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Series Editor: Juan Carlos Kaski

Brendan Madden *Editor*

Treatment of Pulmonary Hypertension

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Current Cardiovascular Therapy

Series editor
Juan Carlos Kaski
London, UK

Cardiovascular pharmacotherapy is a fast-moving and complex discipline within cardiology in general. New studies, trials and indications are appearing on a regular basis. This series created with the support of the International Society of Cardiovascular Pharmacotherapy (ISCP) is designed to establish the baseline level of knowledge that a cardiovascular professional needs to know on a day-to-day basis. The information within is designed to allow readers to learn quickly and with certainty the mode of action, the possible adverse effects, and the management of patients prescribed these drugs. The emphasis is on current practice, but with an eye to the near-future direction of treatment. This series of titles will be presented as highly practical information, written in a quick-access, no-nonsense format. The emphasis will be on a just-the-facts clinical approach, heavy on tabular material, light on dense prose. The books in the series will provide both an in-depth view of the science and pharmacology behind these drugs and a practical guide to their usage, which is quite unique. Each volume is designed to be between 120 and 250 pages containing practical illustrations and designed to improve understand and practical usage of cardiovascular drugs in specific clinical areas. The books will be priced to attract individuals and presented in a softback format. It will be expected to produce new editions quickly in response to the rapid speed of development of new CV pharmacologic agents.

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Treatment of Pulmonary Hypertension

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Chapter 1
The Pathophysiology, Presentation and Diagnostic Investigation of Pulmonary Hypertension

Jenny Bacon and Brendan Madden

Introduction

The definition of pulmonary hypertension (PH) is an elevated resting mean pulmonary artery pressure (mPAP) of greater than or equal to 25 mmHg, determined by right heart catheterisation [1]. It is a progressive and ultimately fatal disease without appropriate management. Many different diseases can be associated with this elevation in mPAP and therefore PH is a diverse clinical entity.

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PH can be broadly categorised into those conditions that are associated with the histological features of plexogenic pulmonary arteriopathy (PPA [2]) and those which are not. Conditions associated with PPA are grouped under the umbrella term pulmonary arterial hypertension (PAH). In PAH the left atrial pressure is usually normal, and is measured as the pulmonary wedge pressure (PWP) during right heart catheterisation (PWP <15 mmHg). The difference between mPAP and PWP is then divided by cardiac output to calculate pulmonary vascular resistance (PVR), and this is significantly elevated in PAH. Examples of diseases in the group PAH include idiopathic, heritable and PAH in association with certain drugs or toxins, scleroderma, human immunodeficiency virus (HIV) infection or portal hypertension.

Many patients develop PH in association with cardiopulmonary diseases. PH is commonly associated with left heart disease (such as mitral valve disease), chronic lung diseases (such as sleep disordered breathing, lung parenchymal and airway diseases) and chronic pulmonary thromboemboli (termed chronic thromboembolic pulmonary hypertension (CTEPH)). These patients do not develop PPA for reasons that are unclear and have different pathophysiology, and therefore require different management strategies.

Pulmonary Hypertension Pathophysiology

The development of PH is multifactorial and complex. It is initiated by different factors according to the underlying disease process. Although PAH occurs in association with diverse aetiologies it results in the distinct pathophysiological process of PPA [3].

Plexogenic Pulmonary Arteriopathy (PPA)

The vascular endothelium normally releases a number of factors that have important roles in the control of vasomotor tone, cellular proliferation and platelet aggregation in the pulmonary circulation. These include nitric oxide, prostacyclin and

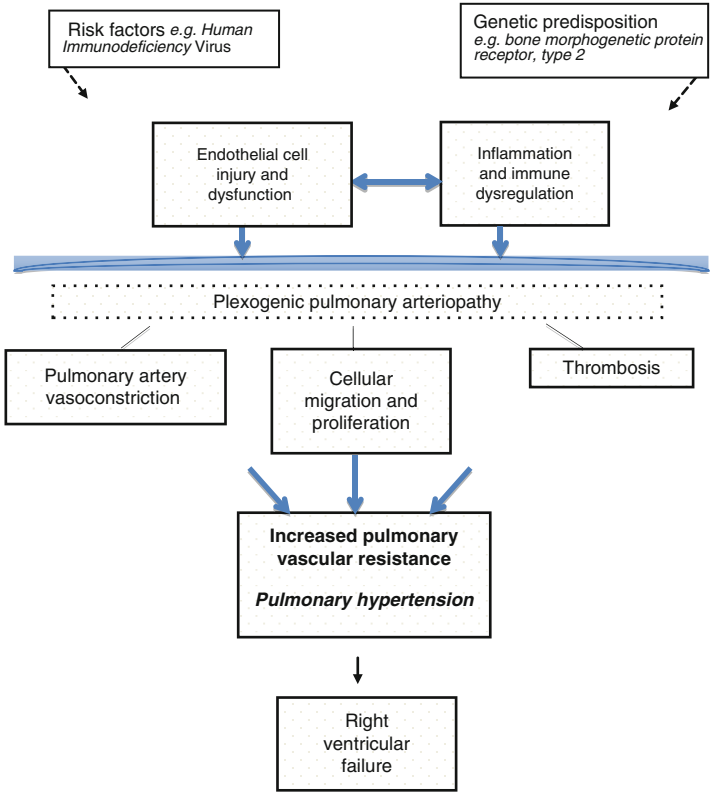

FIGURE 1.1 Factors involved in the pathophysiology of pulmonary arterial hypertension

endothelin and will be detailed in Chap. 2. In PPA, endothelial dysfunction leads to an imbalance in these factors which results in a number of changes that increase PVR (Fig. 1.1):

Vasoconstriction

In accordance with Poiseuille's law the flow of blood through a vessel is proportional to its radius to the fourth power. Consequently, relatively small reductions in vessel radius are accompanied by large reductions in blood flow. For example

if the radius of a vessel is halved then blood flow is decreased by a factor of 16. Paralleling Ohm's law relating to electrical principles, PVR is determined by dividing the pressure drop through the pulmonary circulation by total pulmonary blood flow. Therefore a significant fall in blood flow from a reduction in the radius of vessels is associated with a significant increase in PVR.

The endothelial dysfunction in PAH and the imbalance between tissue and circulating vasoactive factors leads to pulmonary arterial vasoconstriction which reduces vessel radius, significantly reduces blood flow and increases PVR [4–6].

Cellular Proliferation and Thrombosis

In the early stages of PPA hypertrophy, recruitment and proliferation of smooth muscle results in thickening of the subendothelial tunica media layer of the distal pulmonary arteries. Activated vascular cells then obtain migratory and invasive properties in addition to hyperproliferative properties. They migrate from the inner half of the tunica media of pulmonary arterioles and travel to the vascular lumen. In the lumen they become myofibroblasts which proliferate and lay down smooth muscle and fibrous tissue in a concentric fashion. This causes vascular narrowing (i.e., a reduction in vessel radius) and/or occlusion and blood flow is significantly reduced according to Poiseuille's law so PVR increases. At points of weakness, especially when the blood vessels are branching, they rupture with subsequent haemorrhage. Disorganised primitive blood vessels grow into these areas and are termed plexiform lesions. The plexiform lesions are composed of multiple cell types including apoptosis-resistant endothelial cells, progenitor cells and immune cells [3, 7].

The endothelial dysfunction and the associated imbalance in endothelium derived vascular mediators gives rise to a hypercoagulable phenotype in PAH [8]. This promotes the development of *in situ* thrombosis. The development of

thrombus in the already narrowed pulmonary arteries further obstructs and reduces blood flow, increasing PVR.

Mechanisms of Disease

The exact mechanisms behind the development of PPA are not fully understood. Pulmonary endothelial dysfunction has a central role in its initiation and progression [9–12]. Certain risk factors can facilitate this endothelial damage and dysfunction, including autoimmune diseases, toxins and HIV infection. Inflammation, including cytokines and immune cells appear to play a significant role in the initiation and evolution of PPA [13]. Many factors with roles in normal cell growth and/or angiogenesis are altered to promote cell proliferation and disordered angiogenesis [14–16]. Mitochondrial metabolism in proliferating vascular cells in PPA is shifted from oxidative phosphorylation to glycolysis in the same way as cancer [17].

Sometimes genetic factors confer a predisposition to cellular proliferation and the development of PPA (hereditary PAH). TGF-β signalling generally has a negative effect on cell growth, controlling cell proliferation and apoptosis. The bone morphogenetic type 2 receptor (BMPR2) belongs to the transforming growth factor-beta (TGF-β) superfamily and is expressed in pulmonary vascular smooth muscle and endothelial cells. BMPR2 normally has a protective role, suppressing smooth muscle cell proliferation and normalising endothelial cell apoptosis. Reduced expression or loss of function from mutation of the BMPR2 gene leads to a loss of its growth inhibitory effect and a tendency towards the development of PPA [18]. Genetic predisposition to PPA also occurs less commonly from mutation of downstream mediators (e.g., cytoplasmic signalling proteins- smad proteins) or key regulators (e.g., activin A receptor kinase-1 mutations) in TGF-β signalling [19].

The vascular endothelium, vascular remodelling and inflammatory mechanisms in PAH will be discussed further in Chap. 2.

Pulmonary Veno-occlusive Disease and Pulmonary Capillary Haemangiomatosis

In most conditions associated with PAH the pulmonary veins do not offer a significant contribution to the haemodynamic compromise in the pulmonary circulation and cellular proliferation is not present in the capillary bed. However, this is not the case in pulmonary veno-occlusive disease (PVOD) and pulmonary capillary haemangiomatosis (PCH) which belong to a rare subset of PAH. In PVOD, patients develop significant fibro-occlusive lesions, muscularisation and inflammation of the septal veins and pre-septal venules in addition to a degree of distal pulmonary arteriopathy [20]. In PCH, cellular proliferation arises in the alveolar capillaries. Invasion of adjacent vascular, pulmonary and bronchial structures is typically seen, often associated with diffuse alveolar haemorrhage [21]. Both PCH and PVOD can clinically masquerade as idiopathic PAH but the distinction is extremely important for patient management as pulmonary vasodilators may be deleterious in these patients.

The Pathophysiology of Other Clinical Groups

The development of PPA is reserved to conditions which are classified in the subgroup PAH. Although occlusive lesions and plexiform lesions are exclusive to PPA, endothelial dysfunction leads to pulmonary arterial vasoconstriction, structural remodelling and cellular proliferation in other PH clinical groups. This includes CTEPH [22], PH in the setting of chronic lung disease [23] and left heart disease [24].

Left Heart Disease

Patients classified as having PH secondary to left heart disease (for example left ventricular failure or mitral valve disease) have an elevated left atrial filling pressure which is

defined at right heart catheterisation by an elevated pulmonary wedge pressure (PWP >15 mmHg). These patients initially develop a passive rise in mPAP as a consequence of elevated back pressure to the pulmonary circulation from an increase in left atrial filling pressure. This can be associated with a normal or slightly elevated PVR, pulmonary perfusion abnormalities and vascular remodelling. With disease progression, there is superimposed pulmonary vasoconstriction and further vascular remodelling and patients develop established pulmonary vascular disease, associated with significant increases in PVR.

Chronic Lung Disease

Physiological pulmonary vasoconstriction occurs in response to alveolar hypoxia as an important way of matching regional blood flow and alveolar ventilation. In chronic lung disease and or chronic hypoxia, hypoxic vasoconstriction has a key role in PH pathogenesis. However, endothelial dysfunction and inflammation are believed to play the major role in the pathogenesis of PH secondary to chronic lung disease [25].

Chronic Thromboembolic Pulmonary Hypertension

CTEPH is diagnosed when chronically obstructed pulmonary arteries from pulmonary thromboemboli (PE) are associated with pathologically elevated PVR and pulmonary arterial pressure [26]. In this condition, unresolved thrombi become organised and remodel to cause chronic fibrous obstructions within the pulmonary arteries which resists blood flow [27].

The severity of pulmonary artery pressure elevation does not necessarily correlate with the degree of pulmonary vascular obstruction visualised on imaging, nor does the level of PVR necessarily correlate with similar degrees of vascular obstruction associated with acute PE. This is due to progressive distal vasculopathy development in both the occluded

and non-occluded regions [28–31]. Muscular hypertrophy resulting in vasoconstriction and fibrointimal proliferation narrows the lumen of the distal pulmonary arteries [22]. It is therefore both the extent of chronic vascular obstruction from organised thrombi and secondary small vessel arteriopathy that contribute to elevated PVR in CTEPH.

CTEPH appears to develop in only 4 % of patients who have previously been diagnosed with acute PE [32], although 60 % of patients that are diagnosed with CTEPH have never had a clinically apparent acute PE [33, 34]. Mechanisms implicated in the pathogenesis of why some patients develop CTEPH include recurrence of PE, in situ thrombosis, unsuccessful resolution of the initial PE or its propagation into branch pulmonary vessels [35]. Abnormalities in the clotting cascade, platelets and endothelium appear to interact in the coagulation process, initiating or exacerbating the development of thromboemboli and/or *in situ* thrombosis. Some patients have an identifiable abnormality associated with thrombophilia such as protein S or C deficiency or the presence of antiphospholipid antibodies [36].

Pulmonary thromboendarterectomy is the treatment of choice for selected CTEPH patients, offering surgical removal of proximal pulmonary arterial obstruction and therefore potential cure. However, patients with significant distal disease do not benefit from surgery. This will be discussed further in Chap. 4.

Right Ventricular Failure

The pulmonary circulation is normally a low resistance, low pressure network. It can ordinarily accommodate increasing pulmonary blood flow, even during maximal exertion, without a rise in pulmonary arterial pressure. This occurs from passive changes in the compliant pulmonary arteries and capillary beds. Vessels distend and microcirculatory reserves are recruited to lower PVR and to maintain a low pressure circulation [37]. Similarly, early pulmonary

vascular disease can be compensated for and is therefore typically subclinical.

The normal low pressure and resistance in the pulmonary circulation offers a low afterload to the right ventricle (RV). It is therefore not adapted to work at high pressure but is adapted to accommodate the variable haemodynamic demands placed upon it. The RV is relatively thin walled and compliant compared with the thick walled left ventricle, but it hypertrophies as the pulmonary artery pressure increases. Initially the RV can overcome the increased afterload associated with a higher PVR [38] but later, cardiomyocyte contractility declines and as the contractile force weakens the RV dilates. RV dilatation increases wall tension and oxygen demand whilst decreasing perfusion. This further decreases contractile function and a vicious cycle ensues [39]. The contractile reserve and the transition from RV hypertrophy to failure is dependent not only on the severity and time course of increasing afterload but also on the degree of oxidative stress, reduced myocardial perfusion, neuro-hormonal and immune activation and the response of the RV to this including remodelling and fibrosis [37, 38, 40–43].

The usual cause of death in patients with PH is RV failure, when increasing PVR causes progressive elevation in afterload which RV contractility can no longer accommodate [28, 44].

Clinical Presentation

PH typically has an insidious onset, with non-specific symptoms. Clinical findings are commonly attributed to concomitant diseases. It is therefore a challenging diagnosis to consider and investigate, especially early in the disease process. Failure to diagnose or incorrect diagnosis is common [45]. A reported median of 14 months from onset of symptoms to diagnosis has been found [46]. A high clinical index of suspicion is necessary, especially in patient groups at increased risk of developing PH.

Symptoms

Patients with early PH may be asymptomatic. The first symptoms that usually develop are fatigue and dyspnoea on exertion. With disease progression symptoms become more apparent, as the PVR escalates and cardiac output falls. Breathlessness with diminishing exertion and then at rest ensues. Palpitations, chest pain (right ventricular angina), presyncopal episodes and later syncope can develop. As the right heart fails, symptoms advance to include peripheral oedema and abdominal swelling from ascites. Eventually, without successful treatment, patients die from RV failure [38, 47, 48].

Functional Classification

Patients with PH are classified according to the World Health Organisation (WHO) 1998 New York Heart Association functional classification (FC). This classifies the patient according to the symptoms they experience during daily living (Table 1.1) [1]. A patient's functional class is important in determining their prognosis and helps determine disease severity and response to treatment.

Physical Examination

Abnormal physical findings may be subtle in patients with PH and can be missed. A loud pulmonary component to the second heart sound may be heard from forceful pulmonary valve closure secondary to elevated pulmonary artery pressure. The jugular venous pressure may depict a prominent 'a' wave from high RV filling pressures. With RV dilatation the tricuspid apparatus can dilate resulting in functional regurgitation and accentuated 'v' waves identifiable in the jugular venous waveform. Equally the pansystolic murmur of

Table 1.1 Functional classification of patients with pulmonary hypertension according to the World Health Organisation, modified after the New York Heart Association functional classification [1]

Class	Description
I	Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain, or near syncope.
II	Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain, or near syncope.
III	Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain, or near syncope.
IV	Patients with 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 even be present at rest. Discomfort is increased by any physical activity.

tricuspid regurgitation may be audible. A left parasternal lift can occur as a consequence of RV hypertrophy. A right ventricular fourth heart sound (immediately prior to the first heart sound) may result from abnormal turbulent blood flow as the right atrium contracts and forces blood flow into a stiffened RV. Alternatively with RV dysfunction and volume overload a third heart sound may follow the second heart sound in mid diastole during ventricular filling. With RV failure, jugular venous distension, hepatomegaly, ascites and peripheral oedema are common features. Arrhythmia may develop as a consequence of atrial dilatation or RV dilatation, hypertrophy or fibrosis and rhythm disturbance is important to recognise on clinical examination as it can impede cardiac function.

Diagnosis

PH is defined by the resting mPAP measured at right heart catheterisation (>=25 mmHg). Therefore, the diagnosis of PH ordinarily requires invasive confirmation.

The normal value of mPAP is 14 ± 3 mmHg [1, 49]. Patients with borderline mPAP values (17–24 mmHg) should be prospectively monitored for the development of PH and research into the significance and suitable management of these patients is ongoing.

Right Heart Catheterisation

Right heart catheterisation (Fig. 1.2) measures the pressure, flow and resistance in the cardiopulmonary circulation, including measurement of the downstream left atrial pressure (PWP). Cardiac shunting can also be identified and measured by oxygen saturation assessment [50].

PWP is determined by wedging the tip of the right heart catheter with the balloon inflated in the pulmonary artery. The forward flow of blood is temporarily stopped within the small vessel where the catheter lies. When there is no venous obstruction, the measured pressure is the back pressure transmitted from the left atrium, as there are no anatomical valves in the pulmonary veins [51, 52]. A PWP of greater than 15 mmHg defines a significant contribution to raised mPAP from pressure beyond the pulmonary capillary bed, for example from left atrial hypertension.

In general the PWP is not greater than 15 mmHg in patients with PAH [53]. However, the size, shape and compliance of one ventricle has a direct effect on the other ventricle through their mechanical interaction, including a shared septum, myofibres and a joint pericardial space encased by a fibrous pericardium. Therefore, left ventricular dysfunction can result from significant RV dysfunction, and this can lead to elevated left atrial filling pressure and PWP in PAH [54].

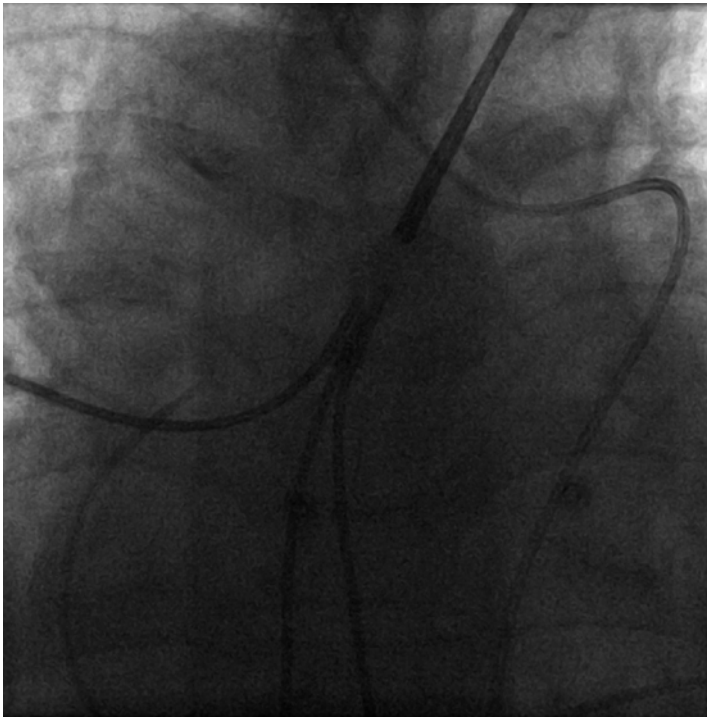

FIGURE 1.2 Plain radiograph showing a right heart catheter in the pulmonary artery of a patient with dextrocardia (precordial leads also shown)

PWP may also be elevated (or normal) in pulmonary veno-occlusive disease. This depends on the size of the veins involved and the degree of collateral communication between the affected venous beds [20].

Ohm's law pertaining to electrical resistance states that resistance equals pressure divided by flow. Therefore, PVR is calculated by dividing the transpulmonary pressure gradient (mPAP – PWP (mmHg)) by cardiac output (L/min). This is an important measurement determined by right heart catheterisation which is commonly measured in arbitrary units called

Wood Units (WU). One Wood Unit is 1 mmHg per litre per minute or 80 dynes.sec.cm^{-5} [55]. PVR is abnormal when above 2WU but is defined as significantly raised when greater than 3WU [53, 56, 57]. A pathological elevation in PVR signifies the presence of significant pulmonary vasculopathy. PVR greater than 3WU is included in the definition of PAH [53].

Right heart catheterisation identifies important prognostic variables for patients with PH. Mean right atrial pressure, cardiac index (cardiac output adjusted for body surface area) and PVR have been shown to predict mortality in national PAH registries [58–60]. Notably PVR is a more important variable than mPAP in the assessment of the severity and prognosis of PH [61]. Progressive pulmonary vasculopathy is translated into an increasing PVR. Paradoxically, with increasing afterload the RV starts to fail and the cardiac output reduces, and this can result in a fall of mPAP despite advancing disease.

Right heart catheterisation procedures are generally well tolerated [62] but due to their invasive nature significant serious adverse events (1.1 %) and mortality (0.1 %) have been reported in multicentre large patient series [63]. However, right heart catheterisation accurately defines an individual's pulmonary haemodynamics to establish a diagnosis of PH. It aids treatment decisions including suggesting contributing factors, identifying important prognostic variables and assessing disease progression.

