines in the lung periphery, presumably indicating lymphatic and venous obstruction (Fig. 16.15.2.9). On ventilation–perfusion lung scanning, the pattern of ventila- tion is usually normal in idiopathic PAH, and uneven ventilation Box 16.15.2.2 Investigation of the patient with suspected idiopathic pulmonary hypertension Blood tests • Full blood count/film/differential • Hb electrophoresis • Urea and electrolytes • Liver function including γ-GT • Thyroid function • Thrombophilia screen: − Antithrombin III − Protein C − Protein S − Factor V Leiden − Anticardiolipin antibody − Lupus anticoagulant • CMV DEAFF • Autoantibodies: − RhF − ANA − ENAs − Anti-dsDNA − Anticardiolipin IgG and IgM − Anti-sm/anti-SCL/anti-SS − Complement C3, C4, CH50 − ANCA • Serum angiotensin converting enzyme • Hepatitis screen • HIV test Imaging • Chest radiograph • Ventilation–perfusion lung scan • High-resolution and spiral CT • Pulmonary artery angiography Lung function • Pulmonary function tests • Exercise tests with saturation monitoring • Arterial blood gases on air Cardiac function • ECG • Echocardiogram • Diagnostic cardiac catheterization Miscellaneous • Urine microscopy • Abdominal ultrasound—cirrhosis Fig. 16.15.2.6 Chest radiograph demonstrating cardiomegaly with dilated right heart chambers and dilatation of the proximal pulmonary arteries in a patient with PAH secondary to an atrial septal defect. Courtesy of Dr Nick Screaton, Addenbrooke’s Hospital. Fig. 16.15.2.7 Image from a CT pulmonary angiogram at the level of the

right main pulmonary artery demonstrating dilatation of the main pulmonary artery (PA) with laminated thrombus in the distal right pulmonary artery (arrow) in keeping with proximal CTEPH. Courtesy of Dr Nick Screaton, Addenbrooke's Hospital.

section 16 Cardiovascular disorders 3702 should suggest underlying lung disease. The pattern of perfusion is also virtually normal, although small patchy perfusion defects may be present. This is in contrast to the appearance in CTEPH when segmental or larger perfusion defects persist, often indistinguishable from the pattern of acute pulmonary embolism (Fig. 16.15.2.10). Pulmonary artery angiography is really only required if the diagnosis is likely to be CTEPH, in which situation angiography will provide precise anatomical information regarding the location of vascular obstruction, indicated by abrupt cut-off of vessels or intravascular webs, that may be of great use if surgical endarterec- tomy is being contemplated. However, CT pulmonary angiography or MR angiography may be employed in place of conventional angiography. The main contribution of MRI is in the assessment of patients with suspected intracardiac shunts or with anomalous vascular anatomy (e.g. if a shunt is suspected on the basis of right heart catheterization but cannot be demonstrated by echocardiography). MRI can also provide further pulmonary angiographic images. Pulmonary function tests The typical pattern for standard pulmonary function test for dis- ease confined to the pulmonary circulation is to find normal lung volumes; normal forced expiratory volume in 1 s (FEV1)/vital cap- acity (VC) ratio (>0.75), indicating no airflow obstruction; and low transfer factor (diffusing capacity, TLco), and low transfer coefficient (Kco). The low diffusing capacity probably results from a combination of a reduced cardiac output and disease affecting the small arteri- oles, thereby reducing local perfusion. If the Kco is less than 50% predicted with normal spirometry, a diagnosis of PVOD/PCH should be suspected. Additional findings in the pulmonary func- tion tests—such as marked airflow obstruction (e.g. severe chronic obstructive pulmonary disease) or a restrictive defect (e.g. pul- monary fibrosis)—would indicate the presence of an underlying cause for the pulmonary hypertension. However, subtle changes in lung volumes and mild airflow obstruction have been reported in a few patients with PAH. In some groups of patients at high risk of developing PAH (e.g. in scleroderma), the low transfer coefficient can be monitored at intervals, with breathlessness accompanied by a fall in the low transfer coefficient sometimes being the first sign of this complication. Exercise testing Significant PAH is always associated with a reduced exercise cap- acity, one of the most useful tests of this being the 6 min walk test, with monitoring of heart rate and oxygen saturation. This can readily be repeated to assess patients over time and as a measure of response to treatment. A normal distance is more than 500 m, with a low 6 min walk predictive of a poor survival. Full cardiopulmonary exercise testing is technically more demanding to perform and is only recommended if the diagnosis is in doubt (e.g. if there was a need to document cardiovascular limitation on exercise). Peak oxygen uptake on exercise is low and the anaerobic threshold is reduced to about 40% of normal. There is excessive ventilation for a given degree of oxygen consumption or CO_2 output, even at rest. There is no ventilatory impairment when underlying lung disease is absent. There is often a pronounced tachycardia at submaximal exercise, and usually arterial oxygen desaturation. ECG In symptomatic PAH, the ECG is abnormal in 80 to 90% of cases, but it has inadequate sensitivity (55%) and specificity (70%) as a Fig. 16.15.2.8 Coronal multiplanar reconstruction demonstrating extensive mosaic perfusion in both lungs in a patient with CTEPH. Courtesy of Dr Nick Screaton, Addenbrooke's Hospital. Fig. 16.15.2.9 Transverse CT image through the lower zones demonstrating heterogeneous attenuation of the lung parenchyma, centrilobular ground-glass opacities, and smooth thickening of the interlobular septa in a patient with pathologically proven