Non invasive Investigations

Although right heart catheterisation is the gold standard diagnostic investigation for PH, non invasive estimates are advantageous in terms of cost, availability and risk. They are used to help identify those patients that require further investigation into a diagnosis of PH but they cannot reliably exclude the diagnosis. Non invasive investigations are important in establishing conditions causing or contributing to the diagnosis of PH such as thromboemboli, left heart or lung disease.

Echocardiography

Echocardiography is used to aid the diagnosis of PH initially, risk-stratify patients and monitor their progress. It is also important in the identification of valvular pathology, cardiac shunts (especially when contrast is used) and primary myocardial disease, that may contribute to a diagnosis of PH [64].

Transthoracic echocardiography determines the pulmonary arterial pressure to aid the identification and monitoring of PH patients. The most common method is determining the pulmonary artery systolic pressure by the velocity of measurable tricuspid regurgitation (Fig. 1.3). A meta-analysis of this method revealed a moderate diagnostic accuracy of 83 % sensitivity (95 % confidence interval 73–90 %) and 72 % specificity (95 % confidence interval 53–85 %) when compared to invasive measurement [65]. The wide confidence intervals highlight the weakness of echocardiography as a sole investigative or screening tool in PH.

Increasing afterload in PH stresses the thin walled and distensible right ventricle to forge its shape, size and functional state. When adequate echocardiography views are obtained, the morphology and function of the RV can be assessed to serially evaluate RV dysfunction and suggest the presence of PH. In addition, the discussed interaction between the right and left ventricle can be visualised, and the size and pressure within the right atrium can be reviewed. The presence of a pericardial effusion can be established easily by echocardiography which has been shown to predict death or transplantation in PAH [66, 67].

As PH cannot reliably be defined by a cut off pulmonary artery pressure value using echocardiography alone, current guidelines suggest incorporating other echocardiography measures and determining the probability of PH. PH is unlikely in the presence of pulmonary artery systolic pressures below 36 mmHg in the absence of additional echocardiogram variables suggestive of PH, possible at higher values and likely when greater than 50 mmHg (Table 1.2) [1, 49]. It

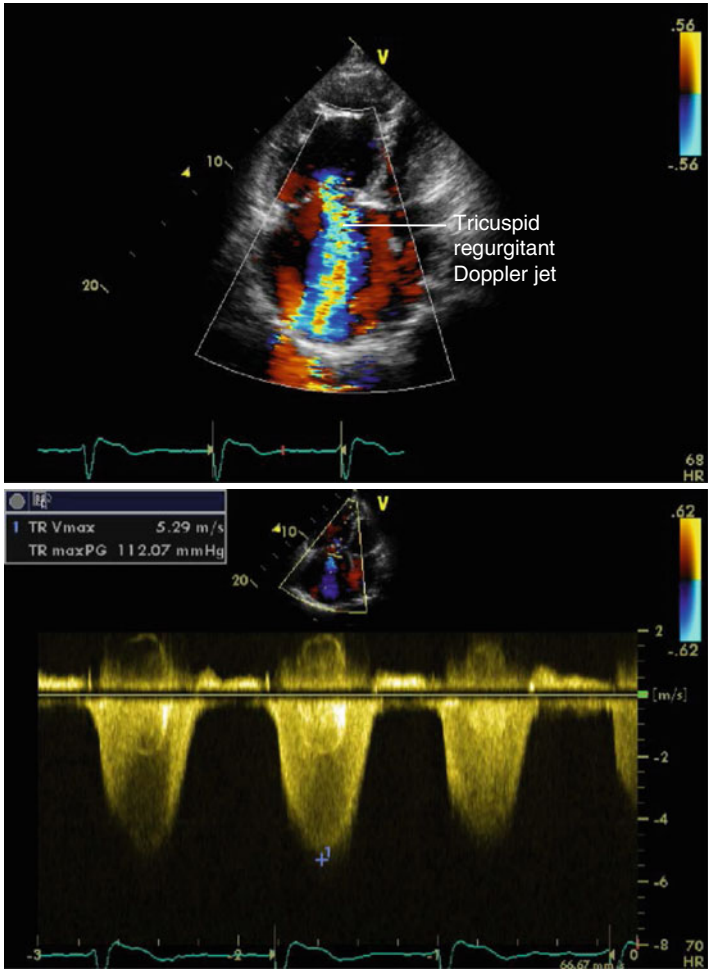

FIGURE 1.3 Pulmonary artery systolic pressure estimation by the continuous wave Doppler tracing of the tricuspid regurgitant jet velocity in a patient with pulmonary hypertension. From a tricuspid regurgitant velocity of 5.29 m/s the right ventricular systolic pressure can be calculated to 135–140 mmHg, equivalent to pulmonary artery systolic pressure in the absence of right ventricular outflow obstruction

Table 1.2 Arbitrary criteria for estimating the presence of pulmonary hypertension (PH) by echocardiography, according to international guidelines [1]

Echocardiography diagnosis of PH	Tricuspid regurgitant peak velocity	Pulmonary artery systolic pressure*	Additional echocardiogram variables suggestive of PH
Unlikely	≤2.8 m/s	≤36 mmHg	No
Possible	≤2.8 m/s	≤36 mmHg	Yes
Possible	2.9–3.4 m/s	37–50 mmHg	Yes/no
Likely	>3.4 m/s	>50 mmHg	Yes/no

*assuming a normal right atrial pressure of 5 mmHg

is essential that the full diagnostic potential of echocardiography is used when assessing PH.

Other Routine Investigations

An electrocardiogram is important in PH to identify and diagnose arrhythmia so that suitable management can be initiated. The electrocardiogram may also show evidence of right atrial enlargement, right ventricular strain or hypertrophy [68] to suggest a diagnosis of PH. However, it is not a sufficient screening tool for the presence of PH, especially in early disease [47].

At present, the place for radiological investigation in patients with suspected PH is mainly in the identification of lung diseases or CTEPH. However, recognition of pulmonary artery enlargement or dilatation of cardiac chambers from imaging can suggest the diagnosis of PH (Fig. 1.4).

A baseline chest radiograph is considered routine and may reveal features suggestive of PH, left ventricular impairment (Table 1.3), or lung disease.

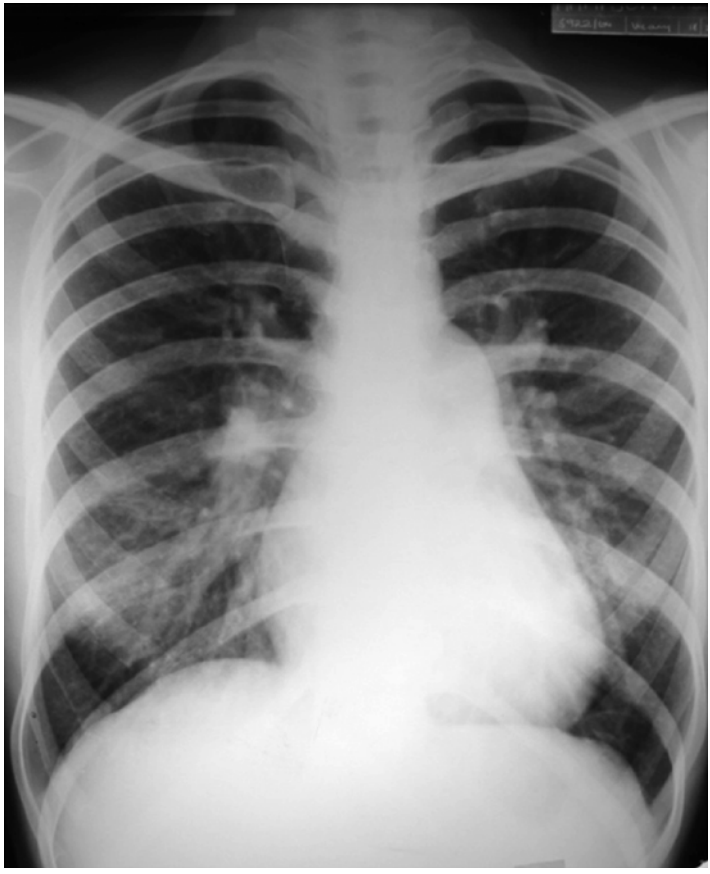

FIGURE 1.4 Chest radiograph showing plethoric pulmonary arterial vasculature with right ventricular enlargement elevating the cardiac apex and reduced size of the aortic knuckle in a patient with pulmonary hypertension from atrial septal defect

Computed tomography (CT) offers a simultaneous assessment of the pulmonary vasculature (pulmonary angiography) and lung parenchyma (high resolution CT) and is the main diagnostic strategy in PH radiological investigation (Fig. 1.5)

Table 1.3 Chest radiograph features suggestive of left ventricular impairment

Chest radiograph feature	Stage of left ventricular impairment progression
Cardiac enlargement	Variable, widely prevalent in chronic cases
Upper lobe venous redistribution	Elevated pulmonary venous pressure
Central venous prominence	Elevated pulmonary venous pressure
Indistinctness of the central perihilar vasculature	Interstitial oedema
Thickening of the minor fissure	Interstitial oedema
Pleural effusion	Interstitial oedema
Diffuse air space disease	Alveolar oedema

[69, 70]. The presence of acute or chronic thromboembolic disease related to CTEPH or lung diseases such as emphysema can be recognised by CT. CT imaging can also be helpful in identifying PVOD and PCH which are typically challenging to diagnose. PVOD typically demonstrates features of pulmonary interstitial oedema without engorgement of the main pulmonary veins or left sided chambers (as the occlusion is in the more proximal post capillary venules). Comparatively, extensive ground glass nodules are typical in PCH [71].

Ventilation perfusion scintigraphy is used to further investigate the presence of CTEPH by identifying the mismatch between perfusion and ventilation from vessel occlusion [72, 73].

Pulmonary function testing is performed to identify lung disease as a contributor to PH. With adequate technique, physiological impairment from underlying respiratory disease can be identified and quantified. However, even without concomitant lung disease, a reduction in carbon monoxide diffusion is typically demonstrated in PAH. Damage to the pulmonary vascular bed in PAH results in decreased capillary

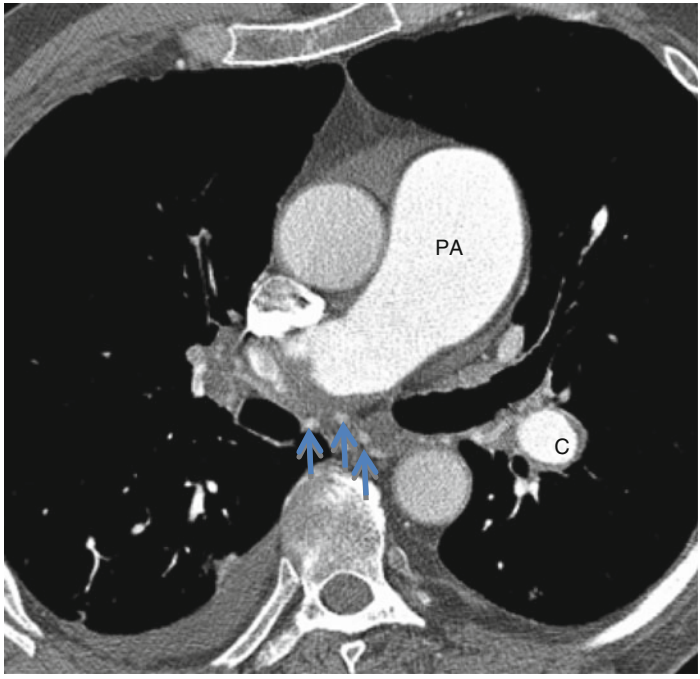

FIGURE 1.5 CT pulmonary angiogram showing bronchial artery hypertrophy (*arrows*) in a patient with chronic thromboembolic pulmonary hypertension. Note the marked enlargement of the pulmonary artery (*PA*) and the rim of clot around the left lower lobe pulmonary artery (*C*)

blood volume and flow and a reduction in the surface area available for gas diffusion [74, 75]. An unexpected reduction in a patient's gas diffusion should guide the physician to consider a diagnosis of PAH.

Routine haematological and biochemical investigations in PH include full blood count, urea and electrolytes and liver function testing. Liver function testing is important to recognise a predisposition to and potential cause of PH, with consideration given to liver ultrasound. Similarly, autoimmune profiles may help identify underlying connective tissue

diseases, and HIV testing in patients with PH is recommended [1]. Screening for thrombophilia or sickle cell disease is appropriate in patients with a suggestive history. Genetic testing is important in idiopathic and heritable PAH including the offer of genetic counselling and testing of relatives.

Brain natriuretic peptide (BNP) and the biologically inactive N-terminal segment (NT-proBNP) can be measured in the blood and are released from the myocardium in response to wall stress. In the presence of right ventricular dysfunction these markers typically rise and therefore they are useful for monitoring disease progression in PH. An elevated or increasing level of BNP or NT-proBNP is a poor prognostic sign suggesting progressive right ventricular dysfunction [76]. However, in early disease before significant cardiac dysfunction, their levels can be normal and their levels will also rise in response to left ventricular dysfunction. An elevation in BNP or NT-pro BNP level is therefore not specific to a diagnosis of PH nor does a normal level exclude the condition [77, 78].

Six Minute Walk Distance

The six minute walk test measures the distance a patient can walk on the flat in a 6 min period without encouragement. It is easily carried out, inexpensive and the results correlate well with functional status [79]. Patients may be used as their own control, to monitor their response to treatment.

A patient's six minute walk distance has historically been used as a common clinical trial end point in PH. However, a patient's six minute walk distance is not necessarily a reliable marker of pulmonary vascular disease progression or improvement as it is a nonspecific general exercise capacity test [80]. Results depend not only on the severity of PH but also are highly dependent on simple demographic characteristics, comorbidities of the patient and other day to day variables. A meta-analysis by Savarese et al. reviewed 22 clinical trials using six minute walk testing to assess pharmacological treatments. Although favourable effects on clinical events were

present such as reduced all-cause mortality, these were not predicted by change in six minute walk distance [81]. Recent drug trials in PH have moved away from change in six minute walk distance and towards time to 'clinical worsening' as a more suitable primary trial endpoint for these reasons [82].

Disease Classification

Once identified, the separate conditions that predispose and or cause PH are used to classify patients into distinct groups according to common pathological and clinical features (Table 1.4) [83, 84]. PAH is classified as group 1, PH associated with left heart diseases are classified as group 2, PH associated with lung diseases and or hypoxia are in group 3, CTEPH belongs in group 4 and group 5 includes diseases with unclear multifactorial mechanisms such as sarcoidosis or sickle cell disease.

PAH has an estimated prevalence of 15–26 cases/million [85]. This likely represents approximately 10 % of all PH patients [86]. No precise estimates for the more prevalent subtypes of PH including groups 2 and 3 are available however they are recognised as major health burdens [25].

Of the diseases associated with PAH, the estimated life time risk of PH in patients with congenital heart disease is 4–15 % [87]; 5–12 % in systemic sclerosis [88]; 0.5–10 % in portal hypertension [89] and 0.5 % in HIV [90]. Those patients that are genetic carriers of the BMPR2 mutation have a 20 % increased life time risk of PAH development [91]. Patients with sickle cell disease have a 2–3.7 % risk of developing pulmonary vasculopathy [92–94].

Survival

The median survival for patients with PAH is 2.8 years when untreated [45]. Unfortunately even with modern management PAH remains a progressive and fatal disease, with 1 year

Table 1.4 The classification of pulmonary hypertension according to the World Congress, Nice 2013

Group	Subtypes	Clinical examples
Group 1: Pulmonary Arterial Hypertension	Idiopathic	
	Heritable	BMPR2, ALK-1, ENH, SMAD9, CAV1, KCNK3
	Drug/toxin induced	Anorexigens, metamphetamines
	Conditions associated with pulmonary arterial hypertension	Connective tissue disease Congenital heart diseases Portal hypertension Human immunodeficiency virus infection Schistosomiasis
Group 1'	Pulmonary veno-occlusive disease and or Pulmonary capillary haemangiomatosis	

(continued)

Table 1.4 (continued)

Group	Subtypes	Clinical examples
Group 2: Pulmonary hypertension due to left heart disease	Left ventricular systolic dysfunction	
	Left ventricular diasystolic dysfunction	
	Valvular disease	
Group 3: Pulmonary hypertension due to lung diseases and/or hypoxia	Chronic obstructive pulmonary disease	
	Interstitial lung disease	
	Other pulmonary diseases with mixed obstructive and restrictive pattern	
	Sleep disordered breathing and alveolar hypoventilation disorders	Obstructive sleep apnoea, obesity hypoventilation, neuromuscular disorders
	Chronic exposure to high altitude	
	Developmental lung diseases	

Group 4: Chronic thromboembolic pulmonary hypertension		
Group 5: Pulmonary hypertension with unclear multifactorial mechanisms	Haematological disorders	Myeloproliferative disorders, splenectomy, **chronic haemolytic anaemia***
	Systemic disorders	Sarcoidosis, lymphamgioleiomatosis
	Metabolic disorders	Glycogen storage disease Thyroid disorders
	Others	Chronic renal failure

The main change made from the Dana point 2008 World Congress is highlighted (*)
BMPR2 bone morphogenic protein receptor type 2, *CAV1-1* caveolin-1, *ENG* endoglin, *ALK-1* ativin-like receptor kinase-1, *KCNK3* potassium channel super family K member –3, *SMAD 9* mothers against decantaplegic 9
*Reclassified from Group 1 to Group 5 at the World Symposium on Pulmonary Hypertension, Nice 2013

incident mortality of 15 % [95] and 55–73 % 3 year survival reported [59, 96]. However, studies on PAH treatment suggest that the earlier that disease modifying therapies are implemented, the better the outcome for patients [89].

Key Learning Points

- Pulmonary hypertension is defined as resting mean pulmonary artery pressure (mPAP) >=25 mmHg.
- Right heart catheterisation is the gold standard diagnostic investigation in PH
- Pulmonary wedge pressure (PWP) approximates left atrial filling pressure.
- Pulmonary vascular resistance (PVR)

$$\left(\text{Wood Units}\right) = \frac{\text{mPAP} - \text{PWP}\left(\text{mmHg}\right)}{\text{Cardiac output}\left(\text{L / min}\right)}$$

- Noninvasive investigations help define the probability of the presence of PH and identify causes or contributors to the diagnosis.
- Conditions classified in Group 1 pulmonary arterial hypertension have similar pathophysiology termed plexogenic pulmonary arteriopathy and therefore distinct management.
- Pulmonary hypertension is a progressive and ultimately fatal disease without appropriate treatment. In the presence of increasing PVR the right ventricle ultimately fails.

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Chapter 2
Molecular Biological Aspects, Therapeutic Targets and New Treatment Strategies

Dongmin Shao, Laura Price, and Stephen John Wort

Introduction

The term pulmonary arterial hypertension (PAH) describes a rare group of diseases characterized by raised pulmonary vascular resistance, resulting from vascular remodelling in the pre-capillary resistance arterioles (<100 μm in cross-sectional diameter) [1]. Left untreated, patients die from right heart failure, with a mortality approaching most serious cancers. To date, most treatment has been focused on the endothelial cell vascular dysfunction seen in these disorders. As such, pulmonary vasodilators, such as endothelin (ET-1)

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receptor antagonists, prostacyclin (PGI_2) analogues and phosphodiesterase type V inhibitors (enhancing endogenous nitric oxide (NO)) have improved both morbidity and mortality. Indeed, there is continuing development into new and improved drugs that target these established pathways. Recent examples are the dual ET-1 receptor antagonist, macitentan [2], and the soluble guanylate cyclase activator, riociguat [3]. However, none are a cure and the treated mortality rate is still unacceptable [4]. Further research into the molecular mechanisms underpinning the pathogenesis of PAH has led to the discovery of new putative pathways that may allow the targeting of vascular remodelling itself; such "reverse remodelling" may provide a cure for this devastating disease in the future and remains the "holy grail".

This review will present a molecular biological overview of the pathobiology of PAH, the basis behind current treatments and molecular targets that may provide future therapies.

Definition of Pulmonary Arterial Hypertension

PAH is defined as a mean pulmonary artery pressure (mPAP) of greater than 25 mmHg at rest, with normal left sided filling pressures (left ventricular end diastolic pressure (LVEDP) or pulmonary artery wedge pressure (PAWP) less than 15 mmHg).

Histology of PAH

The characteristic histological finding in all causes of PAH is hyperplasia of vascular cells comprising the three layers of the vascular wall i.e., intima (endothelial cells), media (smooth muscle cells) and adventitia (fibroblasts and resultant connective tissue) (Fig. 2.1). The changes described are thought to originate in the resistance vessels (<100 μm cross sectional diameter), with "secondary" changes occurring in the larger,

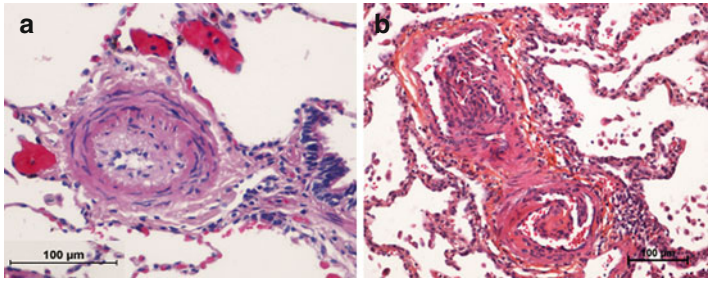

FIGURE 2.1 Histology showing remodelled pulmonary arteries in idiopathic pulmonary arterial hypertension (iPAH). Photographs of paraffin-embedded haematoxylin and eosin-stained human lung sections from patients with iPAH following lung transplantation. Medium sized pulmonary arteries with medial hypertrophy and intimal proliferation (**a**) and plexiform lesions (**b**) (Images kindly supplied by Dr Peter Dorfmuller, Paris)

conduit vessels at a later stage. In severe cases, plexiform lesions, consisting of proliferation of immature endothelial cells and myofibroblasts, are observed, positioned after divisions of the arterial tree and contributing to obstruction of blood flow. *In situ* thrombosis in affected vessels is common and perivascular immune cell infiltrates are seen, suggesting a role for inflammation, either in initiating or propagating the vascular remodelling process. Despite the similarities seen across conditions associated with PAH, there is a more recent realisation that there are distinct histological differences that may be characteristic of the underlying associated condition [5].

Pathogenesis of PAH

It is likely that the pathogenesis of PAH is a multi-hit phenomenon, similar to that described in cancer biology. As such there is evidence for an underlying genetic predisposition and known "hits" such as increased blood flow (Eisenmenger Syndrome), auto-antibodies (connective tissue disease), exposure to drugs (such as appetite suppressants), viruses (HIV) and inflammation. PAH is considered to be a progressive

disease, although the exact rate of progression and the exact order of events remain unknown. Most authorities consider that endothelial damage and resulting endothelial dysfunction is the initial hit. This is characterised by an imbalance of vasoactive hormone production and loss of endothelial barrier integrity, leading to exposure of circulating mediators to the underlying smooth muscle. Activated smooth muscle cells may then respond by proliferation and autocrine production of mediators such as ET-1, which may propagate the process.

Endothelial Dysfunction

The following section will describe the abnormalities seen in the vasoactive hormones ET-1, PGI_2 and NO associated with endothelial dysfunction.

ET-1

ET-1 is both a vasoconstrictor and mitogen that is mainly produced by the endothelium. However, under inflammatory conditions, the vascular smooth muscle is another important source. In patients with PAH there is increased production of ET-1 by the endothelium, and to a lesser extent smooth muscle, in remodelled vessels [6]. Furthermore, circulating plasma levels of ET-1 are raised in patients with PAH [7]and, importantly, increased circulating levels of ET-1 correlate with increased right atrial pressure, increased pulmonary vascular resistance, decreased pulmonary artery oxygen saturation and increased mortality [8–11].

NO

NO is a gaseous, lipophilic, free radical produced by the endothelium, which acts, via activation of soluble guanylate cyclase, to increase intra-cellular cyclic GMP. This, in turn, results in vascular smooth muscle relaxation (vasodilation)

by altering intracellular Ca^{2+} concentrations. With relevance to vascular remodelling, NO also inhibits leukocyte adhesion, platelet aggregation, thrombus formation, and vascular proliferation [12, 13]. Reduced levels of endothelial nitric oxide synthetase (eNOS) are observed in the lungs of patients with idiopathic PAH [14]. There are several other molecular mechanisms explaining the decreased NO bioavailability in PAH including increased levels of endogenous competitive inhibitor of constitutive eNOS (such as asymmetric dimethylarginine (ADMA)), eNOS "uncoupling", decreased L-Arginine levels and increased NO scavenging by haemoglobin and reactive oxygen species (ROS) [15, 16].

PGI_2

The major active metabolite of arachidonic acid (AA), PGI_2, is a critical endogenous regulator of vascular homeostasis. PGI_2 is produced in vascular endothelial cells and acts on neighbouring vascular smooth muscle, as well as circulating platelets [17]. PGI_2 is an agonist of adenylate cyclase and therefore a potent vasodilator with antithrombotic properties, acting via increase in cyclic AMP [17, 18]. An imbalance in AA metabolism has been demonstrated in patients with idiopathic PAH, with evidence for decreased PGI_2 and increased thromboxane (TXA_2) urinary metabolites [19]. Furthermore, expression of the key enzyme for PGI_2 synthesis PGI_2 synthase (PGIS), is reduced in pulmonary arteries of patients with PAH [20].

In the following sections we will describe the pre-disposing factors and secondary "hits" that may contribute to vascular remodelling.

Genetic Predisposition

Although idiopathic and heritable PAH are rare, an improved understanding of the genetics of heritable PAH

(constituting up to 10 % of "idiopathic" PAH cases) has revealed pathobiological mechanisms that may be relevant to PAH associated with other, more common, conditions. Specifically, the genetic defect underlying the majority (80 %) of cases of heritable PAH was identified as heterozygous germ-line mutations in the gene encoding the bone morphogenetic protein receptor (BMPR)-II [21, 22], a member of transforming growth factor-beta (TGF-β) superfamily (Fig. 2.2). Similar mutations have been found in 20 %

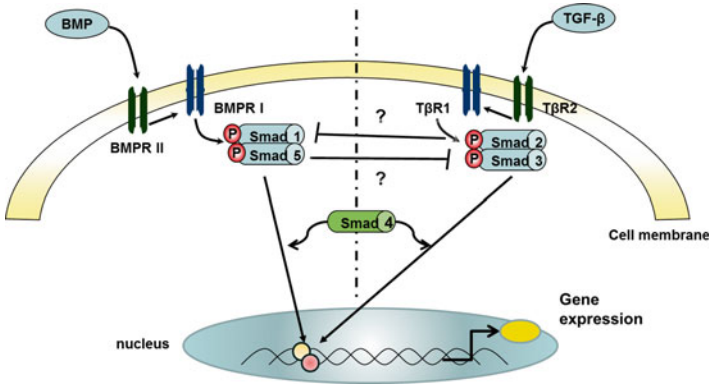

FIGURE 2.2 Schematic representation of bone morphogenetic protein (BMP) signalling via Smads and the interaction with the transforming growth factor (TGF)-β pathway. *Abbreviations*: *BMP* bone morphogenetic protein, *BMPR* BMP receptor, *TGF* transforming growth factor, *TβR- TGF receptor*; *Smad- Mothers Against Decapentaplegic Homolog protein*. Bone morphogenetic protein receptors (BMPRs) are members of the transforming growth factor-β (TGF-β) superfamily. Ligand binding to the BMPR I-II complex activates the signalling molecules Smad 1 and 5, which together with the co-Smad 4 regulate gene expression. In particular, it appears that in the healthy cell, most of the action of these Smads is to down-regulate cell proliferation genes and increase pro-apoptotic genes. BMPR II mutations, seen in patients with idiopathic PAH result in disrupted Smad 1, 5 signalling, and a relative increase in pro-proliferative/anti-apoptotic genes. It remains unclear how the BMPR I-II pathway interacts with traditional TGF-β signalling via Smad 2, 3

of sporadic cases of idiopathic PAH [23]. Segregation analysis of affected families demonstrates that the disease is autosomal dominant often with markedly reduced penetrance (as low as 20 %) [24]. Furthermore, it appears that the predominant genetic mechanism is haplo-insufficiency [25]. A reduction in BMPR II expression has now been observed in other, more common, forms of human PAH [26] and in animal models of PAH [27, 28]. Indeed, selective deletion of BMPR II in animal models results in PAH, although usually at levels milder than in human disease [29]. More recently mutations have been found in genes encoding other members of the TGF-beta superfamily, such as endoglin, ALK-1 and SMAD 8 [30–32]. Interestingly, in a few affected families, abnormalites have also been found in non-TGF-beta superfamily molecules such as caveolin-1 [33] and KCNK3 [34].

Blood Flow

Clearly increased flow is a key initiating event (and likely propagating factor) in the pathogenesis of Eisenmenger syndrome (ES), where increased left-to-right blood flow through a congenital shunt leads to perseverance of the fetal type (high pressure) pulmonary circulation. It is also known that turbulent, non-linear, flow leads to increased shear stress and activation of endothelial cells, through NF-κB dependent mechanisms [35–37]. Areas of turbulent flow are associated with formation of atherosclerosis, overlying thrombosis and vessel wall rupture in patients with ES [38].

There are several lines of evidence to suggest that BMPR II dependent signalling may be important in regulating responses to flow. Firstly, one of the ligands for BMPR II, BMP4 is involved in regulating inflammation and subsequent atherosclerosis production in endothelial cells [39, 40]. Endothelial cells release BMP4 in response to oscillatory flow, which in turn enhances monocyte adhesion. Co-release of endogenous inhibitors of BMP4, such as

noggin and follicostatin, acts to attenuate this inflammatory pathway [41]. Secondly, BMPR II provides a site for multiple proteins to cluster in the plasma membrane, including cytoskeleton proteins, protein kinases (e.g., LIM kinase, Src, PKC, MAPKs) transcriptional factors (e.g., CtBP, NF κBp50) and transient receptor potential canonical 1 (TRPC1), a non-selective Ca2+ channel, some of which have been described as taking part in flow sensing mechanisms[42–47]. Interestingly, mRNA and protein/activity of TRPs are upregulated in lung and smooth muscle cells isolated from patients with idiopathic PAH (although the BMPR II status was unknown [48]). Thirdly, in the pig model of flow associated systemic-pulmonary shunt induced PH, concomitant to the rise of pulmonary vascular resistance and arteriolar medial thickness, there is a decrease in expression of BMPR II (and its co-receptor BMPR Ia). Conversely, pre-treatment with the angiotensin receptor antagonist, losartan decreased shunt-induced pulmonary vascular resistance and medial thickness with a return to normal of the BMPR II expression [49]. These data would suggest a close correlation of BMPR II function and shear stress response in vascular cells. However, this also raises an important question as to whether patients with BMPR II mutation are genetically more susceptible to aberrations in shear stress patterns generated by disturbed blood flow; BMPR II mutations could result in abnormality of intracellular response to blood flow, e.g., Ca^{2+} influx or intracellular Ca^{2+} release (TRPC1), cytoskeleton rearrangement (LIM kinase), and gene expression (PKC, Src, NF κB, MAPKs) or BMPs.

Drugs and Toxins

PAH is associated with a variety of drugs and toxins [50]. The most common class of drugs implicated is appetite suppressants, which include drugs such as dexfenfluramine. As these drugs are involved in serotonin signalling (see later section),

it is likely that serotonin plays an important role in the pathogenesis of PAH associated with these drugs. However, there is an ever increasing list of drugs associated with the development of PAH (see Table 2.1), the latest being interferons [51]. The most well documented toxic insult ("toxic inflammatory PH") occurred after ingestion of adulterated food oil. This led to acute lung injury associated with eosinophilia and myalgia [52]. PAH occurred in 20 % of hospitalized patients, 2–4 months from onset and in 8 % of longer-term survivors.

Table 2.1 Classification for drugs and toxins as risk factors for the development of PAH

Classification of risk associated with drug/toxin	**Drug/Toxin**
Definite group	Aminorex Fenfluramine Dexfenfluramine Toxic rapeseed oil Benfluorex SSRIs
Likely group	Amphetamines L-Tryptophan Methamphetamines Dasatinib
Possible group	Cocaine Phenylpropanolamine St. John's wort Chemotherapeutic agents Interferon α and β Amphetamine-like drugs
Unlikely group	Oral contraceptives Estrogen Cigarette smoking

Adopted from Nice World Congress 2013 guidelines http://www.sciencedirect.com/science/article/pii/S0735109713058725#

Viruses and Parasites

Viruses

The prevalence of PAH in patients infected with HIV is estimated at around 0.5 % [53]. The onset of PAH in these patients confers a worse prognosis [54] . The precise mechanism by which HIV leads to pulmonary vascular remodelling is unknown, but it is likely to be a multifactorial process, and at least in part related to the induction of proinflammatory cytokines and growth factors from the induced chronic state of immune activation. Unsurprisingly, altered BMPR II signaling is likely to be involved [55], although germ-line BMPR II mutations are not usual in these cases [54]. HIV virus has never been detected in vascular lesions [56]; therefore, indirect action by HIV proteins is likely. For example, the envelope protein glycoprotein-120 (responsible for HIV binding and entry into macrophages) has been shown to induce apoptosis and increase ET-1 secretion from endothelial cells *in vitro* [57]. Furthermore, HIV-1 negative factor (*nef*) antigen, crucial for maintenance of the HIV viral load, has been localized to cells within complex vascular lesions in these patients [58], with a proposed mechanism being an increase in endothelial cells apoptosis followed by the emergence of apoptosis-resistant endothelial cells with a hyperproliferative phenotype [59]. Other viruses have also been implicated in the pathogenesis of PAH. For instance, genes coding for human γ herpes virus 8 (or Kaposi sarcoma-associated herpes virus) proteins have been detected in plexiform lesions [60]. In support of this observation, human γ herpes virus 8 infection of pulmonary microvascular endothelial cells *in vitro* results in an apoptosis-resistant cell phenotype [61], as well as a reduction in BMPR II expression [62]. Furthermore, chronic active Epstein-Barr virus infection has been associated with high circulating IL-6 levels in human, and with the development of PAH [63]. However, there is some controversy in these associations and it remains possible that there are geographical differences in possible infectious insults [64–66].

Parasites

Schistosomiasis is likely to be the most common cause of PAH worldwide: 200 million people are infected, and the associated prevalence is 2–5 % [67]. The development of PAH is thought to follow hepatosplenic infection with *Schistosoma mansoni* and the subsequent development of portal hypertension: after entering the skin, the fresh-water parasite migrates to the lungs and then to the portal venous system, where it matures [68]. The deposition of eggs in liver veins leads to presinusoidal granulomatous inflammation, peri-portal fibrosis, and portal hypertension. The resultant opening of portocaval shunts both increases pulmonary blood flow and creates a pathway for eggs to lodge in the pulmonary capillaries [67, 68]. Histologically, pulmonary vascular lesions are similar to those seen in idiopathic PAH, including the presence of plexiform lesions [69]. The development of schistosomiasis-associated PAH is thought to be due to the deposition of eggs in lung tissue causing mechanical vessel impaction and focal arteritis, inflammation relating to the formation of granulomas around the eggs, and increased pulmonary blood flow. The contribution of inflammation to vascular remodelling in this setting is not well understood. However, using murine models, it appears that a switch from a Th1 to a Th2 immune response is important [70, 71]. Although these models are important in enhancing our understanding of this globally important cause of PAH, the phenotype does not accurately reflect human disease in that there is less portopulmonary pulmonary hypertension.

Inflammation

Inflammation is present in all forms of PAH. However, how inflammation may contribute to the pathogenesis of PAH is not clear (Fig. 2.3.). It is possible that inflammation may initiate vascular remodelling (“initial hit”), be integral in its propagation (“secondary hit”), or just be a reactive response to ongoing remodelling (“bystander” phenomenon). Initial

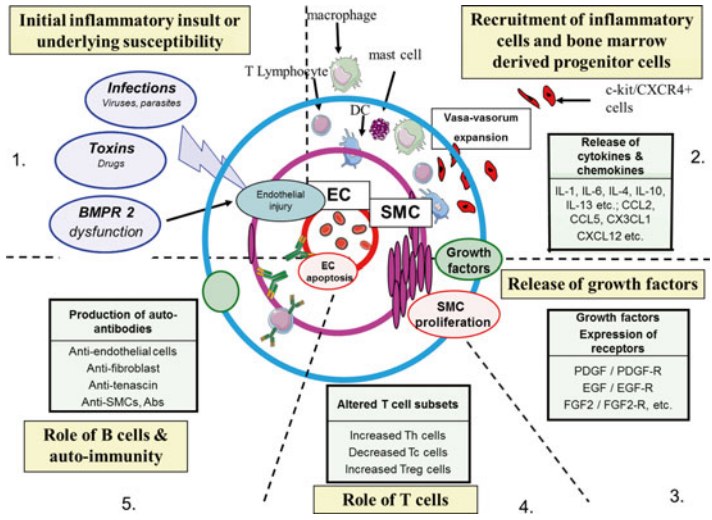

FIGURE 2.3 The role of inflammation on the pathogenesis of pulmonary arterial hypertension. It is likely that there are 5 stages to the influence of inflammation on pulmonary vascular remodelling: *1* Initial inflammatory insult and/or underlying genetic susceptibility; *2* Recruitment of inflammatory cells and bone marrow derived progenitor cells; *3* Release of inflammatory mediators by either vascular cells themselves or associated inflammatory cells; *4* Role of T cells-it is likely that T cells in some way regulate the inflammatory process; *5* Role of B cells and auto-immunity-there is increasing evidence for anti-bodies against key vascular elements driving the inflammatory process

hits may include infections, drugs, or toxins (see previous sections). There may be a relationship between such an inflammatory hit and other factors such as BMPR II status [72], which may alter the subsequent inflammatory response. Whatever the exact relationship, there is evidence for activation of both the innate immune system (activation of macrophages/monocytes) and adaptive immunity (through specific T-cell and B-cell receptors). The cytokines and chemokines subsequently produced may propagate further inflammatory processes and, either on their own, or together with production of growth factors, drive vascular remodelling processes.

Evidence for Inflammatory Cells

T Cells

T cells are essential components of the adaptive immune response. Several lines of evidence support a role for T cells in the development of PAH. In animal models, the athymic nude rat (without T cells) develops PAH more readily than those with intact T-cell production [73]. In the monocrotaline animal model, depletion of Th cells, as well as those of Th2, ameliorates the extent of PAH, again suggesting the importance of a Th2 antigen-driven immune response [74]. Whereas T-cell infiltrates are increased in patients with idiopathic PAH [75, 76], it appears that there is a decrease in $CD8^+$ cytotoxic (Tc) cells and an increase in regulatory (Treg) cells [77]. The precise role of Treg cells in PAH is currently being investigated.

B Cells

B cells generate antibodies to specific antigenic epitopes. Levels of antinuclear antibodies are increased in patients with PAH [78], and autoantibodies directed against endothelial cells [79] and fibroblasts [80] have been described. These autoantibodies may play a role by inducing adhesion molecule expression [81] or inducing endothelial cell apoptosis [82], which may, in turn, contribute to the apoptosis-resistant phenotype. Finally, the development of PAH in patients with systemic sclerosis is seen in association with specific subsets of human leukocyte antigen alleles [83], although the significance of this remains uncertain.

Mast Cells

Accumulation of mast cells has been described in several types of PAH [84, 85]. A recent study has identified an increase in c-kit-positive cells (including mast cells) in remodelled vessels, as well as mobilization of bone marrow-derived circulating progenitor cells [86]. The increase

in mast cell numbers consists mainly of the chymase-secreting subset, numbers of which correlate with the hemodynamic severity of the disease [85]. It is possible that secreted substances from mast cells may be directly vasoactive or have secondary effects such as increased production of matrix metalloproteinases, with consequent involvement in vascular remodelling [84, 87].

Monocytes/Macrophages and Dendritic Cells (DC)

Macrophages are the universal phagocytes that differentiate from tissue monocytes. Along with DC, they are professional antigen-presenting cells, displaying antigen bound to major histocompatibility complex class 2, ready for recognition by T cells. Increased numbers of all these cell types are present around remodelled vessels in PAH [88] . Furthermore, apart from being more numerous in patients with idiopathic PAH, these cells are more "activated" as determined by enhanced nuclear NF-kB immunohistochemical staining [89].

Endothelial Progenitor Cells

Endothelial progenitor cells (EPCs) were first discovered in adult human peripheral blood as a population of CD34 or kinase insert domain receptor (KDR)-positive peripheral blood mononuclear cells which were able to differentiate into mature endothelial cells and were involved in neovascularisation [90]. EPCs are likely to constitute a pool of circulating cells driven from bone marrow in response to stimuli such as tissue ischaemia and vascular damage, and contribute to vascular repair and postnatal neovascularization [91, 92].

Recent animal and clinic studies have suggested that EPCs may be involved in the pathogenesis and progression of PAH [92–94]. For instance, in the mouse hypoxia model of pulmonary hypertension, whole bone marrow transplantation of enhanced green fluorescent protein (GFP)-transgenic mice to lethally irradiated Chimeric mice resulted in the mobilisation of GFP^+ cells to remodelling pulmonary arteries [95, 96].

Furthermore, in the lung from patients with PAH, an upregulation of progenitor cell markers such as CD133 and c-Kit in remodelled arteries is observed, especially in plexiform lesions [97]. In these patients, levels of circulating EPCs ($CD34^+CD133^+VEGFR2^+$) were increased; however, the ability to form vascular networks from late-outgrowth EPCs ($CD34^+CD146^+vWF^+CD133^{+/-}$) was impaired [97].

Evidence for Cytokines/Chemokines

Cytokines

Interleukin (IL)-1-β

IL-1-β is a potent proinflammatory cytokine. In human PAH, serum concentrations are raised [98] and these correlate with a worse outcome [99]. IL-1-β is produced in larger amounts in the monocrotaline animal model, compared with the chronic hypoxic model of pulmonary hypertension [82]. Furthermore, repeated treatment with an IL-1 receptor antagonist reduces pulmonary hypertension and right ventricular hypertrophy in the monocrotaline model, although not in the chronic hypoxia counterpart [100].

IL-6

IL-6 is another proinflammatory cytokine synthesized by many cell types. Plasma concentrations of IL-6 are elevated in idiopathic PAH [98], and they correlate with severity of disease and with increased mortality [99]. In patients with systemic sclerosis, elevated circulating IL-6 concentrations predict the presence of associated PAH [101]. Elevated serum IL-6 concntrations also correlate with hemodynamic severity in pulmonary hypertension associated with COPD [102] and in other forms of PAH, including sickle cell disease-associated PAH [103]. Pulmonary IL-6 production is also increased in experimental pulmonary hypertension and is thought to reflect increased production by both inflammatory cells and vascular cells [104, 105]. In turn, IL-6 has many effects on

inflammatory and vascular cells that may promote vascular remodelling. These include accumulation of perivascular T lymphocytes [106], stimulation of endothelial cells to produce chemokines [107], promotion of pulmonary artery smooth muscle cell and endothelial cell proliferation [99, 105].

IL-13

IL-13 is a cytokine secreted by many cells, especially Th2 cells and mast cells. It is important in forming granulomata in response to parasites (including schistosomiasis) and its effects on immune cells are similar to those of IL-4. Loss of IL-13 signaling reduces pulmonary vascular remodeling in models of pulmonary hypertension and its effects on T cells suggest an indirect role in regulating Th2 responsiveness [70, 74]. A relative increase in the negative-regulating decoy receptor, IL-13Rα2, is observed in pulmonary arterial smooth muscle cells from patients with idiopathic PAH compared with the active receptors (IL-13Rα1 and IL-4R), as well as in monocrotaline and hypoxic pulmonary hypertension models [108]. Perhaps surprisingly, IL-13 is antiproliferative to pulmonary arterial smooth muscle cells *in vitro*, with an associated reduction in ET-1 release [108]. Overall, these data suggest that dysregulated signalling of this Th2 cytokine is likely to contribute to vascular remodelling in PAH.

Chemokines

Monocyte Chemoattractant Protein(MCP-1)

MCP-1 (or CCL2) is a chemokine produced by vascular cells that stimulates monocytes/macrophage activation and migration, with actions mediated via the chemokine (C-C motif) receptor. Elevated levels of MCP-1 are found in the plasma and lung of patients with idiopathic PAH [109], although they do not correlate with disease severity. Furthermore, vascular smooth muscle cells and endothelial cells from patients with idiopathic PAH release high levels of MCP-1. In addition, vascular smooth muscle cells from patients with idiopathic PAH express increased levels of the chemokine (C-C motif)

receptors, exhibit exaggerated migratory and proliferative responses to MCP-1, and these can be blocked by MCP-1 antibodies [109]. Interestingly, an anti-MCP-1 monoclonal antibody has been used in patients with rheumatoid arthritis in a randomized controlled trial, but not yet in PAH [110].