veno- occlusive disease. Courtesy of Dr Nick Screaton, Addenbrooke’s Hospital.

16.15.2 Pulmonary hypertension 3703 screening tool for detecting pulmonary hypertension. The typical appearances are right-axis deviation (more than + 120°) in the limb leads, and a dominant R wave and T wave inversion in the right pre- cordial leads, accompanied by a dominant S wave in the left precor-

dial leads, suggesting right ventricular hypertrophy (Fig. 16.15.2.11). Tall, peaked P waves in the right precordial and inferior leads denote right atrial enlargement. Right bundle branch block is common. Echocardiography Echocardiography remains the best screening test for significant pulmonary hypertension. It detects the presence, and direction, of

intracardiac shunts. Usually this is possible using conventional transthoracic techniques, but if visualization is poor or a small shunt is still suspected, then transoesophageal echocardiography may be necessary. In addition, the left ventricle can be assessed to determine whether there is a

contribution from left ventricular systolic or diastolic dysfunction to elevated pulmonary arterial pressure. The function of the right side of the heart can also be as- sessed qualitatively and quantitatively. Atrial and ventricular dimen- sions and wall thickness can be measured, and paradoxical bowing of the

intraventricular septum into the left ventricular cavity may be seen during systole as a consequence of greatly elevated right- sided pressures. Continuous-wave Doppler echocardiography is used to measure high-flow velocities across cardiac valves, one of the most commonly derived indices in the right heart being the pul-monary artery systolic

pressure estimated by Doppler echocardiog- raphy from measurement of the velocity of the tricuspid regurgitant jet (c.80% of patients with PAH and 60% of normal subjects, have measurable tricuspid regurgitation). The maximum flow velocity (v) of the regurgitant jet is measured and inserted into the modi- fied Bernoulli

equation for convective acceleration pressure change, giving an estimate of right ventricular systolic pressure (RVSP): RVSP v RAP, 2

- 4 where RAP is right atrial pressure, which can be estimated clinically from the height of the jugular venous pressure. In the absence of pul- monary valve stenosis, the right ventricular systolic pressure is equal to the pulmonary artery systolic pressure (PASP). There is a reason- able correlation between Doppler estimates of PASP and catheter measurements. Newer echocardiographic techniques such as three- dimensional echo and tissue Doppler are being evaluated. Right heart catheterization Right heart catheterization remains the best technique for con- firming the diagnosis of pulmonary hypertension and for providing important prognostic information. An elevated mean pulmonary arterial pressure of greater than 25 mm Hg at rest is the accepted definition. In patients with idiopathic PAH the mean pulmonary arterial pressure may exceed 60 mm Hg. The pulmonary capillary wedge pressure (PCWP) can also be determined at catheterization, which is an approximation of left atrial pressure. An elevated PCWP (>15 mm Hg) generally indicates left heart disease. Measurement of PCWP is often unreliable in the presence of CTEPH. Sampling of venous blood oxygen saturation as the catheter passes down from the right atrium to right ventricle may detect a sudden ‘step-up’ in oxygenation, which would indicate the presence of a left-to-right shunt. Cardiac output can be determined by thermodilution or the Fick method. Indicators of right heart failure, and hence poorer prognosis, in- clude (1) an elevated right atrial pressure (>10 mm Hg); (2) an ele- vated right ventricular end-diastolic pressure (>10 mm Hg); (3) a reduced mixed venous oxygen saturation (Svo2 <63%); and (4) re- duced cardiac output (<2.5 litre/min). Vasoreactivity studies A subgroup (5–10%) of patients with idiopathic and anorexigen- associated PAH demonstrate a marked reduction in pulmonary vascular resistance following the administration of a vasodilator. Perfusion Ventilation Fig. 16.15.2.10 Perfusion scintigram demonstrates multiple perfusion defects in a patient with CTEPH. Courtesy of Dr Nick Screaton, Addenbrooke’s Hospital.

section 16 Cardiovascular disorders 3704 These patients are the only group that respond favourably to long- term treatment with vasodilator therapy in the form of calcium channel blockers (see ‘Disease-targeted therapies’), and are thus an important group to identify. Vasodilator studies are undertaken at the time of right heart catheterization, the preferred agent being in- haled nitric oxide, or an intravenous infusion of prostacyclin or ad- enosine. A positive response is defined as a fall in mean pulmonary arterial pressure of at least 10 mm Hg to below 40 mm Hg, accom- panied by an increase or no change in cardiac output. Conventional treatments All patients with suspected severe PAH are best referred to a spe- cialist centre for initial assessment and treatment.
A multidiscip- linary team approach to planning treatment is preferred, with input from respiratory physicians and cardiologists, transplant physicians, and cardiothoracic surgeons, radiologists, specialist nurses, and pal- liative care specialists. Assisting patients to adapt to the uncertainty associated with chronic, life-shortening disease is essential if they are to successfully adjust to the demands of their illness and its treat- ment. The overall aims are to improve symptoms and quality of life, increase exercise capacity, and improve prognosis. Supportive medical therapy Patients with right heart failure and fluid retention may require di- uretics. Decreasing cardiac preload with diuretics is often enough to alleviate episodes of right heart failure. However, caution should be exercised because faced with a reduction in vascular filling pres- sures, patients with severe PAH will not be able to increase cardiac output effectively, which may result in systemic hypotension and syncope. Antiarrhythmics may be required for sustained or paroxysmal atrial fibrillation. Patients with severe PAH are prone to this com- plication because of stretching of the overloaded right atrium, and atrial fibrillation can significantly compromise the already reduced cardiac output in patients with PAH, hence it should be treated ag- gressively. Rate control with digoxin is possible, but if not contra- indicated, pharmacological cardioversion with amiodarone is preferable. Electrophysiological mapping of arrhythmias and ab- lation of arrhythmogenic pathways may be indicated in selected patients. Anticoagulation Warfarin therapy to maintain the international normalized ratio (INR) between 2 and 3 is recommended in all patients with idio- pathic and familial PAH. Two retrospective studies and one small prospective study have demonstrated a survival benefit of anticoagulation, almost doubling survival rate in idiopathic PAH over a 3-year period. The consensus is that patients with PAH as- sociated with autoimmune rheumatic tissue disease should also receive warfarin, unless contraindicated. The risk–benefit ratio of anticoagulation in other forms of PAH is undetermined. Oxygen therapy Oxygen therapy is indicated for symptomatic relief of breath- lessness. There are no published trials of the benefit of long-term oxygen therapy in hypoxaemic patients with PAH. Nocturnal Fig. 16.15.2.11 Twelve-lead ECG from a patient with idiopathic PAH showing a rightward axis, p pulmonale, poor R wave progression, and ST segment changes indicative of right ventricular strain in the anterior chest leads.