Regulated on Activation, Normal T-cell Expressed and Secreted (RANTES)

RANTES (or CCL5) is a chemokine that mediates the trafficking and homing of T lymphocytes, monocytes, basophils, eosinophils, and natural killer cells through different chemokine receptors [111]. Pulmonary RANTES mRNA is elevated in patients with PAH and shown to be of endothelial cell origin [5, 89, 111]. However, the role of RANTES in the pathogenesis and progression in PAH has not been elucidated.

Fractalkine (CX3CL1)

Fractalkine (CX3CL1) is a chemokine expressed as a soluble or as a membrane-bound form. The effects of fractalkine are mediated through the receptor, CX3CR1, expressed by many cell types. Elevated concentrations of soluble fractalkine are seen in patients with PAH [112], although the association of such elevation with disease severity and prognosis is not currently proven. Increase expression of fractalkine mRNA and protein were detected in pulmonary vascular endothelial cells. Furthermore, it has been shown that the CX3CR1 expression and function were upregulated on both $CD4^+$ and $CD8^+$ T lymphocytes in patient with PAH [89, 112]. It is likely that the concomitant increase of expression in ligands in endothelial cells and receptors on T cells may contribute to the perivascular inflammatory cell influx [113]. Fractalkine and CX3CR1 expression were also shown to be upregulated in pulmonary smooth muscle cells in the monocrotaline rat model of pulmonary hypertension. Finally, fractalkine treatment increased pulmonary arterial smooth muscle cell proliferation *in vitro*, indicating a direct role of fractalkine in vascular remodelling [113].

Platelet Derived Growth Factor (PDGF)

PDGF is secreted as a homodimer of genetically distinct but structurally similar polypeptides (chains A-D) [114]. Additionally, only chain A and chain B can form a functional heterodimer. Increased expression of PDGF-A, PDGF-B and PDGF receptor (R)-α, PDGFR-β mRNA and protein have been found in pulmonary arteries from transplanted PAH patients. Further study demonstrated that PDGF-A and PDGF-B proteins were localised in smooth muscle and endothelial cells, whilst PDGFR-α, PDGFR-β proteins predominated in smooth muscle cells in remodelled pulmonary arteries including plexiform lesions. In addition, intense staining of the ligands and receptors has also been observed in perivascular inflammatory infiltrates [115].

PDGF is a strong mitogen for cells of mesenchymal origin including smooth muscle cells and fibroblasts [114, 115]. Imatinib, a well-established tyrosine kinase inhibitor of the kinase BCR-ABL; the receptor for the stem cell factor, c-KIT; and the PDGFR [116], has been shown to have antiproliferative and pro-apoptotic effects on pulmonary artery smooth muscle cells taken from patients with PAH *in vitro* [115], and has also been shown to reverse pulmonary vascular disease in animal models of PAH [117, 118]. See later section for clinical evidence.

Epidermal Growth Factor (EGF)

EGF promotes chemotaxis, mitogenesis and cytoprotection in epithelial and mesenchymal cells through binding to its receptor (EGFR). The EGFR belongs to the ErbB family of tyrosine kinase receptors [119]. EGF has been shown *in vitro* to increase pulmonary arterial smooth muscle cell proliferation [120]. In the monocrotaline animal model of pulmonary hypertension, the use of serine elastase inhibitors has been shown to reverse pulmonary vascular remodelling. In this study it was suggested that serine elastases, by breaking down extracellular matrix, could lead to the release of EGF and promote vascular remodelling [121].

Vascular Endothelial Growth Factor (VEGF)

VEGF is an endothelial cell specific mitogen and a potent angiogenic mediator. VEGF is produced by a variety of cells and has been implicated in physiological and pathological conditions associated with endothelial cell proliferation [122]. It has been suggested that VEGF is important in attenuating the development of PAH possibly by protecting endothelial cells from injury and apoptosis [123, 124]. Indeed, an overall decrease in pulmonary VEGF expression has been reported, in concert with a dramatic decrease in pulmonary vessel number and a significant increase in vessel wall thickness in the monocrotaline model of pulmonary hypertension [125]. Pulmonary VGEF and VEGF receptor were also down regulated in a rat model of pulmonary hypertension associated with idiopathic pulmonary fibrosis [124]. In contrast, serum VEGF levels are increased in systemic sclerosis patients with PAH [126]. Upregulation of VEGF has also been described in association with plexiform lesions, possibly representing an incomplete attempt at revascularization distal to an arteriolar occlusion [122, 127].

Fibroblast Growth Factor 2 (FGF2)

FGF2 is a member of a large family of heparin-binding growth factors. Increased lung and circulating FGF2 levels have been reported in both experimental and human pulmonary hypertension. Abnormally high levels of FGF2 were found in the blood of 51 % and in the urine of 21 % of patients with idiopathic PAH [128] and in 3 animal models: a lamb model of pulmonary hypertension developed by inserting an aortopulmonary vascular bypass graft [129] and the rat chronic hypoxic and monocrotaline models of pulmonary hypertension[130, 131]. It has been shown that excessive autocrine release of endothelial-derived FGF2 in idiopathic PAH contributes to the acquisition and maintenance of an abnormal endothelial cell phenotype *in vitro* and *in vivo*, enhancing proliferation through constitutive activation of ERK1/2 and decreasing apoptosis by increasing BCL2 and

BCL-xL [132]. Finally, a recent study on apelin knockout mice showed that apelin deficiency led to increased expression of FGF2 and its receptor FGFR1 as a consequence of decreased expression of microRNA (miR)-424 and miR-503, which directly target FGF2 and FGFR1[133].

Serotonin (5-hydroxytryptamine, 5-HT)

Serotonin is an important vasoactive and mitogenic compound that is synthesised by endothelial cells and acts on pulmonary arterial smooth muscle cells [134]. The serotonin transporter (5-HTT) is required for serotonin to elicit its mitogenic effects and transgenic mice overexpressing 5-HTT have been shown to spontaneously develop PH. Serotonin receptors (5-HT_{2B}) also appears to play important role in mediated vascular remodelling: mice with restricted expression of 5-HT_{2B} receptors in bone marrow cells exacerbate hypoxia or monocrotaline-induced increases in pulmonary pressure and vascular remodeling, whereas restricted elimination of 5-HT_{2B} receptors on bone marrow cells confers a complete resistance to the development of PH [135]. The role of serotonin system in the pathogenesis of PAH was further supported by the development of PAH in a sub-set of patients taking the anorexigenic drugs aminorex and dexfenfluramine. Both of these drugs are 5-HTT substrates and indirect serotinergic agonists [134]. The overexpression of 5-HTT in pulmonary vascular media may be caused by a polymorphism in the promoter region of the human 5-HTT gene which alters the level of transcription or, alternatively, by BMPR II dysfunction [136–139].

Evidence for Autoantibodies/Autoimmune Phenomenon

Anti-endothelial cell antibodies (AECAs) and anti-fibroblast antibodies (AFAs) have been detected in plasma from patients with idiopathic PAH and with systemic sclerosis-associated PAH (SSc-PAH) [79, 80]. AECAs and AFAs from

patients with idiopathic PAH and SSc-PAH showed a distinct reactivity profile; AECAs from patients with idiopathic PAH bound more strongly to a 58 kDa band in dermal microvascular endothelial cells and to a 53 kDa band in lung microvascular endothelial cells. AECAs from patients with limited cutaneous SSc with or without PAH bound to two major bands (75 kDa and 85 kDa) in microvascular endothelial cells [79]. One the other hand, AFAs from these patients predominantly bound to 25-, 40-, and 60-kD protein bands [80]. Further study has identified 16 proteins: vimentin, calumenin, tropomyosin 1, heat shock proteins 27 and 70, glucose-6-phosphate-dehydrogenase, phosphatidylinositol 3-kinase, DAP kinase, and others as the target antigens of AFAs [140]. These proteins are involved in regulation of cytoskeletal function, cell contraction, oxidative stress, cell energy metabolism, and other key cellular pathways. Therefore autoantibodies may play an important role in PAH pathogenesis [140].

Current Treatment of PAH

As mentioned before the current treatment of PAH is based on endothelial dysfunction: hence endothelin receptor antagonists are used to counter increased ET-1 levels; phosphodiesterase type V inhibitors enhance endogenous NO levels; exogenous prostanoids replace deficiencies in PGI_2 production. The evidence for and the use of these drugs is covered in depth in separate chapters. It is also worth noting that to improve safety and efficacy, a number of new drugs targeting these pathways have been tested in clinic trials and will be mentioned here.

Macitentan is a novel dual ET-1 receptor antagonist (ERA) with sustained receptor binding and optimised physiochemical properties, leading to enhanced tissue penetration [141, 142], an improved side-effect profile and limited drug–drug interactions [143, 144]; it also has no significant inhibitory effects on hepatic bile salt transport [145] and therefore has the potential for a favourable liver safety profile [146].

In the recently published SERAPHIN study, macitentan was shown to be superior to placebo in reducing the number of combined mortality and morbidity events in a large group of patients with PAH [2].

Riociguat is a first-in-class drug that augments cGMP biosynthesis (and therefore vasodilation) through direct stimulation of the enzyme, soluble guanylate cyclase (sGC) in an NO-independent fashion, and by sensitization of sGC to low endogenous NO levels [147]. Results from a multicenter, open-label, uncontrolled phase II trial involving 75 patients with PAH ($n = 33$) and chronic thromboembolic pulmonary hypertension ($n = 42$) showed that 12 weeks of oral riociguat given 3 times daily conferred improvements in symptoms, NYHA functional class, exercise capacity, NT-proBNP level, and pulmonary hemodynamics [148]. A decrease in systemic arterial diastolic pressure was the only significant side effect reported, with none associated with symptoms leading to a permanent discontinuation of riociguat [148]. Riociguat is also under investigation in other form of PH such as PH associated with chronic obstructive pulmonary disease, with interstitial lung disease or with left ventricular dysfunction [149–151]. Two large multicentre, randomized, double-blind, placebo-controlled phase III studies have just been published. In PATENT-1, riociguat was shown to be superior to placebo in terms of 6MWT and haemodynamics in patients with PAH [152]. In CHEST-1 riociguat resulted in greater 6MWT and improved haemodynamics in CTEPH patients, either inoperable or with persistent PAH post pulmonary endarterectomy [153].

Future Therapeutic Targets

The following section will cover future potential targets, many of which may target vascular remodelling itself, rather than endothelial cell dysfunction.

PDGF/Tyrosine Kinase Inhibitors

Imatinib, a PDGF/tyrosine kinase receptor inhibitor, was initially shown to be beneficial in a patient with vasodilator-resistant, severe idiopathic PAH [154]. This effect was sustained after 6 months of treatment [154]. A Phase II trial involved 59 patients who were classified as FC II to IV PAH and had an inadequate response to previous therapy were enrolled in a 24 weeks study. The imatinib treated group showed a mean improvement of 22 m in 6MWD compared with a decline of 1 m in the placebo group, although this difference was not significant [155]. However, significant improvements were seen in pulmonary vascular resistance (PVR) (imatinib −300 versus placebo −78 dyn.s.cm-5; $p < 0.01$) and cardiac output (imatinib +0.6 versus placebo −0.1 L/min-1; $p = 0.02$). In the recently published Phase III study, IMPRES, imatinib was used as add-on therapy for advanced patients with PAH who were symptomatic despite treatment with two or more PAH-specific therapies. The imatinib treated group showed significantly improvement in exercise capacity and haemodynamics. However, imatinib did not provide a benefit in terms of FC, time to clinical worsening or mortality [156]. There was also a higher incidence of intracranial haemorrhage in the imatanib treated group. As yet it is not known whether further tyrosine kinase receptor inhibitors will have a better efficacy to side-effect profile. Indeed, dasatinib has been shown to induce PAH in certain patients [157].

The EGF receptor tyrosine kinase inhibitors gefitinib, erlotinib and lapatinib have been tested in rats with monocrotaline-induced pulmonary hypertension. These inhibitors have been shown to inhibit EGF-induced smooth muscle cell proliferation *in vitro* [120]. However, at their highest tolerated dose there was no significant improvement in RV systolic pressure or hypertrophy in animal models. Therefore, more work needed to evaluate the potential of EGFR antagonists as the treatment of PAH.

Epigenetic Modulators

Epigenetics describes changes in phenotype or in gene expression states independent of DNA sequence and include chromatin remodelling, DNA methylation, histone modification and RNA interference. Epigenetic modifications can be inherited or acquired *de novo*, and provide a mechanism that allows the stable propagation of gene activity states from one generation of cells to the next [158]. It has been shown that epigenetic modifications are involved in many diseases mechanisms including cancer, asthma, several hereditary disorders and recently PAH [159, 160].

DNA Methylation

In the heritable fawn hooded rat pulmonary hypertension model, the expression of superoxide dismutase 2 (SOD2) is decreased and yet no mutations are found in the SOD2 gene [161, 162]. However, CpG islands in the SOD2 gene are selectively hypermethylated, which result in ~50 % reduction of SOD2 expression in pulmonary arterial smooth muscle cells from fawn hooded rats compared to those from genetically matched rats [161].

Histone Methylation and Acetylation

It has been shown that constitutive eNOS expression is increased 6-fold in pulmonary vascular endothelial cells derived from a neonatal rodent perisitent pulmonary hypertension of the newborn (PPHN) model. The eNOS upregulation was associated with increased H3 and H4 histone acetylation in the eNOS promoter [163] and a small decrease in eNOS methylation. Indeed, increased histone deacetylase (HDAC1 and HDAC5) expression and activity has been found in lungs from patients with idiopathic PAH. Treatment with the HDAC inhibitors, valproic acid, and suberoylanilide

hydroxamic acid, reduced the constitutive proliferative phenotype of adventitial fibroblasts and rhomboidal cells from hypoxic rat *in vitro*, and attenuated the development and ameliorated established pulmonary hypertension in a chronic hypoxic rat model [164].

MicroRNAs (miRNAs)

Micro RNAs are small, non-coding RNA molecules that regulate gene expression. miRNAs often target groups of genes that are related in terms of function. There is an increasing literature describing associations of miRNAs with the development of pulmonary hypertension both in *in vivo* models and in human disease [165–167]. For instance miR 150 is downregulated in the plasma and lungs of patients with idiopathic PAH, and is associated with poorer outcome [168]. Work is currently underway to develop methods to target miRNAs as a novel therapy for PAH and other cardiovascular diseases [169].

Anti-Inflammatory/Immunosuppressive Treatments

There are reports of successful treatment of patients with PAH associated with lupus and mixed connective tissue disease with immunosuppressive agents [170]. Furthermore, a case study reported successful treatment of a patient with Castleman's-related PAH with the anti-IL-6 monoclonal antibody, tocilizumab [171]. Interestingly, rapamycin, an immunosuppressive agent, has also been investigated in animal models of PAH. Rapamycin is also a potent anti-proliferative agent, and has been shown to be effective in preventing the RV wall thickening in rat monocrotaline model [172]. In addition, rapamycin also inhibited the proliferation of pulmonary vascular cells *in vitro* and reversed pulmonary vascular remodelling in mice hypoxia-induced pulmonary hypertension model [173]. Finally, the steroid dexamethasone, has been shown to reverse the haemodynamic and structural changes seen in the

monocrotaline model of pulmonary hypertension and prednisolone inhibits proliferation of pulmonary artery smooth muscle cells from patients with idiopathic PAH *in vitro* [174, 175]. Therefore, anti-inflammatory therapy including immunosuppressants steroids, rapamycin and tocilizumab, may provide novel treatments in the future.

Novel Vasoactive Factors

Apelin

Apelin is a vasodilatory peptide which is thought to play a role in angiogenesis and regulate endothelial and smooth muscle cell apoptosis and proliferation [176]. Interestingly, patients with PAH have lower levels of apelin [176]. Currently, clinical trials are testing whether the administrating apelin is beneficial in humans with PAH.

Vasoactive Intestinal Peptide (VIP)

VIP is also a vasodilator [177]. VIP Knockout mice showed significant increases in right ventricular (RV) systolic pressures, vascular remodelling, and inflammation [178], which was attenuated by treatment with VIP. Two clinic trials showed conflicting results. A multicentre Phase II study in 56 patients with PAH suggested that there was no reduction in PVR, or increase in exercise capacity over 12 weeks compared with placebo [179]. The other, single centre, open-label study of eight patients found that haemodynamics and 6MWD were improved following 3 months' treatment with VIP [180].

Endothelial Nitric Oxide Synthase (eNOS) Couplers

Endothelial nitric oxide synthase can mediate the production of both vasorelaxants and vasoconstrictors: the coupling of

eNOS could therefore have a twofold impact on the balance of vasoactive factors released by the endothelial cells [181]. A pilot study of the eNOS coupler, sapropterin dihydrochloride, showed significant improvements in exercise capacity and the treatment was well tolerated, although NO synthesis was not effected [182].

IP Receptor Agonists

The IP receptor is the main receptor for PGI_2. Selexipag, a non-prostanoid, selective IP receptor agonist was recently used in a Phase 2, proof of concept study in patients with PAH. Compared to placebo, there was a significant decrease in PVR with an acceptable side-effect tolerability profile [183]. Given these favourable results a large Phase 3 study (Grython, Actelion Pharmaceuticals) is now underway.

Serotonin Receptor Antagonism

The serotonin receptor antagonist, terguride, has been shown to prevent the development and progression of monocrotaline-induced pulmonary hypertension in rats [184]. However, a 16-week study in 78 patients with PAH showed no overall significant improvements in PVR or other endpoints. Subgroup analysis found that PVR significantly improved in patients who were also treated with an ERA [185].

Rho-kinases

The small GTPase, RhoA and its downstream effectors, ROCK1 and ROCK2, regulate many essential cellular processes such as cell contraction, migration, proliferation, survival, and differentiation. There was a twofold increase in Rho kinase and RhoA activity in lungs from patients with idiopathic PAH as compared to control patients [186].

The activity of ROCK was closely related to the disease duration. In addition, beneficial effects of fasudil [187] and SB-772077-B [188] specific ROCK inhibitors, has been observed in different animal models of pulmonary hypertension [189–193]. However, ROCK inhibitors appear to have serious systemic side effects. Hence, inhalation form of fasudil has been trialed in 15 PAH patients[193] and in 19 patients with high-altitude pulmonary hypertension [194]. This treatment was shown to significantly reduce mPAP and decrease PVR.

Peroxisome Proliferator-Activated Receptor-γ (PPARγ)

PPARγ is a transcription factor which is also a downstream target of BMPR2 signalling. On formation of a complex with catenin, PPARγ triggers the transcription of several genes that appear to be associated with PAH, such as apelin [195] and apoE [196]. Endothelial or smooth muscle cell specific PPARγ knockout mice have been shown to develop pulmonary hypertension [196, 197]. Treatment of rats with experimental pulmonary hypertension using the PPARγ agonist rosiglitazone attenuated the development of hypoxia-induced pulmonary hypertension [198]. Interestingly, PPARγ antagonists pioglitazone and rosiglitazone have been shown to be potent vasodilator on isolated human pulmonary arteries [199].

Cell Therapy

Administration of EPCs in rats with monocrotaline-induced pulmonary hypertension led to the prevention of pulmonary hypertension and restoration of pulmonary microvasculature structure [200]. Pulmonary hypertension and Cell Therapy (PHACeT) is a clinical trial ongoing in Canada in order to assess safety of administrating autologous mononuclear cells transduced with eNOS in patients with isiopathic PAH [201].

Associated to this safety study, efficacy of EPC infusion have been reported in adult and children patients with idiopathic PAH with improvement on exercise capacity and pulmonary hemodynamics [202, 203].

Summary

This chapter has described the molecular biological aspects that underpin both current and future treatment of patients with PAH. It has emphasized the shift away from treating the abnormalities associated with endothelial dysfunction, towards therapy aimed at reversing pulmonary vascular remodelling. Only then will we be able to make a significant impact on the morbidity and mortality associated with this devastating condition.

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Chapter 3
Current Treatment Strategies, Guidelines and New Therapies

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Historically, primary pulmonary hypertension (as it was then termed) has been considered a rapidly progressive, fatal condition with no effective therapies with an average life expectancy of less than 3 years at diagnosis [1]. It has been labelled as a "desperate disease" and upon diagnosis one enters "the kingdom of the near-dead" [2].

In the 1980s, the vasodilatation caused by high dose calcium channel blockers was discovered to have a beneficial effect. These results were shown to improve pulmonary artery pressure, pulmonary vascular resistance, right ventricular hypertrophy and survival. It did however become quickly apparent that the treated population could be clearly sub-divided into two categories – those who responded and those who did not [3].

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Over the past 15 years there has been rapid progress in the field, predominantly in the treatment of class 1, pulmonary arterial hypertension (PAH). Several classes of advanced, targeted vasodilator medication have been developed and there is now a wealth of evidence supporting their use. Given the rapid progress being made, optimal treatment strategies are constantly evolving. The three major classes of therapy (namely endothelin receptor antagonists, phosphodiesterase-5 inhibitors and prostacyclin analogues) and the evidence behind their use are discussed below.

Since 2001, all decisions regarding the commencement of targeted vasodilator therapy in the UK and Ireland are made by the National Pulmonary Hypertension Service. There are nine centres as designated by the National Commissioning Group. These are Western Infirmary (Glasgow), Mater Misericordiae University Hospital (Dublin), Freeman Hospital (Newcastle), Royal Hallamshire Hospital (Sheffield), Papworth Hospital (Cambridge) and in London, the Royal Brompton Hospital, Hammersmith Hospital, Royal Free Hospital and Great Ormond Street Hospital [4].

Individual agents have shown both clinical (symptomatic, functional and delayed time to worsening) and haemodynamic improvements and when the trials are taken together there is a survival benefit. A mortality reduction of 43 % was shown by a 2009 meta-analysis of targeted vasodilator therapy versus placebo [5]. Pulmonary arterial hypertension patients can now expect a median prognosis of approximately 9 years at diagnosis, threefold that of the pre-vasodilator era [6] (Fig. 3.1).