16.15.2 Pulmonary hypertension 3705 oxygen has been shown to be of no benefit in Eisenmenger’s syn- drome. Ambulatory oxygen may be beneficial if there is evidence of correctable desaturation of 4% and to less than 90% during a 6 min walk test. Consideration should be given to in-flight supplemental oxygen for air travel. Disease-targeted therapies Calcium channel blockers Patients with idiopathic PAH and a documented acute vasodilator response at cardiac catheterization, as defined just now, should be offered long-term treatment with a calcium channel blocker. This is associated with very significant improvement in symptoms and prognosis in this subset of patients, although only 50% of those who respond in the cardiac catheterization laboratory will maintain a long-term response. Long-term responders account for less than 5% of idiopathic PAH patients. Calcium channel blockers should be avoided in any patient with significant signs of right ventricular

failure, or until this is controlled, because of their negative inotropic effects. For this reason, and the risk of systemic hypotension, calcium channel blockers should not be prescribed without confirmation of a vasodilator response at cardiac catheterization: indiscriminate prescribing will lead to increased mortality in the PAH population. Treatment should be started in hospital, using diltiazem, amlodipine, or nifedipine, and carefully titrated against systemic blood pressure. The aim is to in- crease the dose to the maximum tolerated. Targeted PAH therapy In recent years, remarkable advances have been made in the avail- ability of therapeutic agents for PAH. In the early 1980s, carefully timed heart–lung transplantation was the only option known to im- prove prognosis. We now have a range of pharmacological agents available and licensed for treatment in this condition, based on data from clinical trials that have almost exclusively recruited patients with idiopathic and anorexigen-associated PAH, although often including a subset of patients with PAH associated with systemic sclerosis. The drugs are used to reduce pulmonary vascular resist- ance and improve cardiac output: they all improve exercise perform- ance, and some prolong life. Fig. 16.15.2.12 presents an algorithm summarizing the pharmacological approach to treating PAH, based on current recommendations. Prostanoids Epoprostenol was the first treatment to be developed for the treat- ment of PAH during the 1980s. This has minimal oral bioavailability, has a half-life in the circulation of less than 2 min, and thus must be given by continuous intravenous infusion. It produces acute haemodynamic effects in some patients; most experience a fall in pulmonary vascular resistance with long-term use even in the ab- sence of acute improvements. These observations support the view that long-term administration of these agents may reverse some of the vascular remodelling, as well as having a vasodilator effect. Epoprostenol has been shown to improve haemodynamics, exercise PDES inhibitors Continue calcium- channel blockers Atrial septostomy or lung transplantation Intravenous epoprostenol or endothelin-receptor antagonist or prostacyclin analogues Endothelin-receptor antagonist or prostacyclin analogues or intravenous epoprostenol Class IV Class III Pulmonary arterial hypertension (NYHA functional class III or IV) Conventional therapy (oral anticoagulant ± diuretics ± oxygen) Acute vasodilator response Oral calcium-channel blockers Sustained response No improvement or deterioration YES NO NO YES Fig. 16.15.2.12 Algorithm showing the evidence-based approach to treatment in patients with PAH. Reproduced from Humbert M, Sitbon O, Simonneau G (2004). Treatment of pulmonary arterial hypertension. N Engl J Med, 351, 1425–36.

 tolerance, quality of life, and survival in patients in NYHA class III and IV. The dose may have to be increased on a regular basis because of tachyphylaxis, and side effects are usually experienced when starting epoprostenol or when escalating the dose, including jaw pain, cutaneous flushing, nausea, and diarrhoea, as well as myalgias. Acute withdrawal of epoprostenol (e.g. if the infusion pump fails, can causes severe rebound pulmonary hypertension that can be fatal). Recurrent sepsis due to line infection can also be problematic. Although epoprostenol remains a proven therapy in PAH, the complexity of its administration and the availability of newer oral agents mean that its use tends to be reserved for patients with se- vere haemodynamic compromise. Stable analogues of prostacyclin have been developed with longer half-lives and improved bioavail- ability: iloprost can be given by the intravenous or inhalation route; treprostinil can be given subcutaneously, intravenously, or by inhal- ation, and is approved for use in patients in NYHA class II, III, and IV. Beraprost is an orally available prostacyclin analogue, although the dose may be limited by gastrointestinal side effects. Selexipag is an oral selective prostacyclin receptor agonist that is structurally distinct from prostacyclin. Endothelin

receptor antagonists Bosentan, an orally active dual-selective ETA/ETB receptor antag- onist, has been shown to improve exercise capacity, functional class, haemodynamics, echocardiographic, and Doppler variables, and time to clinical worsening in idiopathic PAH. Its most significant side effect is elevation of the hepatic transaminases, which is usu- ally reversible on stopping the drug. Sitaxentan and ambrisentan are newer ETA selective agents with similar efficacy to bosentan, though sitaxsentan was recently withdrawn due to reports of irre- versible hepatotoxicity. All patients on these agents require monthly monitoring of liver function tests. The United States Food and Drug Authority (FDA) recently approved a new dual-selective ET receptor antagonist, macitentan, for PAH. Phosphodiesterase inhibitors Sildenafil is an orally active selective inhibitor of cGMP- phosphodiesterase type 5. It acts by inhibiting the breakdown of cGMP, with vasorelaxant and antiproliferative effects in pulmonary vascular smooth muscle. Sildenafil improves exercise tolerance and pulmonary haemodynamics in short-term studies in PAH. Tadalafil is a once daily PDE5 antagonist licensed for use in PAH. Stimulators of soluble guanylate cyclase Riociguat, a novel stimulator of soluble guanylate cyclase, was re- cently approved by the FDA for use in patients with PAH and in patients with chronic thromboembolic pulmonary hypertension. Hypotension may limit dosing and the drug should be avoided in combination with a PDE5 inhibitor. Combination therapy There is considerable theoretical and experimental evidence to sup- port the use of combinations of the aforementioned disease-targeted therapies in PAH, which is a progressive disease. Most patients even- tually deteriorate on monotherapy, and the addition of further agents has been shown to provide clinical benefit. Indeed, early introduc- tion of initial combination therapy (ambrisentan and tadalafil) has been shown to improve outcomes in a clinical trial. Other strategies Atrial septostomy Atrial septostomy involves creating a right-to-left shunt between the atria, the preferred technique being percutaneous graded balloon dilatation. The rationale for this procedure is that patients with PAH and a patent foramen ovale have improved survival. Creating the shunt reduces right ventricular preload, which relieves the failing right ventricle and can increase cardiac output and improve exercise capacity. The increase in cardiac output is at the expense of a re- duction in systemic arterial oxygen saturation, but systemic oxygen delivery is usually improved. The procedure is usually reserved for patients who are failing on maximal medical therapy or as a bridge to transplantation for PAH patients in NYHA class IV. Patient se- lection is vital. A high right atrial pressure (>20 mm Hg) and low arterial oxygen saturation (<80% on air) prior to septostomy are as- sociated with a high mortality related to the procedure, although impact on survival has not been formally assessed. Transplantation Transplantation of the lungs or heart and lungs developed as a treat- ment for end-stage PAH during the 1980s. The advent of modern, targeted therapies has reduced the number of patients referred for transplantation, but the long-term outcome of patients who remain in NYHA functional class III or IV remains poor. Lung or heart– lung transplantation therefore remains an important mode of treat- ment for patients failing medical therapy. Patients with PVOD/PCH have a particularly poor outlook; they respond poorly to available medical therapies and should be referred early for transplantation assessment. In general, patients presenting with NHYA class IV symptoms should be referred for transplantation assessment at the time of presentation, because their prognosis is poor. Additional indica- tors of poor prognosis include (1) a 6 min walking distance less than 332 m; (2) peak oxygen consumption less than 10.4 ml/min per kg; (3) cardiac index less than 2 litre/min per m2; (4) right atrial pres- sure greater than 20 mm Hg; (5) mean pulmonary arterial pressure greater than 55 mm Hg; (6) mixed venous oxygen saturation of less than 63%. Those with significant improvement after 3 months of medical therapy can be removed or suspended from listing for trans- plant. The choice of procedure varies between centres, but single lung, bilateral lung, and heart–lung transplantation are used in pa- tients with