Endothelin Receptor Antagonists

Endothelin-1 is a peptide produced by the endothelium with potent vasoconstricting and smooth muscle proliferating properties. It is found at higher concentrations in pulmonary hypertension and has also been implicated in the pathogenesis of atherosclerosis and systemic hypertension. Oral endothelin receptor antagonism has been used since the late 1990s in pulmonary arterial hypertension.

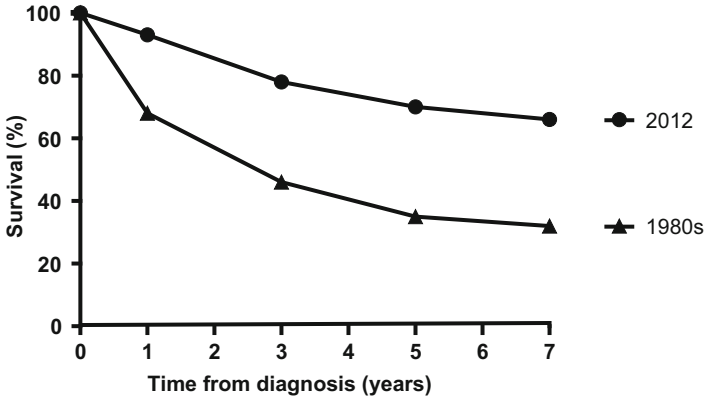


FIGURE 3.1 Survival plot before and after the advent of targeted vasodilator therapy, using REVEAL registry data (2012) of idiopathic and familial PAH matched to that from National Institutes of Health registry (1980s) (Adapted from Benza et al. *Chest* [6] with permission)

The two receptor isoforms A and B are more prominent in pulmonary artery smooth muscle and vascular endothelium respectively. Bosentan and macitentan act on both receptors whereas ambrisentan (and sitaxentan) are selective for endothelin receptor A. Despite endothelin receptor B having vasodilatory effects and playing a role in endothelin-1 clearance, the selective antagonists have not been shown to be clinically superior to date.

Transaminitis is the most important side-effect and hence monthly blood test monitoring is required. Sitaxentan was initially reported to be efficacious and to have a low incidence of hepatic complications [7] but was taken off the market in 2010 due to several reported deaths from hepatotoxicity [8].

Other side-effects of these agents are peripheral oedema, nausea, hypotension, teratogenicity, anaemia, headaches/jaw pain and flushing. Ambrisentan needs to be used with caution in idiopathic pulmonary fibrosis [9].

Bosentan

The BREATHE-1 trial was a 2002 randomised controlled trial (RCT) with 213 idiopathic and associated PAH patients who were highly symptomatic, namely functional class (FC) III or IV. After 16 weeks' treatment, the mean 6 min walk test (6MWT) increased by 35 m and 54 m (125 mg and 250 mg BD respectively versus placebo), and 34–38 % had improved to WHO FC II. In addition the time to clinical worsening was prolonged. There was a 7 % reported transaminitis rate at the higher dose [10].

The EARLY study from Italy in 2008 recruited 185 FC II, group 1 patients. After 6 months, the haemodynamics and symptoms improved and time to clinical worsening was delayed. Pulmonary vascular resistance (PVR) was 83 % of baseline in the treated arm and 6MWT 19 m further between the two arms [11].

Ambrisentan

ARIES 1 and 2 were concurrent double-blind trials involving a total of 394 idiopathic and associated PAH patients who were targeted vasodilator treatment naive and had a 6MWT between 150 and 450 m. The randomisation was to different dosing regimens (2.5, 5 and 10 mg OD) and placebo controlled. The primary end-point of 6MWT increased by between 31 and 54 m with dose dependency seen. Also seen was statistically significant improvement in functional class, health related questionnaire, time to clinical worsening, Borg dyspnoea and BNP level. The initial study time period was 12 weeks but an extension studies showed persistent benefits to 48 weeks and 2 years. Elevation in transaminases was quoted at 3.9 %. Hence ambrisentan is considered to have a safer liver side-effect profile than bosentan [12, 13].

ARIES 3 was an open label, uncontrolled study that broadened the patient selection criteria to include Dana Point groups 3 and 4. Overall 6MWT increased by 21 m. This improvement was seen in groups 1 and 4 but not group

3. The COPD and ILD sub-group demonstrated a slight deterioration in their exercise capacity but their BNP levels did decrease in keeping with the other aetiologies [14].

Macitentan

This novel unselective endothelin receptor antagonist is believed to be more potent due to prolonged binding time and tissue penetration. Macitentan had initially shown promising results in animal models and now has a large international RCT with morbidity benefit supporting its use.

The SERAPHIN study of 742 group 1 patients, with the primary outcome measure of morbidity events and mortality, was reported in 2013 [15]. The study population were mainly FC II and III and approximately 60 % were already taking targeted vasodilator medication, predominantly a phosphodiesterase-5 inhibitor. There was a highly significant reduction in adverse events, usually clinical worsening of PH, and the hazard ration for the 10 mg dose of macitentan compared with placebo was 0.55. There was also a non-significant trend towards mortality benefit. 6MWT and FC also showed significant improvement (the former by 22 m) with a degree of dose dependency. The transaminitis incidence was lower than placebo at 3.5 %.

Phosphodiesterase-5 Inhibitors

Sildenafil, tadalafil and vardenafil are selective cyclic GMP phosphodiesterase type 5 inhibitors which are administered orally. cGMP acts as a second messenger in the nitric oxide pathway and PDE5 is upregulated in the pulmonary hypertension vascular bed. The PDE5 inhibitors prevent the breakdown of cGMP and hence cause potentiation of the endothelial smooth muscle relaxtion of NO. In addition they are believed to be anti-proliferative and have shown pulmonary vascular remodelling in vitro.

Side-effects include postural hypotension (hence the contraindication with concurrent nitrates), visual disturbance

including cyanopsia (with cGMP PDE5 particularly prevalent in the retina), headache, hearing loss, flushing and dyspepsia. They are the most recently developed class, with sildenafil first licensed in 2005. Two newer PDE5 inhibitors, tadalafil and vardenafil, are longer acting (hence requiring less frequent administration) and appear to be equally efficacious. Vardenafil may be more potent due to prolonged binding time.

Sildenafil

Case reports, small non-randomised studies and one RCT from the early 2000s first showed the benefit of sildenafil [16–20] but the strongest evidence for its use as monotherapy comes from the SUPER-1 trial. 278 PAH patients were recruited into a 12 week double blind RCT with four arms, placebo versus 20, 40 and 80 mg TDS. The population studied were IPAH, connective tissue disease and a few congential patients post-surgical correction. There was improvement in 6MWT (improved by 45–50 m, which represented 13.0–14.7 %), mean PA pressure (small absolute reduction but statistically significant) and WHO FC (improved by at least one in 7 % of placebo and up to 42 % at the highest dosage) [21]. The same trial population also undertook health related quality of life questionnaires SF-36 and EQ-5D with significant improvement [22].

259 of the above patients underwent a 3 year open label, uncontrolled extension in SUPER-2. Approximately half at least maintained their 6MWT and functional class over the 3 years from pre-treatment baseline. 3 years survival was 79 %. The majority were uptitrated to 80 mg TDS (with good safety profile) and 18 % had had a second agent added by the end [23].

Tadalafil

The PHIRST RCT involved 405 idiopathic or associated PAH patients. The highest dose 40 mg OD increased 6MWT by a mean 44 m after 16 weeks as single agent [24].

Vardenafil

Vardenafil was studied by RCT in treatment naive PAH over 12 weeks in the EVALUATION trial. 6MWT improved by 69 m. Haemodynamics were also significantly improved in terms of pulmonary artery pressure (down 5.3 mmHg), cardiac output (up by 0.39 l/min) and pulmonary vascular resistance (down by 4.7 WU). WHO FC and Borg dyspnoea were also improved. For the first time a PDE5 inhibitor was shown to reduce clinical worsening events, namely death or hospitalisation [25].

Prostacyclin Analogues

Prostacyclin (or prostaglandin I2) is a prostinoid produced by vascular endothelium that has vasodilatory, anti-thrombotic, anti-proliferative and anti-inflammatory properties. The pathway has a significant role in the pathogenesis of pulmonary hypertension. Intravenous epoprostenol was the first advance targeted vasodilator licensed for treatment of PH (in 1998). Several analogues have been developed but the mode of administration remains problematic.

Epoprostenol

Initial trials from the 1990s showed benefit from continuous IV epoprostenol infusion in idiopathic pulmonary arterial hypertension [26–29].

As with the other classes, the best level of evidence comes from group 1 PAH patients who have advanced disease, i.e. WHO FC III or IV. The above unblinded RCT by Barst et al. in 1996 involved 81 such patients and showed statistically significant improvement in terms of exercise tolerance (6MWT differential of 47 m between the arms and functional class improved in 40 % compared with only 3 % in the placebo arm), haemodynamics (PVR reduced by

21 % compared with a 9 % increase in placebo) and even a survival benefit (zero deaths compared with 8) over a 12 week period.

Epoprostenol has a half-life of only a few minutes and consequently does require continuous infusion without interuption. The syringe needs to be changed every 8 h due to the medication degrading unrefrigerated. Specific complications include pump disruption, infusion pain, line thrombosis and infection. Should there be any disruption to the flow then there is a 10–15 min window to rectify matters. If this is unsuccessful then there is the potential for a rebound pulmonary hypertensive crisis and death. Other complications include hypotension, jaw pain, flushing, wheeze, nausea, diarrhoea, agitation and arthralgias.

Treprostinil

Treprostinil is an epoprostenol analogue which has been developed to have greater stability at room temperature. Consequently it has the advantage that is can be given subcutaneously as well as intravenously. Subcutaneously it has been shown to have a survival benefit and improved functional class in PAH patients [30]. Oral preparations are being developed but their efficacy has not been proven to date [31].

Iloprost

Inhaled or nebulised iloprost has been shown to be beneficial in a range of aetiologies including group 1 and group 4 with FC III and IV. It has to be administered every 2–4 h and proves a significant time burden on those using it [32]. There is only limited evidence with the use of intravenous iloprost with its efficacy called into question.

Beraprost

Beraprost as an oral preparation that demonstrates an improvement in symptoms which is only temporary. It appears to work for the first 3–6 months but this is not sustained at the 12 months mark [33, 34].

Selexipag

This novel prostacyclin receptor agonist can be administered orally and has phase 2 evidence behind it. It is discussed later in the novel/future therapies section (Table 3.1).

Combination Therapy

In the future it seems likely that dual or even triple therapy will be commenced at an earlier stage. Randomised controlled trials are being reported every year but have had mixed results to date. All of the following studies are exclusively in group 1 PAH patients.

One relatively early prospective cohort showed the benefit of sildenafil added into iloprost in the context of clinical deterioration [35].

Bosentan and prostanoids in combination in idiopathic PAH has shown contradictory results with the following studies being positive and negative respectively [36, 37]. However the best calibre of evidence comes from the 2006 STEP-1 trial with 67 PAH patients randomised to placebo versus iloprost added into bosentan monotherapy. The 6MWT improvement at 12 weeks was 26 m and 34 % improved functional class (compared with 6 % in placebo arm) [38].

BREATHE 2 saw bosentan added into epoprostenol and although there was a trend towards functional improvement with both therapies, it was not significant [39].

Table 3.1 Summary of advanced, targeted pulmonary vasodilator medication

Endothelin receptor antagonists

Side-effects	Hepatic dysfunction, peripheral oedema, nausea, hypotension, teratogenicity, anaemia, headaches/jaw pain and flushing					
Name	**Brand name**	**Route of administration**	**Initial Dose**	**Up-titration dose**	**Monitoring**	**Notes**
Bosentan	Tracleer	Oral	62.5 mg BD	250 mg BD	Monthly liver function required	Interaction with warfarin (bosentan) Contra-indicated with cyclosporin
Ambrisentan	Volibris	Oral	5 mg OD	10 mg OD		
Macitentan	Opsumit	Oral	3 mg OD	10 mg OD		

Phosphodiesterase-5 inhibitors

Side-effects	Postural hypotension, visual disturbance including cyanopsia, headache, hearing loss, flushing and dyspepsia					
Name	**Brand name**	**Route of administration**	**Initial Dose**	**Up-titration dose**	**Monitoring**	**Notes**
Sildenafil	Revatio, Viagra	Oral	20 mg TDS or 25 mg TDS	50 mg TDS	History of visual impairment	Contra-indicated with nitrates First line in hepatic dysfunction
Tadalafil	Adcirca	Oral	20 mg OD	40 mg OD		
Vardenafil	Levitra	Oral	5 mg BD	20 mg BD		

Prostacyclin analogues						
Side-effects	Hypotension, jaw pain, flushing, wheeze, nausea, diarrhoea, agitation and arthralgias. Administration may be complicated by pump disruption, infusion pain, line thrombosis and infection					
Name	**Brand name**	**Route of administration**	**Initial Dose**	**Up-titration dose**	**Monitoring**	**Notes**
Epoprostenol	Veletri, Flolan	Intravenous	2 ng/kg/min	200 ng/kg/min		High risk of rebound pulmonary hypertension if infusion is disrupted
Treprostinil	Remodulin, Tyvaso	Intravenous, subcutaneous or nebulised	1.25 ng/kg/min IV/SC	40 ng/kg/min IV/SC		
Iloprost	Ventavis	Nebulised	2.5 µg 6–9× per day	5 µg 6–9× per day		

Sildenafil plus epoprotenol in 267 class III patients showed significant improvement in a range of clinical and haemodynamic parameters [40].

The PHIRST trial increased 6MWT by 23 m when tadalafil was added into bosentan [24].

The positive SERAPHIN study into macitentan had almost two thirds of its participants already taking a phosphodiesterase-5 inhibitor and revealed a significant morbidity benefit [15].

TRIMUPH in 2010 involved 235 severe patients (functional class III and IV) where inhaled treprostinil was added into bosentan or sildenafil. There was an improvement in the primary end-point of 6 min walk testing (improved by 20 m) but no change in time to clinical worsening or level of dyspnoea [41].

The FREEDOM-C and FREEDOM-C2 trials have been published in the last 12 months. Oral treporostinol, at different dosages, was added to patients already on advanced vasodilators, be that a PDE-5 inhibitor, endothelin receptor antagonist or both. There was no improvement in the primary end-point of 6MWT and there was a 22 % discontinuation rate with high incidence of side-effects. There was however some benefit in secondary outcomes such as dyspnoea [31, 42].

The AMBITION study is evaluating combination ambrisentan and tadalafil versus single agent arms in 614 treatment naive PAH patients and should be publishing in the near future.

Initial triple therapy was evaluated in 10 idiopathic and heritable PAH patients with FC III and IV and haemodynamic severity (cardiac index less than 2 l/min/m^2 or pulmonary vascular resistance more than 12.5 Wood units) at diagnosis. The results were very impressive with all patients at 4 months (n of 7) improving to FC II but one requiring transplantation due to lack of improvement. There was a mean improvement in 6MWT of 164 m, mean PA pressure reduction of 13 mmHg, PVR reduction of 16.7 Wood units and cardiac index improvement of 2.l/min/m^2 which was maintained at (median) 18 months and well tolerated [43].

Calcium Channel Blockers

Prior to the advent of targeted vasodilators, inhaled nitric oxide response was used as a predictor of response to high dose calcium channel blockers. Those not responding had, in addition to the lack of clinical efficacy, a far higher incidence of side-effects including severe complications such as cardiogenic shock and hypoxaemia (due to loss of hypoxic pulmonary vasoconstriction and subsequent worsening V/Q matching).

Vasoreactivity testing (with inhaled nitric oxide or intravenous adenosine/epoprostenol at the time of right heart catheterisation – RHC) should be performed in all group 1 PH patients. Calcium channel blockers are not used as the testing agent due to the high risk of serious side-effects in the non-responders [44]. Testing is relatively contraindicated in pulmonary veno-occlusive disease due to the risk of pulmonary oedema.

The test is considered positive should the mean PA pressure fall by at least 10 mmHg to a value of under 40 mmHg without any fall in the cardiac output. There is approximately a 10 % chance that this will be the case. This rises significantly in the anorexigen induced PH population. The importance of a positive vasoreactivity test is a significantly better prognosis and it is a strong predictor for good response to calcium channel antagonists. High dose, sustained release preparations of nifedipine and diltiazem (with the strongest evidence base) are most commonly used. Observational studies have shown a symptomatic and survival benefit that can be prolonged over years [3].

There is however the suggestion that responders have less severe disease at baseline with a longer duration of symptoms [45]. Consequently they are likely to represent a distinct, more indolent phenotype and there is evidence to show the survival benefit is seen even when not treated with calcium channel blockers [46].

Close follow-up is suggested to ensure the calcium channel antagonist response is maintained (some guidelines suggesting a repeat RHC at 3–4 months) with only 54 % reported to maintain the beneficial response [45]. Targeted vasodilators should be commenced early when the response is not maintained.

Guidelines

The joint European Society of Cardiology (ESC) and European Respiratory Society (ERS) guidelines were published in 2009 [47]. The World Symposium on Pulmonary Hypertension took place in Nice in February/March 2013. Consequently there have been a number of recently published updates to the classification and treatment regimen [48]. The guidelines are summarised below.

A holistic approach to treatment is suggested including general measures (such as oxygen, diuretics and warfarin, as detailed in general measures), exercise, infection prevention, pregnancy advice, psychosocial support, multi-disciplinary approach and palliative care when appropriate.

There are a number of established treatment goals with an evidence basis behind them. Essentially it orientates around keeping patients in the "stable and satisfactory" group and the prevention or reversal of poor prognostic indicators. The precise therapeutic goals are as follows:

- Clinical – no signs of right ventricular failure or history of syncope, WHO functional class I or II, 6MWT >500 m, peak VO_2 > 15 ml/min/kg and normal or near-normal BNP;
- Echocardiography – no pericardial effusion and TAPSE >2.0 cm;
- Right heart catheterisation – right atrial pressure <8 mmHg and cardiac index ≥2.5 l/min/m^2.

First line in the treatment algorithm of PAH patients is the vasoreactivity testing and commencement of calcium channel blockers if positive. In non-responders, choice of targeted vasodilator depends on functional class, with treatment usually indicated when in FC II and above. First line choice is not usually specified due to lack of data. Therefore that choice is made by the treating physician with the knowledge of the individual circumstances to guide therapy for example hepatic or renal dysfunction.

However there are some caveats. The one exception to specified therapy is intravenous epoprostenol as first line in

FC IV. This is also the only group where combination therapy should be considered from the outset. In FC II an endothelin receptor antagonist or phosphodiesterase-5 inhibitor should be considered first line.

Although not always specified in the guidelines, it would be usual practice to routinely uptitrate the dose of single vasodilator if tolerated. Should there be insufficient clinical improvement then this would trigger the addition of initially a second agent and then full triple therapy. Inadequate response is defined as "stable and not satisfactory" (i.e. therapeutic goals not met) or "unstable and deteriorating" (such as the development of right heart failure) in FC II or III. At the most severe end of the spectrum, there is also emphasis on rapidly leaving FC IV.

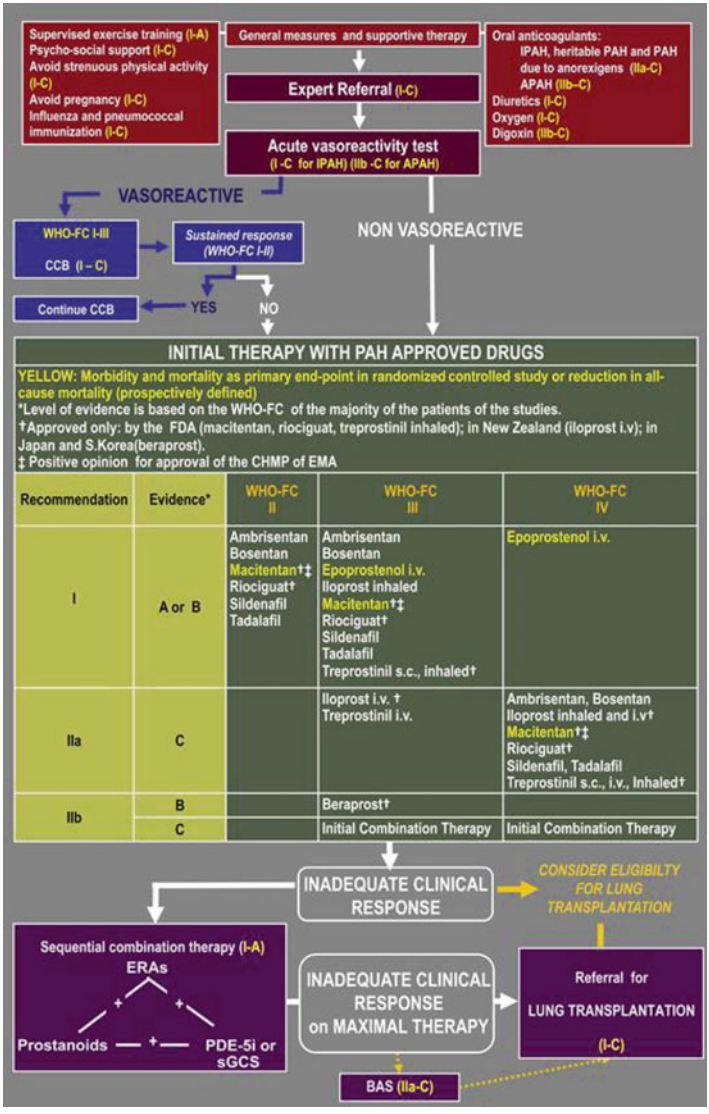
The precise treatment algorithm with grades of supporting evidence is reproduced below (Fig. 3.2).

There are also guidelines from the American College of Cardiology Foundation and American Heart Association published in 2009 [49]. These are similar to the ESC/ERS guidelines except instead of using functional class to guide treatment, patients are divided into lower and high risk. As per FC IV, high risk patients are suggested to commence intravenous prostanoids but either epoprostenol or treprostinil is suggested. The risk stratification is determined by clinical criteria. High risk criteria being FC IV, rapid progression, right ventricular failure, 6MWT <300 m, peak VO2 < 10.4 ml/kg/min, pericardial effusion, significant right ventricular enlargement or dysfunction, right atrial enlargement, RA pressure >20 mmHg, CI <2.0 l/min/m^2 and significantly elevated BNP.