PAH. International registry figures show that the 1-year mortality post-transplantation is highest in patients with idiopathic PAH, compared with any other indications, with median survival post-transplantation between 4 and 5 years. Prognosis The prognosis of PAH varies depending on the underlying associ- ation or cause. Prognosis is most closely linked to indices of car- diac function, especially cardiac index. Historical data in the period prior to the availability of modern, targeted therapies suggest an expected median survival for idiopathic pulmonary arterial hyper- tension between 2.5 and 4 years, and a 3-year survival of about 60%. The prognosis is worse for patients with underlying systemic scler- osis, autoimmune rheumatic disease, HIV disease, and anorexigen-associated PAH, and that for patients surviving to adulthood with PAH associated with a congenital intracardiac defect is substantially

16.15.2 Pulmonary hypertension 3707 better than patients with idiopathic disease. At least in patients with idiopathic PAH, targeted therapies seem to improve survival to some extent, though definitive studies are awaited. Women with se- vere PAH should be advised that pregnancy carries a very high mor- tality because of the associated increased burden on the right heart. Other conditions associated with pulmonary hypertension One of the commonest causes of pulmonary hypertension is that occurring as a complication of chronic lung disease including interstitial lung disease and chronic obstructive pulmonary dis- ease (COPD). In COPD, pulmonary hypertension is due to a combination of hypoxic pulmonary vasoconstriction, hypoxia- driven pulmonary vascular remodelling, and a reduction in capil- lary cross-sectional area in emphysema. Lung hyperinflation and polycythaemia may also contribute. The prevalence of pulmonary hypertension in patients with severe COPD may be as high as 50%, but the average mean pulmonary arterial pressure is of the order of 25 mm Hg and progresses slowly (<1 mm Hg/year). It is likely that ventilatory impairment due to obstructed airways contributes most to the exercise limitation in these patients. Nevertheless, there are relatively unusual cases of COPD in which the pulmonary hyper- tension dominates. Patients with combined pulmonary fibrosis and emphysema are particularly prone to develop severe pulmonary hypertension. These patients are often profoundly hypoxic, have emphysema with variable degrees of fibrosis on CT scanning, and demonstrate a low DLCO. Severe pulmonary hypertension in the setting of chronic lung disease is defined as a mean pulmonary ar- terial pressure of 35 mm Hg or more, or 25 mm Hg or more with low cardiac index (<2.0 litres min−1 m−2). In these patients targeted therapy for PAH may be indicated in addition to optimization of their lung disease medication. Pulmonary hypertension is detectable in some 5% of patients with sarcoidosis. This may develop in the context of end-stage pulmonary fibrosis, but may also present as an isolated sarcoid vasculopathy in patients with relatively little parenchymal lung involvement. A falling DLCO in the face of preserved lung volumes may be the first clue to this in a sarcoid patient with worsening dyspnoea. In patients with vasculopathy, there may be a marked response to immunosup- pression with prednisolone, which is worth trying before embarking on targeted PAH therapy. It is often stated that the commonest worldwide cause of pul- monary hypertension is schistosomiasis. When one considers how many patients are infected with schistosomiasis, this may be true, but true prevalence figures are hard to come by. The clinical pic-ture in schistosomiasis is usually dominated by the effect on the urinary tract (Schistosoma haematobium) or liver (S. mansoni and S. japonica). Pulmonary hypertension is thought to be due to granu- lomata in or adjacent to pulmonary arterioles caused by the reaction to the presence of schistosome eggs. Likely future developments The next few years will see further important advances in our under- standing of the pathobiology of PAH. The application of whole genome and whole exome sequencing at scale will allow greater understanding of the genetic contribution to

PAH. Intensive research into the TGFβ/BMP signalling pathway in pulmonary vascular cells and tissues are elucidating the mechanisms by which mutation in the BMPR2 gene leads to PAH. This knowledge is allowing the de- velopment of experimental therapies aimed at prevention, arrest, or reversal of the process of pulmonary vascular remodelling in PAH. Trials are already exploring the impact of growth factor inhibition and anti-inflammatory strategies in PAH, and the next few years is likely to see more of these experimental studies using drugs initially developed for use in oncology and autoimmune diseases. Cell-based therapy using circulating progenitor cells is also being evaluated. New pathways are being targeted which impact on ion channels, cell survival, cell metabolism and endothelial function, including activators of the peroxisome proliferator activated receptors. Novel biomarkers of disease activity and progression are being identified. Imaging modalities using the latest advances in echocardiography, CT scanning, and MRI are being developed to maximize the infor- mation derived from these techniques, which may then replace in- vasive right heart catheterization. Chronic thromboembolic pulmonary hypertension (CTEPH) Pathogenesis CTEPH occurs when a clot fails to resolve completely after an acute pulmonary embolic event. The rate of resolution of clots after acute pulmonary embolism varies and is longer in patients with pre- existing cardiopulmonary disease, but normal perfusion should be restored by 4 to 6 weeks after an acute event. To some extent, the rate of resolution depends on the initial clot burden or the size of the acute pulmonary embolism. If the clot fails to resolve, it be- comes organized before it can be completely fibrinolysed, and this organized thrombus is incorporated into the wall of the pulmonary artery, becomes covered by endothelial cells, and forms a false in- tima. The organized material occludes the vascular lumen, which increases pulmonary vascular resistance and leads to pulmonary hypertension. The true prevalence of CTEPH is hard to ascertain, because it is not usually sought in patients who are recovering from acute pul- monary embolism, but it is almost certainly underdiagnosed. One well-designed study found that 4% of patients with a history of acute pulmonary embolism had a persistent elevation of pulmonary ar- terial pressure after 2 years. Those with a higher initial clot burden (massive pulmonary embolism) are more likely to develop CTEPH than those with minor pulmonary embolism. The more widespread use of thrombolysis for acute pulmonary embolism is often assumed to reduce the prevalence of CTEPH, but no data at present support this view. It is of note that some of the classic risk factors for acute deep vein thrombosis (DVT)/pulmonary embolism are not found with increased frequency in the population that develops CTEPH. For example, the factor V Leiden polymorphism, which leads to ac- tivated protein C resistance and is found with high prevalence in the population of patients with acute DVT, is not overrepresented in patients with CTEPH. By contrast, the prevalence of protein C and S deficiency is increased in patients with CTEPH, but these con- ditions account for only a few patients. The strongest genetic risk factor is a non-O blood group, which is driven by the A1 allele. In addition, some 10% of patients with CTEPH may have circulating

 antiphospholipid antibodies. Recent research points to a deficiency in the ability to fibrinolyse established clots as a predisposing factor. Other important predisposing factors include previous splenectomy and inflammatory bowel disease. Clinical presentation Patients often present with persistent symptoms of dyspnoea after an acute embolic event despite the recommended period of anticoagulation, up to 60% having a prior documented episode of previous venous thromboembolism, although some patients may present with gradually worsening dyspnoea in the absence of acute events. On physical examination, there may be pulmonary flow murmurs resulting from turbulent flow across partially obstructed large pulmonary arteries: these are audible on chest auscultation in up to 30% of patients with CTEPH. Otherwise,