General Measures

Anticoagulation

Several observational, predominantly retrospective, studies performed in the 1980s showed an improvement in survival when taking warfarin in idiopathic pulmonary hypertension. Subgroup analysis from the 1992 calcium channel antagonist


Supervised exercise training (I-A)
Psycho-social support (I-C)
Avoid strenuous physical activity (I-C)
Avoid pregnancy (I-C)
Influenza and pneumococcal immunization (I-C)
General measures and supportive therapy
Expert Referral (I-C)
Acute vasoreactivity test
(I -C for IPAH) (IIb -C for APAH)
Oral anticoagulants:
IPAH, heritable PAH and PAH due to anorexigens (IIa-C)
APAH (IIb-C)
Diuretics (I-C)
Oxygen (I-C)
Digoxin (IIb-C)
VASOREACTIVE
NON VASOREACTIVE
WHO-FC I-III
CCB (I – C)
Sustained response (WHO-FC I-II)
Continue CCB
YES
NO
INITIAL THERAPY WITH PAH APPROVED DRUGS
YELLOW: Morbidity and mortality as primary end-point in randomized controlled study or reduction in all-cause mortality (prospectively defined)
*Level of evidence is based on the WHO-FC of the majority of the patients of the studies.
†Approved only: by the FDA (macitentan, riociguat, treprostinil inhaled); in New Zealand (iloprost i.v); in Japan and S.Korea(beraprost).
‡ Positive opinion for approval of the CHMP of EMA
Recommendation
Evidence*
WHO-FC II
WHO-FC III
WHO-FC IV
I
A or B
Ambrisentan
Bosentan
Macitentan†‡
Riociguat†
Sildenafil
Tadalafil
Ambrisentan
Bosentan
Epoprostenol i.v.
Iloprost inhaled
Macitentan†‡
Riociguat†
Sildenafil
Tadalafil
Treprostinil s.c., inhaled†
Epoprostenol i.v.
IIa
C
Iloprost i.v. †
Treprostinil i.v.
Ambrisentan, Bosentan
Iloprost inhaled and i.v†
Macitentan†‡
Riociguat†
Sildenafil, Tadalafil
Treprostinil s.c., i.v., Inhaled†
IIb
B
Beraprost†
C
Initial Combination Therapy
Initial Combination Therapy
INADEQUATE CLINICAL RESPONSE
CONSIDER ELIGIBILTY FOR LUNG TRANSPLANTATION
Sequential combination therapy (I-A)
ERAs
Prostanoids
PDE-5i or sGCS
INADEQUATE CLINICAL RESPONSE on MAXIMAL THERAPY
Referral for LUNG TRANSPLANTATION (I-C)
BAS (IIa-C)

study revealed a 3 year survival benefit from 31 to 62 % with warfarin in the non-responder population [3], albeit those selected out for treatment by non-uniformity on a perfusion scan. A 2006 literature review found a survival benefit in 5 out of 7 studies involving idiopathic PAH [50].

The rationale behind anticoagulation is prothrombotic tendency (with abnormal clotting cascade, platelet function and fibrinolysis) and altered right sided haemodynamics (sluggish flow in dilated atrium and ventricle). Thrombotic arteriopathy has a strong histopathological association with pulmonary arterial hypertension although the cause/effect relationship is unknown [51].

Current best practice is to commence warfarin, in the absence of contraindication, in certain group 1 (namely idiopathic, hereditable and anorexigen induced) and naturally group 4 Dana Point pulmonary hypertension. It is not usually recommended in connective tissue disease associated PH due to an increased bleeding risk. The optimal target INR or functional class for treatment has not been established.

There is currently no data (even in CTEPH) regarding the use of the novel oral anticoagulant agents (such as the direct

FIGURE 3.2 Evidence-based treatment algorithm for pulmonary arterial hypertension patients (for group 1 patients only) (Reproduced from Galiè et al., *Journal of the American College of Cardiology* [48] with permission) Key: *APAH* associated pulmonary arterial hypertension, *BAS* balloon atrial septostomy, *CCB* calcium channel blockers, *ERA* endothelin receptor antagonist, *sGCS* soluble guanylate cyclase stimulators, *IPAH* idiopathic pulmonary arterial hypertension, *i.v.* intravenous, *PDE-5i* phosphodiesterase type-5 inhibitor, *s.c.* subcutaneous, *WHO-FC* World Health Organization functional class

thrombin inhibitor dabigatran and the factor Xa inhibitors rivaroxaban and apixaban) and there are also interactions with endothelin receptor antagonists and phosphodiesterase 5 inhibitors.

Digoxin

Digoxin is often prescribed at a low dose more for its inotropic effect than as an antiarrhythmic. Despite being prescribed in up to half of all patients with pulmonary hypertension, the evidence basis is weak. A small RCT from 1981 in cor pulmonale (Group 3) patients did show an improvement in right ventricular function after 8 weeks but only when in the context of biventricular dysfunction [52].

Acute administration of digoxin at time of right heart catheterisation shows physiological improvement in idiopathic PAH. There is haemodynamic improvement, namely a 10 % increase in cardiac output with no change in pulmonary vascular resistance, and also a reduction in circulating levels of noradrenaline [53]. There is however no long term data supporting the use of digoxin in pulmonary hypertension.

Beta Blockers

Beta-blockers have been considered relatively contraindicated in pulmonary arterial hypertension due to the negative inotropic and chronotropic effects impacting on right ventricular function. Due to the inability to increase stroke volume, the PH cardiac output in exercise is predominantly rate dependent [54].

In addition beta-blockers may cause pulmonary vasoconstriction as suggested by animal models. However 12 % of group 1 patients were taking beta-blockers in the REVEAL registry [55].

Contrary to the above, more recent evidence suggests beta-blockade may be safe in PAH. First beta-blockers were

found to reverse right ventricular remodelling and improve function and cardiac output in a rat model [56]. A prospective controlled cohort of 94 patients of group 1 PAH patients revealed no statistical difference in clinical end-points including mortality and right sided heart failure [57].

Their prescription needs to be weighed up with the strength of indication. For example all group 2 patients should be on beta-blockers as optimisation of their left sided heart failure [58].

One problematic situation is propranolol used as secondary prophylaxis for oesophageal varices due to liver cirrhosis. Intuitively risk-benefit analysis would point towards treatment (ie. prevention of life-threatening haemorrhage) but evidence from a 10 patient prospective, uncontrolled study in PH associated with portal hypertension (group 1.4.3) showed that withdrawal of beta-blockers improved both functional status and cardiac output without adverse incident [59]. There were no variceal bleeds off beta-blockers over 1½ years, although 60 % with large varices at time of endoscopy were prophylactically banded before discontinuation.

Anti-arrhythmics

Restoration of sinus rhythm (whenever possible) is the best therapeutic strategy for atrial arrhythmias. This is due to the optimisation of haemaodynamics and is especially true for congenital heart disease patients given how poorly tolerated atrial arrhythmias can be. Hence amiodarone, electrical cardioversion and/or electrophysiology studies with ablation are frequently used.

Atrial fibrillation appears to be the most malignant and treatment resistant. One retrospective study of 231 patients with pulmonary arterial hypertension and medically treated CTEPH over 6 years identified 31 episodes of atrial tachyarrhythmia. Sinus rhythm was restored in all atrial flutter patients (n of 12, 3 of which were ablated) but in only 2 out of 13 atrial fibrillation.

Cumulative mortality was 82 % in rate controlled atrial fibrillation compared with 6.3 % when sinus rhythm was restored [60]. Contrary to left heart disease, ventricular arrhythmias appear to be less problematic.

The ESC/ERS guidelines do state digoxin "may be considered" as a rate-controlling strategy for atrial tachyarrhytmias [47].

Diuretics

Over half of all pulmonary hypertension patients are prescribed diuretics and there is undoubtedly symptomatic improvement in the context of right ventricular failure and fluid overload. There is no evidence behind their usage and RCTs will not be forthcoming due the ethics of a placebo arm.

Consequently current best practice, as suggested by the ESC guidelines, is an individualised, clinical decision in the hands of the physician regarding choice, dose and timing of any diuretic therapy, taking into account renal function and serum potassium level [47].

Oxygen

The best evidence for supplemental oxygen therapy comes from the hypoxaemic, group 3 patient population, predominantly COPD. Long term oxygen therapy (LTOT) was proven to confer a survival advantage in hypoxaemic COPD (especially with signs of PH) patients over 30 years ago [61, 62].

In COPD associated PH, LTOT has been shown to improve mean PA pressure at repeat right heart catheterisation by 4.1 mmHg over 19 months [63]. It does appear that approximately only 60 % respond to oxygen therapy and this group has a marked mortality benefit (88 % 2 year survival compared with 22 %) [64].

Hence the ESC guidelines for all PH suggest following the COPD guidelines (most recently reaffirmed by NICE in 2010 [65, 66], namely long term oxygen therapy (used for at least 15 h a day) when resting p_aO_2 is less than 8.0 kPa [47].

40 % of PAH patients in the REVEAL registry were on LTOT [55]. Nocturnal desaturation is likely to be common even in the IPAH group (77 % in this 2001 study of 13 patients, predicted by resting p_aO^2, exertional desaturation and impaired spirometry/gas transfer) [67]. Therefore even in the absence of sleep disordered breathing, consideration should be given to overnight oximetry. Nocturnal oxygen therapy in PH has not been studied (except for Eisenmenger's syndrome) but keeping oxygen saturations above 90 % seems sensible.

Exercise

There is a growing body of evidence that supervised rehabilitation programmes are beneficial in PH. The putative mechanism is not dissimilar to skeletal muscle weakness as in COPD. First examined by prospective cross-over trial in 2006 showed a 22 % improvement in 6 min walk test after 15 weeks. There was also statistically significant improvement in functional class, quality of life questionnaires and VO_2 max. Due to safety concerns the exercise regimen was commenced whilst participants were hospital inpatients but there were no adverse events witnessed. There was not any difference in echocardiographic measurements [68].

Such symptomatic improvement has been reproduced in several studies over a range of aetiologies and supervised graded exercise appears safe even at the severe end of disease spectrum [69–71].

Specific Aetiologies

Anorexigen Induced (Nice Group 1.3)

Several of the targeted vasodilator studies included PAH secondary to anorexigen usage and it seems to behave in a not dissimilar fashion to IPAH [72] and hence its treatment follows suit. One difference is a slightly higher response rate

to vasoreactivity testing (and hence calcium channel blocker use), 13.4 % in one study [73].

Connective Tissue Disease (Nice Group 1.4.1)

As above, connective tissue disease (CTD) associated PH was often included in the targeted vasodilator studies and hence its treatment algorithm mirrors that of IPAH [47]. It is however generally believed that the CTD cases respond less well to vasodilators than IPAH and often subgroup analyses of the above landmark trials failed to reach significance.

The strongest body of evidence comes from endothelin receptor antagonists and this uncontrolled trial of bosentan in all CTD PH revealed an improvement in functional class in 27 % [74].

There is one RCT with system sclerosis which showed an improved 6MWT on intravenous epoprostenol [75].

Systemic lupus erythematous and mixed connective tissue disorder patients with milder PH (FC I, II or III with a cardiac index of more than 3.1 l/mi/m^2) appear to benefit from immunospressive therapy alone (cyclophosphamide and corticosteroids) [76].

Although there is a degree of vasoreactivity at right heart catheterisation, CTD related PH patients do not respond longer term to calcium channel blockers and consequently their use should be avoided. One postulated mechanism is the increased incidence of veno-occlusion, giving a PVOD like picture [73, 77]. Care needs to be given to anticoagulation due to the higher incidence of bleeding diatheses.

Human Immunodeficiency Virus (Nice Group 1.4.2)

Patients with Human Immunodeficiency Virus (HIV) have an increased risk of PAH development which increases their morbidity and mortality. The pathogenesis may involve a

direct insult from the virus itself causing endothelial dysfunction in the lung vasculature, with the HIV Nef protein implicated in several studies [78]. PAH can develop in patients with well controlled HIV infection, on or off antiretroviral therapy.

Patients with confirmed HIV associated PAH are treated with antiretroviral therapy and stabilisation or improvement in pulmonary haemodynamics has been reported [79–81]. In the majority of cases advanced pulmonary vasodilator therapy is also commenced following diagnosis. This decision is made according to the patient's symptoms and other prognostic factors including their PVR, with careful prospective monitoring to ensure treatments are initiated and escalated when appropriate. Patients in WHO functional class III and IV are routinely offered both therapies at diagnosis.

Drug interactions between antiretroviral therapy and advanced pulmonary vasodilator therapies are important in patient management. HIV protease inhibitors mediate Cytochrome P450 isoenzyme inhibition. This markedly increases the levels of phosphodiesterase inhibitors as they are metabolised by Cytochrome P450 [82]. Sildenafil is mainly metabolised by Cytochrome P450 and a safe and effective dose for its concurrent use with protease inhibitors has not been established and its use is therefore contraindicated. If used, therapeutic drug monitoring is necessary [83]. The US Food and Drug Administration advise that when patients are taking protease inhibitors to instead start tadalafil when clinically necessary at a reduced dose of 20 mg once daily, increased to 40 mg once daily based upon individual tolerability.

Endothelin receptor antagonists (ERA) are also metabolised in the liver by Cytochrome P450 and therefore when prescribed with protease inhibitors, elevated ERA plasma concentrations can result [84, 85]. When prescribing bosentan in combination with protease inhibitors dose reductions are therefore recommended at 62.5 mg once daily or every other day [86]. There is less potential for increased ambrisentan levels when taking protease inhibitors and therefore only careful clinical monitoring is deemed appropriate with no

dose change necessary. Co-administration of bosentan and the protease inhibitor atazanavir (Reyataz) without ritonavir is not recommended as the level of atazanavir is significantly reduced by the Cytochrome P450 isoenzyme inductive effects of bosentan (unlike ambrisentan) [87]. This has not been demonstrated with other protease inhibitors.

Bosentan has been successfully used as advanced pulmonary vasodilator therapy in HIV associated PAH [81, 88, 89] including 5 % of patients in the EARLY study bosentan treatment arm [11]. Other pulmonary vasodilator therapies that have been successfully used in the treatment of HIV associated PAH include intravenous epoprostenol [90–92], subcutaneous trepostinil [93] and inhaled iloprost [94]. Significant drug interactions with antiretroviral agents are not anticipated with these therapies. The use of combination therapies in patients with HIV associated PAH have only been published as single cases [81] and in positive RCTs inclusive of but not powered to investigate HIV subpopulations [38, 41, 42].

Data relating to the treatment of HIV associated PAH is limited and the management of patients is not well established. Treatment choices are influenced by the potential interactions between advanced pulmonary vasodilator treatments and co-administered anti-retroviral agents. Especially at the beginning of combined treatment, patients are carefully monitored for evidence of drug toxicity, with regular clinical review. In our current practice we routinely commence tadalafil as first line targeted treatment in HIV associated PAH, at the lower dose advised if on a concurrent protease inhibitor. If dual advanced pulmonary vasodilator treatment is appropriate we would then commence an ERA at the advised dose.

Portal Hypertension (Nice Group 1.4.3)

Pulmonary hypertension secondary to liver disease occurs only in the context of portal hypertension. The overall prevalence of PAH in portal hypertension is 2 % [95] and up to

8.5 % in the most severely affected population awaiting liver transplantation [96]. It is important to note that porto-pulmonary hypertension is a very distinct clinical entity from hepatopulmonary syndrome which is caused by microscopic arteriovenous malformations and lowers PVR.

The exact pathophysiology of porto-pulmonary hypertension has not been elucidated but is believed to be due one or more vasoactive cytokines (for example endothelin-1) bypassing their usual metabolism in the liver via porto-systemic shunting and directly impacting on the pulmonary vascular bed [97]. Histological findings are identical to IPAH. In addition to vasoconstriction, contributing factors likely include smooth muscle proliferation, in situ thrombosis, thromboembolism and a hyperdynamic circulation.

The same IPAH treatment algorithm for advanced therapy is followed but the evidence basis is less strong [47]. There are observational studies with each class of advanced vasodilator showing efficacy [98–100]. Consideration needs to be given to the vasodilatory impact on the portal circulation with prostacyclin analogues reported to cause increased flow and progressive splenomegaly [101]. Despite the adverse effect of hepatic dysfunction with endothelin receptor anatgonists, they do appear safe to use [102].

One difference is that vasoreactivity testing need not be performed as calcium channel blockers would not be used due to their effect on systemic vascular resistance. Anticoagulation is not advised due to the coagulopathy and the (especially variceal) bleeding risk. Beta blockers are discussed above.

Historically porto-pulmonary hypertension was considered an absolute contra-indication to liver transplantation. This is no longer the case, especially with mild disease, and there are case reports of PH resolving post-transplantation [103]. However outcomes are worse with more advanced PH [96]. Advanced vasodilators (usually intravenous prostanoids) are frequently employed in the perioperative period.

In terms of patients with co-existent liver dysfunction and pulmonary hypertension of another cause, care is needed

with the choice of targeted vasodilator. Ambrisentan is preferred over bosentan but a PDE5 inhibitor would be first-line. Close monitoring of liver function tests is necessary.

Congenital Heart Disease (Nice Group 1.4.4)

Most severely affected (and well-studied) in congenital heart disease associated PH are those in whom Eisenmenger's syndrome has developed (elevated pressures causing reversal of flow via intra-cardiac shunt or patent ductus arteriosis). Historically considered untreatable, vasodilators have shown to improve clinical and haemodynamic outcomes [104].

Bosentan carries the most weight of evidence. Some non-Eisenmenger congenital heart disease patients were included in the EARLY trial [11]. The BREATHE-5 trial showed good efficacy of bosentan in terms of function and haemodynamics with FC III over 16 and 40 weeks (placebo RCT and open label respectively) [105]. In addition, by having similar impact on pulmonary and systemic vascular resistance, there was no worsening of shunt and hence oxygenation was maintained.

There is unblinded prospective evidence for sildenafil that it can also improve oxygenation levels as well as functioning [106, 107].

Advanced vasodilators also carry a reduction in all-cause mortality as seen with the Royal Brompton Hospital's cohort of 229 Eisenmenger's patients. The majority were talking bosentan and were followed-up for several years [108].

Anticoagulation is an individualised risk-benefit decision given both thrombotic tendency (reduced pulmonary flow, secondary erythrocytosis) and haemorrhagic complications (haemoptysis, cerebrovascular) seen in this population. Calcium channel blockers should not be prescribed as they can worsen the right to left shunt with disastrous consequences. Despite being contrary to common sense, nocturnal oxygen does not appear to have any effect [109] and long term oxygen therapy is only recommended if

there is improvement if terms of symptoms and oxygenation. Aggressive correction of arrhythmias is particularly important.

Schistosomiasis (Nice Group 1.4.5)

Schistosomiasis may be the commonest cause of PH worldwide but, other than antiparasitic agents, its best treatment is completely unknown. It is caused by infection with the trematode (blood fluke) parasite *Schistosoma* and affects over 200 million people worldwide. 7.7 % of those with chronic hepatosplenic schistosomiasis have pulmonary hypertension at RHC [110]. Transmission is through contaminated water with freshwater snails the intermediate hosts and it is endemic in wide areas of Africa, Asia, the Middle East and South America.

Of the three commonest species of the parasite, two especially (*Schistosoma mansoni and japonicum*) cause pulmonary hypertension. The larval form enters through the skin and travel through the circulation to the liver and intestine. After 2 months' maturation, eggs are produced and deposit in the pulmonary vascular bed, both causing mechanical obstruction and a granulomatous endarteritis through inflammatory cytokine secretion. Portal hypertension also contributes to the pathophysiology.

Given the high prevalence of schistosomiasis and the likelihood of re-infection post treatment, public health strategies have focused more on prevention, especially the provision of clean water and snail control. Praziquantel is the first-line antihelminthic and effective as a single dose, however does not appear to improve the haemodynamics [110]. The advanced vasodilators have not been well studied and given the global distribution of the disease and the large costs entailed it does unfortunately seem unlikely that they will be in the near future. There is some very limited evidence (essentially case reports) behind sildenafil's use [111, 112].

One uncontrolled, observational study on 12 patients using either phosphodiesterase-5 inhibitor or endothelin receptor antagonist showed a FC and 6MWT improvement [113].

Pulmonary Veno-occlusive Disease (Nice Group 1')

Vasodilators carry a higher risk in pulmonary veno-occlusive disease (PVOD) as being selective for the arterial side there is the chance of pulmonary oedema developing secondary to hydrostatic capillary pressure. There have been fatalities reported with IV epoprostenol [114]. In specialised centres, prostanoids may be commenced safely when done very cautiously and they appear to be efficacious [115, 116].

There is no data with endothelin receptor antagonists or phosphodiesterase-5 inhibitors. Warfarin, oxygen and early referral for lung transplantation are usually considered. There are case reports of immunosuppressive medication (in this case steroids and azathioprine) being used in the context of autoimmune features [117].

Left Heart Disease (Nice Group 2)

The primary therapy of group 2 PH is optimisation of the heart failure [58]. This is the same for heart failure with reduced and preserved left ventricular systolic function and secondary to valvular disease. Reducing left ventricular end-diastolic pressure reduces the passive transmitted PH. ACE inhibitors and beta blockers are the mainstay and neither are contraindicated in PH.

There have been a number of trials of advanced vasodilators in heart failure without much benefit seen and significant adverse events [118, 119]. Currently they are not recommended but trials are ongoing. Sildenafil carries some supporting data predominantly in terms of improved haemodynamics [120, 121].

Chronic Obstructive Pulmonary Disease (Nice Group 3.1)

The mainstay of treatment for all Dana point group 3 patients (lung diseases and/or hypoxia) is, as the name implies, oxygenation. The evidence for oxygen in COPD associated PH is discussed in the previous section. In summary there is improvement of PA pressures but not reversal to normality.

Early observational evidence suggested a role for targeted vasodilators in PH secondary to lung disease, sildenafil especially [122]. However they are of limited use due to the deleterious side-effect of worsening oxygenation. Despite acutely improving haemodynamics, they have the significant downside of worsening of ventilation/perfusion mismatch. This is secondary to deregulation of the hypoxic pulmonary vasoconstriction mechanism. Hence any potential benefit is offset by worsening of the hypoxaemia that is driving the pulmonary hypertension. A cut-off point of FEV1 60 % predicted is sometimes used as a complete contraindication.

In COPD specifically, sildenafil has been shown to improve haemodynamics but this is countered by worsening degree of hypoxaemia [123]. This blinded RCT of sildenafil in COPD did show an improvement in 6MWT [124]. Results for bosentan in COPD have been mixed [125].

Intriguingly, pravastatin has been shown by RCT to improve exercise capacity and pulmonary vascular resistance in COPD associated PH [126]. The proposed mechanism is inhibition of endothelin-1 production.

Severe PH not explained by the severity of lung disease (the recently discarded concept of “out of proportion” disease) is more worthy of advance vasodilator treatment due to the possibility of additional pathophysiological processes. If the mean PA pressure is over 40 mmHg then referral onto specialist centre for consideration of vasodilators may be warranted.

Interstitial Lung Disease (Nice Group 3.2)

The supplemental oxygen guidelines are as those for COPD, although this has not been investigated on a stand-alone basis. Concerns about worsening mismatch with targeted vasodilators are equally prominent.

Sildenafil once again has the most support although the evidence basis is limited. Both sildenafil and epoprostenol acutely lower PVR but gas exchange actually improved with sildenafil maybe by acting more locally and hence enhancing ventilation-perfusion matching [127].

Nebulised iloprost is the preferred prostanoid (with presumed less systemic effects impacting on hypoxic pulmonary vasoconstriction) with demonstrated improvement in function, symptoms and haemodynamics [128]. Intravenous epoprostenol worsens gas exchange and hence increases hypoxaemia.

There is no place for the use of endothelin receptor antagonists. Bosentan is not efficacious in idiopathic pulmonary fibrosis or systemic sclerosis associated ILD as seen by the placebo controlled RCTs [129–131]. Ambrisentan in the ARIES-3 study actually reduced 6MWT by 23 m in ILD associated PH (as it also did to a lesser extent in COPD) [14].

This was supported and made even more concerning by ARTEMIS-IPF which was terminated early after recruiting 492 idiopathic pulmonary fibrosis patients. Of note only 10 % of the study group had PH. The ambrisentan treatment arm showed statistically significant disease progression and more hospitalisation episodes compared with placebo. There was also non-significant higher mortality of 7.9 % compared with 3.7 % (p of 0.10) [9].

Sleep Disordered Breathing (Nice Group 3.4)

Continuous positive airways pressure treating obstructive sleep apnoea has been shown to reduce pulmonary artery pressure in a well-designed cross-over trial using sham CPAP

(subtherapeutic positive end-expiratory pressure) as the control arm [132]. Repeat polysomnography on nocturnal CPAP therapy is indicated to ensure the apnoea-hypopnoea index and level of oxygenation is acceptable.

In the context of PH secondary to obesity hypoventilation syndrome then non-invasive ventilation plus/minus oxygen therapy is likely to be needed and beneficial to the PH but has not been directly studied.

Weight loss is highly important but often difficult to achieve. The wide health benefits of bariatric surgery include significant reduction in mean PA pressures [133].

There is no evidence to support the use of targeted vasodilator medication in sleep disordered breathing associated PH.

Chronic Thromboembolic Disease (Nice Group 4)

Pulmonary thromboendarterectomy for chronic thromboembolic pulmonary hypertension (CTEPH) is discussed in the next chapter. There remains a role for advanced vasodilators as a bridge to surgery and in those not amenable to surgical intervention (for example with distal thromboembolic disease or co-morbidities precluding such major surgery) [134].

Medical therapy results in only limited improvement and, unlike surgery, is in no way curative. Bosentan is the best researched and the BENEFiT placebo RCT showed a 22 % reduction in PVR but no benefit in terms of exercise capacity [135]. A 2010 metanalysis of 10 (mainly open label, uncontrolled) bosentan studies showed significant but modest improvements in 6MWT and PA pressure [136]. Ambrisentan increased the mean 6MWT by 17 m and reduced BNP by 22 % in 28 uncontrolled, proximal and distal CTEPH patients [14].

Prostacyclin analogues and phosphodiesterase-5 inhibtors do also have some supporting evidence [137–140]. Riociguat has also been investigated with promising results in this group and more detail is given below.

The use of vasodilators as a bridge to surgery is only done at the severe end of the spectrum with evidence of right ventricular dysfunction. FC III and IV patients with high a PVR (over 15 Wood units) have been tested with intravenous epoprostenol. This revealed haemodynamic improvement and a post-operative mortality of 8.3 % that (although far higher than those with less severe disease) compared favourably with other studies in similarly advanced patients [141]. There is a evidence against the need for routine use pre-operatively [142].

The final patient group in whom medical therapy is considered are those with persisting PH post pulmonary endarterectomy. There is limited evidence but the BENEFiT trial included this group and they comprised 28 % of the cohort [135]. Despite PH persisting at the 3 month mark post-operatively, when advanced vasodilators are commenced, there is no increased mortality for at least 4 years compared with those who responded well [143].

Sickle Cell Disease (Nice Group 5.1)

Previously in group 1, the haemolytic anaemias including sickle cell have been moved to group 5 following the 2013 world symposium in Nice [144]. The results with targeted vasodilators in sickle cell disease related PH have been disappointing. There is pathophysiological rationale for using phosphodiesterase-5 inhibitors, given the lack of NO bioavailability in its pathogenesis, but sildenafil has shown a high rate of complications, specifically vaso-occlusive crises [145].

L-arginine, a precursor of NO, given orally, produces an acute reduction in PA pressures (by a mean of 15 %) [146].

Sarcoidosis (Nice Group 5.2)

Corticosteroids are the mainstay of treatment for many of the manifestations of sarcoidosis. The evidence for their use in pulmonary hypertension is mixed. This likely reflects the

multifactorial pathophysiology. One retrospective study suggests that the steroid response is only seen in the absence of pulmonary fibrosis [147].

Targeted vasodilators do have case studies suggesting efficacy but RCTs are awaited. Complicating matters is the heterogeneity of clinical manifestation and hence extrapolation within subsets. Caution is required with vasodilator commencement due to the worsening of gas exchange (as per other causes of ILD), pulmonary oedema (with post-capillary disease similar to PVOD) and myocardial involvement [148].

Intravenous epoprostenol demonstrated haemodynamic and functional response but with the risk of complication [149]. Sildenafil and bosentan have both been shown to significantly improve pulmonary haemodynamics but not benefit 6MWT [150, 151].

Contrary to corticosteroids, those with fibrotic lung disease may benefit more (especially if the fibrosis is milder) and this retrospective review of different classes of vasodilators did demonstrate an improvement in 6MWT [152].

Special Circumstances

Air Travel

Air travel is a convenient method of transport but exposes passengers with cardiorespiratory disease to potentially hazardous conditions. Although aircraft cabins are pressurised, cabin air pressure at cruising altitude is still lower than air pressure at sea level at an equivalent altitude of 1800–2400 m above sea level. The reduced barometric pressure determines a reduced partial pressure of oxygen in ambient air and this results in a degree of hypoxia for travellers. The normal physiological response to low alveolar oxygen is pulmonary arterial vasoconstriction. The response to prolonged hypoxia in PH patients in flight is unpredictable but can lead to a degree of pulmonary vasoconstriction that increases

PVR. Allied to this, air travel is associated with relative dehydration and extended immobility increasing thromboembolic risk, and air recirculation in a confined environment risking cross infection. The condition of patients with PH is typically only stable within narrow limits and therefore any increase in PVR can result in a patient's condition deteriorating exponentially in flight.

There is a distinct lack of evidence and no strict guidelines recommending the safety of flying or suitable pre-flight assessments in PH patients. The 2008 ESC/ERS guidelines [47] suggest that consideration should be given to the use of in-flight oxygen for patients in WHO functional class 3 or 4. Patients with arterial oxygen concentration consistently below 8 kPa are considered for long-term oxygen therapy and these patients should continue therapy in flight. The British Thoracic Society air travel guidelines 2011 [153] support these recommendations and do not advocate routine hypoxic challenge testing.

We would encourage careful consideration on an individual level, for any patient with PH who wishes to fly. This should incorporate an assessment of symptom severity, haemodynamic impairment (PVR) and the degree of hypoxia pre travel. Any concurrent diseases associated with PH or separate to their PH diagnosis which may be adversely affected by air travel should also be incorporated into this assessment.

In general we would suggest that if resting oxygen saturation levels are above 92 % on room air and the patient is WHO functional class I or II then supplementary oxygen therapy may not be required in flight. For all other PH patients we would recommend up to date arterial blood gas analysis to accurately determine their arterial oxygen concentration at sea level. Supplementary oxygen should then be prescribed appropriately (to achieve arterial oxygen saturation of >8kPa) for the duration of the flight.

Our centre performs formal fitness to fly assessments for patients that require long term oxygen therapy and who are in WHO functional class III and IV. We also refer patients for

these assessments if they have previously had adverse symptoms in flight. If a patient does not fulfil the criteria for long term oxygen therapy on blood gas analysis then 15 % inspired oxygen concentration (FiO2) is delivered via an occlusive mask with a one way valve for twenty minutes. If the measured arterial oxygen concentration is below 6.6 kPa then supplemental oxygen is prescribed as standard in flight. In order to discern the appropriate supplementary oxygen delivery rate for patients requiring oxygen therapy in flight, supplemental oxygen is delivered via nasal cannulae inside a body box containing 15 % FiO_2. Blood gas analysis is not possible inside the body box, instead peripheral oxygen saturation level and transcutaneous carbon dioxide monitoring are used. The delivery rate of supplemental oxygen is titrated up until a peripheral saturation level above 85 % is achieved. Provided that patients do not become unwell or develop hypercapnia during testing they are then prescribed oxygen in flight at the delivery rate identified. Most patients require a delivery rate of 2 L/min if they do not require long term oxygen therapy at sea level. If a patient has high PVR and /or high oxygen requirements at sea level or during fitness to fly assessment, then we do not recommend air travel on medical grounds given the unpredictable potential dangers the situation imposes.

In patients with congenital heart disease associated PAH, oxygen would not be predicted to improve the arterial oxygen saturation due to the presence of significant intracardiac shunting. Patients in WHO functional class I and II may often travel by air without the need for supplemental oxygen therapy or fitness to fly assessment.

It is important that all PH patients understand the unpredictable risk involved in air travel. Patients must be aware of the individual airlines policy regarding in-flight oxygen and contact the airline in plenty of time to inform them of their requirements. When abroad, all PH patients should have written information available describing their condition(s) and know who to contact in the case of deteriorating health.

Pregnancy

Many patients with PH are of child bearing age. During pregnancy and postpartum many physiological changes occur which present a significant risk for patients with PH. In normal pregnancy, circulating blood volume expands by 30–50 %, which is maximal between 28 and 34 weeks gestation and largely due to increased plasma volume. This increases cardiac preload and hence stroke volume and cardiac output. An increase in resting heart rate also contributes to increasing cardiac output. Cardiac output progressively rises from the first trimester to reach up to 150 % of pre-pregnancy levels. Systemic vasodilatation also occurs during pregnancy and together with the presence of a low resistance placental circulation drops systemic vascular resistance. This can result in a fall in systemic blood pressure. During labour, cardiac output increases by a further 25–50 %. This is partly due to greater intravascular blood volume from the contracting uterus redirecting blood to expand circulating blood volume. Also, catecholamine secretion related to the pain and apprehension of labour increases cardiac output. After delivery, the inferior vena cava is decompressed and uterine blood again increases circulating volume, cardiac filling pressure and cardiac output. Only 6 weeks after delivery do the cardiovascular physiological changes associated with pregnancy approach normal pre-pregnancy levels [154, 155].

The right ventricle and the pulmonary circulation receive the entire cardiac output but can ordinarily adapt to accommodate variable loading conditions. The chronic elevation in PVR in patients with PH can result in right ventricular dysfunction with tricuspid regurgitation from ventricular dilatation and predisposition to arrhythmia. Remodelling in the pulmonary circulation also limits the ability to adapt to variable blood flow. It is therefore predictable that the significant haemodynamic changes associated with pregnancy and peripartum are poorly tolerated. PAH patients may not be able to endure the increased blood volume and heart rate

demanded by pregnancy and labour. They are at risk of circulatory collapse, therapy resistant right heart failure and arrhythmia. The PVR may rise acutely, reducing venous return to the left side of the heart with profound systemic hypotension, termed PAH crisis. All of these situations can be fatal.

The hypercoagulable state in pregnancy and particularly post-partum is also a concern in PAH patients. Any thromboembolic event afflicting the already compromised pulmonary vasculature can be life threatening. Similarly, stroke may result from paradoxical embolism when intracardiac shunting is present [156].

The evidence supporting management decisions for patients in pregnancy with PAH is limited to individual reports and case series. However it is universally acknowledged that multidisciplinary input and close monitoring throughout pregnancy is central to a successful outcome [157]. The multidisciplinary team must meet regularly and include a high-risk obstetric anaesthetic team with experience in PH. We also advocate that patients should have at least monthly echocardiograms and clinical review by a PH specialist through their pregnancy. Admission to hospital for monitoring is advocated when approaching labour or with any clinical deterioration. Supportive care includes fluid regimes, diuretics, appropriate oxygen therapy, advanced pulmonary vasodilator therapies and inotropic support when necessary.

Sildenafil is often given as first line advanced pulmonary vasodilator therapy in pregnancy [158–161]. Sildenafil causes uterine artery vasodilation and is also used in the treatment of pre-term and term neonatal PH [162]. Alternatively, or if there is any clinical deterioration, prostanoids such as illoprost [157, 163, 164] or epoprostenol are prescribed [165, 166]. There have also been positive reports using oral calcium channel blockers [167, 168]. Inhaled NO may cause an acute drop in PVR when given, in Eisenmenger syndrome [169], idiopathic PAH [170] and CTEPH [171], and has been successfully used in pregnancy [172, 173]. Endothelin receptor antagonists are

contra-indicated in pregnancy due to animal studies showing possible teratogenic effects [174]. Women of child bearing age are notified of this prior to commencing therapy and alternative classes of advanced pulmonary vasodilator therapy are used. In our centre, all patients with PH on oral advanced pulmonary vasodilator therapies that are planning pregnancy or become pregnant are converted to sildenafil treatment when possible. If increased disease modifying therapy is necessary then patients are commenced on intravenous prostanoid treatment. Anticoagulation is considered in pregnancy in patients with PH but must be carefully controlled when nearing delivery [175].

Planned elective births are advised [47]. Less patients are undergoing vaginal birth and more patients are undergoing planned premature deliveries in the modern management era [157, 175]. For most patients we advocate an elective planned delivery using caesarean section and regional anaesthesia, avoiding the adverse haemodynamic consequences of labour, which may be prolonged. Patients receiving general anaesthesia appear to have higher mortality compared to the use of regional anaesthesia (odds ratio 3.7) [175]. There is however no consensus regarding the mode and timing of delivery in PAH parturients. Maternal safety needs to be compared to the risk of premature delivery, intrauterine growth restriction and the need for neonatal care input.

There is evidence to suggest that with better knowledge and multidisciplinary management in pregnancy, improved outcomes have been achieved in pregnant patients with PAH. A systematic review of published outcomes of pregnancy in PAH and CTEPH compared reported mortality from 1978 to 1996 [176] with results from 1997 to 2007. Mortality decreased from 30 to 17 % in idiopathic PAH, 36–28 % in congenital heart disease associated PAH and from 56 to 33 % in other groups. Seventy eight percent of maternal deaths occurred within the first month following delivery [175]. Neonatal or foetal death occurred in 10 % of cases and intrauterine growth restriction was reported in 18 % of pregnancies [175]. Notably publication bias towards a positive

outcome may have artificially lowered published figures in both review periods. There appears to be no statistically significant difference in maternal or foetal outcome between different subgroups of patients with PAH or CTEPH [175].

Despite improving experience and outcomes, pregnancy is associated with significant mortality in PAH and CTEPH patients. Thirty percent of pregnancies in women with PAH occur in patients who were not aware of their disease prior to pregnancy [177]. However, many patients diagnosed with PH are of childbearing age and early discussions regarding the risks of pregnancy are mandatory. This ensures an informed decision is made and suitable contraception is prescribed as appropriate. Bosentan may reduce the efficacy of regular oral contraceptive agents as it induces cytochrome P450 enzymes. Therefore alternative contraceptive methods are used if this drug is given to patients of child bearing age. Levonorgestrel can be taken within 72 h to terminate pregnancy if chosen but the dose must be doubled if given to patients taking bosentan.

Renal Failure

Patients with chronic or end stage renal disease have a high prevalence of PH owing to unclear multifactorial pathophysiology that remains poorly understood. They therefore are placed in group 5 of the clinical classification of PH. No specific intervention trial aimed at reducing PH in patients with chronic kidney disease has been performed to date. Correcting volume overload and treating left ventricular disorders are important in this patient population. When clinically appropriate, treatment with advanced pulmonary vasodilator therapy is however routinely commissioned for patients in the UK with PH associated with chronic renal failure using dialysis [4].

Patients with PH from any cause may develop acute or chronic renal impairment. According to the British National Formulary the following advanced pulmonary vasodilator therapies should be modified within the context of renal

impairment. Consideration should be given to a reduction in the prescribed dose frequency of sildenafil if the drug is not tolerated in renal failure, from three times daily to twice daily, especially when the estimated glomerular filtration rate is below 30 ml/min/1.73 m^2. The starting dose of tadalafil should be halved in mild to moderate renal impairment and titrated up to full dose as tolerated. Ambrisentan should be used with caution when the estimated glomerular filtration rate is below 30 ml/min/1.73 m^2.

Assessment and Peri-operative Management of Patients with Pulmonary Hypertension

It is essential that patients with pulmonary hypertension who are being considered for elective surgery attend a pre-operative anaesthetic/high risk clinic and for the clinicians involved to have close contact with those working in the pulmonary hypertension centre. It is important to be aware of the patient's baseline state, their predicated life expectancy without the proposed surgical intervention, the complications which may arise and what treatment strategies should be put in place if the patient is unable to take their usual oral maintenance therapy. Additional attention (in conjunction with the surgeon) will be given to the type of operation performed. For example for some patients laparoscopic abdominal surgery may not be possible as the patient would be poorly tolerant of the adverse haemodynamic and cardiothoracic physiological impacts of abdominal gas insufflation causing reducing venous return and reducing lung volumes and adversely affecting lung perfusion, pulmonary vascular resistance and gas exchange capabilities. Finally if the patient has other co-morbidities or if the pulmonary hypertension is part of a multisystem disease then consultation with other specialists involved in the patient's management should be sought. It may be considered appropriate for the patient to have their surgery in the pulmonary hypertension centre although this is

not always possible as many of these centres are primarily cardiothoracic and will not necessarily have the infrastructure to look after patients with pulmonary hypertension who have other pathologies or require other forms of surgical intervention. Patients with congenital heart disease should have all their management undertaken whenever possible in the congenital heart disease centre.

It is often advisable for a cardiothoracic anaesthetist to be involved during the operative procedure. A perioperative pulmonary artery catheter is frequently deployed to help guide fluid resuscitation, monitor pulmonary vascular resistance and cardiac output and to diagnose and assess response to treatment should a pulmonary hypertension crisis arise. Post operatively patients are usually managed in a high dependency or intensive care unit. It is most important during the peri-opertive period that the patients systemic vascular resistance does not fall below the pulmonary vascular resistance as under such circumstances profound haemodynamic disturbance and death can occur. If patients are tolerant of ongoing oral therapy this may be given nasogastricaly assuming the patient is absorbing through this route. If oral therapy is not possible there are no routinely available intravenous alternative formulations for phosphodiesterase type 5 inhibitors and endothelin receptor antagonists and therefore other agents must be considered. These include nebulised or intravenous prostacyclin, nebulised nitric oxide or intravenous milrinone or vasopressin. Subcutaneous therapy may be unreliably absorbed particularly if the patient's circulation is compromised and if they are receiving inotropic support such as adrenaline or noradrenaline which may compromise skin perfusion. For those patients with congenital heart disease it is most important to continuously maintain the systemic vascular resistance above the pulmonary vascular resistance, to ensure that hydration is optimal and that there is close monitoring of haemoglobin and iron stores. Some patients may be candidates for intra-operative transesophageal echo cardio graphic monitoring.

Normal baseline advanced pulmonary vasodilative therapy is commenced as soon as possible after surgery. An early appointment with the pulmonary hypertension clinic will be made and appropriate follow up will continue possibly with ongoing surgical follow up appointments as indicated. Throughout the whole pathway, close communication between the health care professionals involved in the patients care is mandatory to ensure the best possible outcome.

Novel/Future Therapies

Despite the vast progress made in the field, pulmonary arterial hypertension still confers a high burden of functional impairment and remains a progressive, fatal condition. Targeted vasodilators have ameliorated the symptoms and improved life expectancy but only prolong the inevitable. Pulmonary thromboendarterectomy for CTEPH is the only potentially curative treatment. PH secondary to other conditions universally confers a worse prognosis and there is a far more limited understanding of therapeutic strategies with these groups.

There is no inclinication from the PH community to rest on its laurels [178]. Work continues apace to better understand the optimal use for those therapies we already have and develop new classes of medication. Multiple possible future therapies are already at the clinical trial stage. In addition to looking at other targets within the endothelin, NO and prostacyclin pathways, new candidate drugs are targeting the immune system and cellular proliferation with the ultimate goal of reverse remodelling. Some already have proven benefit whereas many others have had success in animal models but this has not transitioned into efficacious proof of concept trials in humans.

Riociguat

Soluble guanylate cyclase is the intracellular receptor for nitric oxide. Riociguat (BAY 63–2521) stimulates soluble

guanylate cyclise both directly (mimicking NO) and by increasing its sensitivity to endogenous NO. This leads to cGMP augmentation with vasodilatation and anti-proliferation. There are promising results in both PAH and CTEPH and it has just been licensed by the FDA but not yet by the MHRA. It has a good safety profile with infrequent syncope the main adverse effect.

Versus placebo in the PATENT-1 trial, riocigulat gave a highly significant increase in 6MWT of 36 m over 12 weeks. This involved 443 most PAH group patients, both treatment naive and already on ERAs or prostanoids and the benefit was seen regardless. Secondary endpoints of PVR, FC, dyspnoea, clinical worsening and BNP were also significantly improved on the highest dose [179]. The extension study PATENT-2 is in progress.

Building on phase 2 evidence in CTEPH was the recently reported CHEST-1. 261 inoperable or persistent CTEPH patients were involved in this placebo RCT. The 6MWT increased by 46 m and PVR decreased by 3 Wood units [180]. Again a long term extension in CHEST-2 is in progress.

Given such early promise, riociguat is also being investigated in other aetiologies of pulmonary hypertension. The RCT LEPHT looked at group 2 PH secondary to systolic dysfunction. The primary endpoint of reduction in mean PA pressure was not met but there was significant improvement in both pulmonary vascular resistance and cardiac index [181]. There is also the suggestion of benefit in group 3 patient, namely ILD and COPD, in these small, open label studies [182, 183].