the clinical presenta- tion is similar to that described earlier for PAH. Investigation The work-up of patients referred with a suspected diagnosis of CTEPH requires a multidisciplinary approach involving surgeons, physicians, and radiologists. Imaging plays a key role in determining whether a patient is suitable for the surgical procedure of choice, pul- monary endarterectomy. CT pulmonary angiography with modern multislice scanners is a rapid and noninvasive technique that can provide several important pieces of information in the assessment of patients with suspected CTEPH, both assessing the presence of any associated lung disease or tumours, and most importantly giving an accurate assessment of the extent of proximal organized clots (Fig. 16.15.2.7). Although occlusion of very small arteries cannot be visualized directly in the case of predominantly distal disease, the characteristic appearance of 'mosaic perfusion' suggests the presence of peripheral disease (Fig. 16.15.2.8), and ventilation– perfusion lung scans also usually show multiple segmental perfusion defects not matched by defects in ventilation in this circumstance (Fig. 16.15.2.10). CT can also reveal the extent of right ventricular hypertrophy and dilatation, although this is probably best seen by MRI. Three-dimensional reconstruction of the two-dimensional CT and MR images can help decide whether the distribution of dis- ease is suitable for pulmonary endarterectomy. The use of a combin- ation of these techniques means that the more invasive traditional pulmonary angiogram can be avoided in most patients. Treatment About 60% of cases of CTEPH is potentially suitable for surgery. Of the patients who are not suitable for surgical management, many may be suitable for targeted therapy with the new pharmacological agents described previously for PAH. Pulmonary endarterectomy involves removal of organized thrombi from the proximal pulmonary arteries. The procedure is a major operation that usually requires the patient to undergo re- peated cycles of cardiopulmonary bypass with cerebral cooling, which ensures a bloodless field of view for the surgeon, who can then enter the left and right main pulmonary arteries via an arteri- otomy. The aim is to identify a dissection plane along the base of the false intima and to dissect distally as far as possible, when it is often possible to remove organized material down to the level of seg- mental pulmonary arteries (Fig. 16.15.2.13). With successful clear- ance of proximal clots, the pulmonary vascular resistance can fall dramatically postoperatively, and near normalization of resistance can be achieved in the long term. There are two main aspects to patient selection for this pro- cedure. Comorbidities are important predictors of perioperative mortality and require careful assessment. A further important consideration is the distribution of the disease, as organized clots need to be anatomically accessible to the surgeon. If the organ- ized material is predominantly of a distal distribution within the pulmonary arteries (i.e. involves subsegmental vessels), there is a high risk that pulmonary vascular resistance will not decrease after the procedure and that the patient will be left with significant pul- monary hypertension. (a) (b) Fig. 16.15.2.13 The surgical technique of pulmonary endarterectomy (a) and the surgical specimen obtained from a patient undergoing surgery for CTEPH (b). Reproduced from Huikuri HV, Castellanos A, Myerburg RJ (2001). Sudden death due to cardiac arrhythmias. N Engl J Med, 345, 1473–82. Copyright © 2001, Massachusetts Medical Society. All rights reserved.

16.15.2 Pulmonary hypertension 3709 Despite careful patient selection, the operation is high risk, with perioperative mortality varying between 3% and 20% depending on the experience of the centre. However, in those who survive surgery, the long-term outlook is often excellent after a successful procedure, with marked improvements in exercise cap- acity, NYHA functional status, and quality of life. To prevent further thromboembolism, patients have an inferior vena cava filter sited prior to the operation and are maintained on lifelong warfarin. Likely future developments Much remains unknown about the natural history of CTEPH and the risk factors for failure of

resolution of an acute embolic event. Large studies designed to prospectively follow up patients with acute embolism over many years will be necessary to get a clearer picture of the underlying causes. Whether chronic thromboembolic pulmonary embolism always results from embolic phenomena or whether in situ thrombosis also contributes remains uncertain. The distinction between CTEPH leading to occlusion of small periph- eral pulmonary arteries and idiopathic PAH can be difficult in some cases, and indeed they may be part of the same spectrum of disease. Selection of patients likely to respond favourably to surgery can be difficult, and improved imaging or physiological assess- ments are needed. These, along with advances in anaesthetic technology and surgery, are likely to improve further the already impressive results of surgery. The use of balloon angioplasty for the dilatation of proximal partially occlusive chronic thrombo- embolic disease is currently being evaluated. The response of in- operable CTEPH to targeted pharmacological therapy has been evaluated recently and has led to the recent approval of riociguat, a stimulator of soluble guanylate cyclase, in CTEPH. We are also likely to see further medical interventions aimed at reducing the incidence of CTEPH after acute pulmonary embolism.

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Updated 2026-01-22 16:39:24 UTC by Omar Ayman