Cinaciguat is another guanylate cyclase activator with slightly different mechanism which is being developed for use in decompensated heart failure. It has only been studied in sheep models of persistent pulmonary hypertension of the newborn.

Selexipag

An efficacious oral prostanoid would be a big advance and selexipag has been developed as a prostacyclin receptor agonist that is showing far more promise than beraprost.

Selexipag and its active metabolite selectively target the prostaglandin I2 receptor (IP). Currently it is only at the proof of concept stage but a phase 3 randomised controlled trial, GRIPHON, should report in 2014. There is some phase 2 evidence that it is efficacious (with 30 % reduction in PVR and the non-significant 24 m increase in 6MWT) and is well tolerated [184].

Tyrosine Kinase Inhibitors

Receptor tyrosine kinases are cell surface receptors that trigger inflammatory cascades via phosphorylation. Important in the pathogenesis of pulmonary hypertension are those pathways of platelet derived growth factor (PDGF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), insulin receptor (IR), fibroblast growth factor (FGF) and c-KIT with the end result of cellular proliferation and remodelling. Multiple tyrosine kinase inhibitors have been developed with marked success in the treatment of various cancers. They are exciting candidates for reverse remodelling in PH.

The IMPRES placebo RCT study looked at imatinib (targeting, amongst others, PDGF receptors) and has just resulted. The inclusion criteria were severe PAH patients despite already being on at least 2 advanced vasodilator medication. 202 patients were recruited and 6MWT increased by 32 m over 24 weeks (p of 0.002). These results were maintained at 48 weeks extension. There were also improvements in haemodynamics and BNP but neither functional class nor time to clinical worsening. Concerningly there were significantly more adverse events in the treatment arm (44 % versus 30 %), including 8 subdural haematomas on anticoagulation, and a high discontinuation rate [185].

Sorafenib acts on the VEGF receptor and is only at the phase 1 trial stage assessing safety in PAH [186]. Other tyrosine kinase inhibitors are being evaluated and developed.

Vasoactive Intestinal Peptide

Given vasoactive intestinal peptide's reduced concentration in PH and its effect on smooth muscle proliferation, it has been postulated as a therapy for PH. There was some early success in animal models but its promise has not been realised in humans and it has fallen by the wayside [187].

Adrenomedullin

Adrenomedullin is also a vasoactive peptide that was discovered in phaeochromcytomas. It cause vasodilatation and is associated with PAH disease severity. Inhaled, it causes acute benefit to haemodynamics at right heart catheterisation and cardiopulmonary exercise testing [188]. To date, studies have only been with single dose administration.

Fausdil

Rho-associated protein kinase (ROCK) is involved in smooth muscle contraction and remodelling. It is inhibited by fausdil which can be given via inhalation or intravenously. Inhaled it causes acute reduction in mean PA pressure and pulmonary vascular resistance equivalent to that of inhaled nictric oxide [189]. There is no longer term data.

Statins

Statins also inhibit the Rho pathway and there has been some success with their use in animal models and COPD associated PH [126]. However this benefit was not seen in PAH with several disappointing studies using simvastatin [190, 191].

Inhaled Nitric Oxide

Often used in the acute intensive care setting (in addition to vasoreactivity testing) with well documented haemodynamic effects, inhaled NO is now being evaluated as a chronic therapy. Currently the evidence is restricted to case reports and one series from the 1990s [192, 193] but a phase 2 trial in PAH as an add-on therapy is underway.

Cicletanine

Cicletanine is a diuretic that upregulates NO production (via coupling of endothelial nitric oxide synthase) and is used for systemic hypertension in Europe. By targeting endothelial dysfunction it is hoped that it may impact on PH's pathogenesis. The evidence behind it is currently limited to animals models and individual case studies [194]. Phase 2 trials are awaited.

Dichloroacetic Acid

Dichloroacetate is a chemical compound that affects the metabolic functioning of mitochrondria and has been researched in cancer. It reverses the remodelling of PH in rats and mice via increased apoptosis [195] but has not been studied in humans.

Terguride

Serotonin has a role in the pathogenesis of PH with remodelling effects on pulmonary artery fibroblasts and smooth muscle cells. Terguride is a partial dopamine D2, adrenergic and serotonin antagonist. It has anti-proliferative, anti-thrombotic and anti-fibrotic effects and causes relaxation of smooth muscle. Once again despite

promising animal results, those in humans were disappointing [196].

Stem Cells

Circulating endothelial progenitor cells are involved with angiogenesis and remodelling and have been implicated in PAH pathogenesis with various reports of increased and decreased numbers [197].

Autologous transfusion of endothelial progenitor cells was useful in animal models and one prospective open label study in humans with IPAH. This showed a 42.5 m improvement in 6MWT plus improved haemodynamics [198].

Gene Therapy

BMPR2 gene therapy via adenovirus vector has been successful in a rat model of PH, improving haemodynamics and reducing vascular remodelling [199]. Given the difficulties experienced with gene therapy in other diseases, it remains only a distant possibility.

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Chapter 4
The Role of Surgery in Pulmonary Hypertension

Caroline Patterson

Introduction

The past three decades have seen parallel advancement in medical and surgical treatment options for pulmonary hypertension. The greatest impact on survival has been achieved through innovations in pulmonary vasodilator use (principally, the discovery of eproprostenol) and transplantation. Surgical intervention is typically considered in patients whose disease is refractory or progresses despite maximal medical therapy. In chronic thromboembolic pulmonary hypertension, where surgery is the only definitive treatment, surgery is considered as soon as the diagnosis is confirmed. All surgery for pulmonary hypertension should be performed in centres with experience and expertise in these techniques.

This chapter will consider the indications, peri-operative management and outcome of pulmonary thromboendarterectomy, atrial septostomy and transplantation as well as the developing roles for right ventricular assist devices and extracorporeal membrane oxygenation in patients with pulmonary hypertension.

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Pulmonary Thromboendarterectomy

Pulmonary thromboendarterectomy (PTE) is the procedure by which organised and incorporated fibrous obstructive tissue is removed from the pulmonary arterial tree. PTE is the only recognised cure for chronic thromboembolic pulmonary hypertension (CTEPH) and should be considered for all patients with the condition. Nevertheless, a significant proportion of patients with CTEPH are unsuitable for PTE and up to 35 % of patients undergoing surgery have persistent pulmonary hypertension following the procedure [1, 2]. Thus, medical management also has a role to stabilise and improve pulmonary haemodynamics following surgical assessment.

Persistent pulmonary hypertension is more prevalent with distal thromboembolic disease, presumably associated with co-existent small-vessel arteriopathy. Early surgical intervention is believed to reduce the risk of progression to irreversible (secondary) vasculopathy; however, some patients with severe microvascular disease may have primary vasculopathy with secondary thrombosis [3].

Patient Selection

At present, there is no standardised pre-operative classification system for CTEPH to define patients suitable for surgical intervention, although proposals have been made [3]. There is evidence of variability between centres and countries in the selection of patients for PTE. Data from the international CTEPH registry suggests at time of diagnosis, around 63 % of patients are considered operable and around 57 % (range 12–61 % across countries) ultimately undergo surgery. Operable patients are younger but have comparable disease severity (measured by NYHA functional class) to inoperable patients. Low-volume surgical centres, historically performing less than 10 PTEs per year, report higher percentages of inoperable patients, suggesting centre expertise may influence the decision to operate [4].

Operability has traditionally been determined by the degree of proximal thromboembolic disease accessible to surgery, the degree of microvascular disease (suggested by a high peripheral vascular resistance in the absence of substantial chronic thromboembolic disease on angiography), an acceptable surgical risk and patient consent for the procedure. CTEPH registry data indicates the main causes of inoperability are surgically inaccessible disease, imbalances between increased PVR and the amount of accessible disease, PVR greater than 1,500 dyn/s/cm^{-5} (equivalent to 18.75 Wood Units (WU)), age and comorbidity [4].

Pre-operative Assessment

Non-invasive imaging techniques including echocardiography, ventilation-perfusion scanning and computed tomography angiography are widely used in the diagnostic workup of patients with suspected CTEPH. MRI has an increasing role in the morphological, anatomical and functional assessment of cardiopulmonary circulation. Right heart catheterisation with pulmonary angiography remains the gold standard for the confirmation of CTEPH and the assessment of operability [5].

Pulmonary angiography facilitates evaluation of thrombus distribution within the pulmonary vasculature. Patients with thrombus originating in the main, lobar and segmental arteries are generally characterised as having proximal disease, which is more surgically accessible. In the future, pulmonary intravascular ultrasound may become more widely used to determine suitability for PTE. Pulmonary artery occlusion waveform analysis is being used in the research setting but is yet to be adopted in routine clinical practice.

Once the thrombus distribution has been determined, the clinician must decide whether the proportion of proximal disease is sufficient that thromboendarterectomy will decrease pulmonary vascular resistance. Nevertheless, proximal disease is not the sole determinant of whether PTE will be successful and preoperative assessment of the degree and

FIGURE 4.1 Material removed at pulmonary thromboendarterectomy, courtesy of Dr J Haney, Duke University Medical Center

contribution of microvascular disease is essential. Assessment is largely subjective, based on haemodynamic and radiographic findings, but PVR is a useful objective measure.

Surgical Technique

Although supportive evidence is limited, it is standard practice to place an inferior vena cava filter prior to PTE. PTE is performed during circulatory arrest, under deep hypothermia, via a median sternotomy. Following a proximal pulmonary artery incision, all dissection occurs within the pericardium and neither pleural cavity is entered. Loose thrombus is removed and a dissection plane is established within the media of the artery [6]. The dissection plane is then followed circumferentially from the main pulmonary arteries to the subsegmental branches. The procedure is usually performed within 15–20 min of circulatory arrest (Fig. 4.1).

Reperfusion is followed by a second period of circulatory arrest to allow completion of thromboendarterectomy in the

contralateral lung [7]. Additional cardiac procedures can be performed after arteriotomy closure, during rewarming, if necessary (e.g. coronary bypass grafting, foramen ovale closure, mitral valve repair). The use of selective antegrade cerebral perfusion for pulmonary endarterectomy appears to be technically feasible in preliminary trials and is a potential alternative to complete circulatory arrest [8].

The Jamieson intra-operative classification of CTEPH defines patients according to the surgical specimens obtained. There are 4 so called "types". In type 1 fresh thrombus is present in the main-lobar pulmonary arteries; in type 2 there is intimal thickening and fibrosis proximal to the segmental arteries; in type 3 there is disease within distal segmental arteries only; in type 4 there is distal arteriolar vasculopathy without visible thromboembolic disease (i.e. misdiagnosed IPAH) [9].

There have been no randomised controlled trials to support the insertion of inferior vena cava filters at the time of PTE and the level of evidence for recommending their use is low [2].

Outcomes of PTE

PTE can be performed with low perioperative mortality, with significant improvements in functional capability, hemodynamics and survival. In-hospital mortality is now <5 % in experienced centres [2]. In the majority of cases post-PTE, there is an immediate and sustained fall in pulmonary artery pressure and pulmonary vascular resistance, with a parallel increase in pulmonary blood flow and cardiac output. There is rapid normalisation of right ventricular geometry and tricuspid valve function, such that tricuspid annulopasty is not routinely indicated.

The most significant complications of the procedure are reperfusion pulmonary oedema and persistent pulmonary arterial hypertension. Reperfusion oedema most often develops within 72 h of surgery, and corresponds to anatomic

locations distal to where PTE is performed [10]. Mechanical ventilation, inhaled nitric oxide (NO) and intravenous iloprost are advocated to improve the oedema. Up to one third of patients undergoing PTE require >2 days ventilatory support because of reperfusion injury, and this complication is responsible for approximately half the mortality associated with the procedure [11].

Persistent pulmonary hypertension, suggestive of inadequate endarterectomy or underlying small vessel/microvascular disease, is a key determinant of short and long term outcomes. Patients with an elevated post-operative PVR have difficulties weaning from cardiopulmonary bypass, early postoperative hemodynamic instability and early postoperative death, particularly in the context of right ventricular dysfunction [2]. Mortality amongst patients with a postoperative PVR exceeding 500 dyn/s/cm^{-5} (6.25 WU) is around 30 times greater than for those with a postoperative PVR of less than 500 dyn/s/cm^{-5}. Although postoperative PVR is the greater predictor of mortality, preoperative PVR in excess of 1,000 dyn/s/cm^{-5} (12.5 WU) has also been associated with poor outcomes [12].

Patients with distal thromboembolic disease (intraoperative classification type 3–4) have higher perioperative mortality, require longer inotropic support, and have longer hospital stays than patients with type 1 or 2 thromboembolic disease [13].

Overall mortality for PTE is reducing with increasing experience of the procedure and is currently less than 5 % [12], with long-term survival exceeding medical therapy or transplantation and persistent improvements in functional status. Four years after PTE around three quarters of patients are in NYHA class I [14].

Surgical Alternatives to PTE

Small scale observational studies in specialist centres have highlighted a potential role for percutaneous pulmonary balloon angioplasty in the management of patients with CTEPH deemed unsuitable for PTE [15, 16]. The technique, which

was initially dismissed in the 1980s, has been demonstrated to reduce mean pulmonary artery pressure and effect improved functional capacity. Reperfusion injury is a recognised complication of the procedure and there have been incidences of wiring perforation of the pulmonary vasculature. Systemic and cerebral embolisation are additional hazards. Transplantation remains the definitive surgical alternative for patients with CTEPH not suitable for PTE.

In the acute setting of submassive/massive pulmonary embolism, there is a role for emergency surgical thrombectomy, in preference to thromboendarterectomy. When surgical intervention is contraindicated, percutaneous interventions for removing pulmonary emboli and decreasing thrombus burden include aspiration thrombectomy, thrombus fragmentation, and rheolytic thrombectomy [17].

Atrial Septostomy

Atrial septostomy was originally conceived as a treatment for transposition of the great arteries in neonates [18, 19]. A role for septostomy in the management of pulmonary hypertension was considered when patients with Eisenmenger's syndrome and idiopathic pulmonary arterial hypertension (IPAH) with a patent foramen ovale were noted to have a survival advantage over those without a patent foramen ovale [20]. The first reported use of atrial septostomy in the palliative treatment of refractory primary pulmonary hypertension was in 1983 [21].

Atrial septostomy involves the formation of an intra-atrial right-to-left shunt, diverting blood flow to bypass the pulmonary vasculature, decompressing the right heart, increasing left ventricular preload and augmenting systemic blood flow (particularly during exercise). The resulting increase in cardiac output enhances tissue perfusion, albeit with a reduced systemic arterial oxygen saturation.

Severe IPAH is the most common indication for atrial septostomy. The procedure has also been used for patients

with pulmonary arterial hypertension associated with surgically corrected congenital heart disease, peripheral CTEPH and connective tissue disease.

Patient Selection

Atrial septostomy is recommended only for patients with severe pulmonary arterial hypertension and intractable right heart failure resistant to maximal medical therapy (including inotropic support) [22]. Evidence suggests a benefit in patients in WHO functional class IV with refractory right heart failure or severe syncopal symptoms.

For optimum benefit, the procedure should be performed before there is advanced end-organ dysfunction and haemodynamic compromise. Contraindications to the procedure are the requirement for cardio-respiratory support, mean right atrial pressure >20 mmHg, pulmonary vascular resistance index >55 WU/m^2 (where PVRI is defined as the pressure drop across the pulmonary circulation divided by cardiac index), resting oxygen saturation <90 % on room air, and left ventricular end diastolic pressure >18 mmHg [23]. Patient selection therefore requires experience and judgment. If clinically indicated, patients may undergo serial septostomy procedures.

Surgical Technique

Atrial septostomy is performed by surgical incision (the blade technique), graded balloon dilation or a combination of the two. The balloon dilatation technique is preferred as it offers comparable improvements in symptoms and haemodynamics but a lesser procedural risk than the blade technique.

In the balloon dilatation approach, a Swan-Ganz catheter is placed via the right internal jugular vein for haemodynamic monitoring (right atrial pressure, mean pulmonary artery pressure and cardiac index using the thermodilution method). A sheath is passed into the left atrium by needle puncture. Thereafter, a balloon catheter is passed across the septum

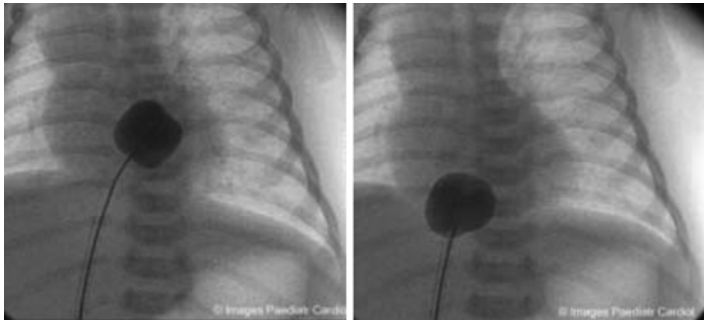

FIGURE 4.2 Balloon atrial septostomy under fluoroscopic guidance (paediatric image) [25]

through the sheath on a guide wire and the sheath withdrawn to the right atrium. The balloon is inflated at low pressures under fluoroscopic guidance. The procedure is repeated with increasing balloon sizes until a septal defect is created that results in a 10 % fall in arterial oxygen saturation [24]. Oxygen delivery is optimised by the transfusion of packed red blood cells or darbepoetin administered pre and post-procedure (Fig. 4.2).

In the blade-balloon approach, balloon dilatation is preceded by the use of a surgical blade, withdrawn across the intra-atrial septum. A total of 3–6 incisions are made at orthagonal angles to achieve a 5–10 % fall in arterial oxygen saturation [26].

The use of intra-cardiac echocardiography to guide the location and extent of septostomy formation has been reported [27]. Recently, a novel septostomy device has been trialled, comprising an atrial septal defect closure device, customised with four 5 mm diameter holes in the central region, but this is not yet in routine use [28].

Outcomes of Atrial Septostomy

There is concern regarding high procedural mortality for septostomy, which is estimated at 16 % but has been reported from 5 to 50 % [29]. Mortality is higher for the blade balloon

technique, which carries a greater risk of septal laceration and fatal hypoxaemia. Septostomy is largely restricted to critically ill patients with severe pulmonary hypertension and right ventricular impairment, therefore patient selection contributes to the high mortality. A mean right atrial pressure >20 mmHg, PVR index >55 WU/m^2, and an estimated 1-year survival less than 40 % are significant predictors of procedure-related death [29]. Septostomy is primarily a palliative or bridging procedure and reported success rates for bridging patients to transplantation range from 30 to 40 % [30]. Improved cardiac output appears to be the principal hemodynamic benefit. There is an associated symptomatic and functional improvement measured by NYHA class and 6 min walk test [31, 32]. Worldwide experience has demonstrated a median survival of 19.5 months (range, 2–96 months), and late deaths primarily result from progression of underlying pulmonary vascular disease [29].

Surgical Alternatives to Atrial Septostomy

An innovative alternative to septostomy is the Potts shunt procedure, in which needle perforation of the descending aorta is performed at the site of apposition to the left pulmonary artery to create a tract for deployment of a stent between these vessels [33, 34]. The stent acts as a shunt between the pulmonary and systemic circulation, avoiding an intra-cardiac shunt. At present this procedure is limited to the research setting.

Transplantation

The first heart-lung transplant was performed in 1981, for a female patient with IPAH. With the evolution of single and bilateral lung transplant procedures, transplantation is now considered the final definitive treatment for carefully selected patients with advanced pulmonary hypertension. The most

common indication is IPAH; less common indications are scleroderma, histiocytosis, and sarcoidosis. Improved disease-specific medical management has reduced the number of patients referred for transplantation; however, around 25 % of patients with IPAH fail to respond to medical therapy.

There is a lack of consensus on the optimal transplantation procedure for patients with pulmonary hypertension. Single lung, bilateral lung and combined heart-lung transplantation have all been performed historically. Single-lung transplantation has been widely discontinued for IPAH due to poor outcomes and International Society for Heart and Lung Transplantation Registry data indicates the majority of pulmonary hypertension patients worldwide receive bilateral lungs. At present, around 5 % of bilateral lung transplants, 3 % of all lung transplants and 28 % of all heart-lung transplants performed worldwide in adults are for IPAH [35].

Patient Selection

Transplantation should be considered and/or discussed with all patients at the time of diagnosis of pulmonary arterial hypertension. Early referral minimises the transplantation of patients with established significant comorbidity. The timing of referral is a recognised challenge given the poor prognosis of patients with disease refractory to medical management and the limited availability of organs.

The International Society for Heart and Lung Transplantation (ISHLT) has published guidelines for the referral and listing of potential transplant candidates. Referral is recommended for patients in NYHA functional class III or IV (irrespective of on-going therapy), or those with rapidly progressive disease. Listing is recommend for patients with persistent functional class III or IV on maximal medical therapy, failure to respond to intravenous epoprostenol (or equivalent), 6 min walk distance <350 m or declining, cardiac index <2 L/min/m^2 and right atrial pressure >15 mmHg.

The majority of patients are listed for bilateral lung transplant. Heart-lung transplantation is reserved for patients with intractable right heart failure, especially those who are dependent on inotropic support. Patients with pulmonary hypertension secondary to congenital heart disease (particularly those with Eisenmenger's) are also more likely to be considered for the combined procedure, although isolated lung transplant may be performed concurrently with cardiac repair. Rarely, the combined procedure is offered to patients with pulmonary hypertension and coexistent advanced left heart disease [36].

Surgical Technique

Anaesthesia in the intended transplant recipient is generally postponed until the donor lungs have been inspected and approved by the retrieval team. The recipient is intubated with a double lumen tube to allow single-lung ventilation. In severe pulmonary hypertension, single-lung ventilation is not attempted. Trans-oesophageal echocardiography is used to monitor right ventricular function and cardiac filling.

Bilateral lung transplantation is typically performed via a transverse thoracosternotomy (clamshell incision). Median sternotomy and bilateral anterolateral thoracotomies with sternal sparing are also used. Bilateral lungs are implanted separately and sequentially. The first lung to be transplanted is generally the one with the least perfusion on V/Q scanning [37].

Cardiopulmonary bypass is often commenced electively in patients with pulmonary arterial hypertension or when concomitant coronary artery bypass graft or cardiac repair is planned. If cardiopulmonary bypass is required for hemodynamic or ventilatory support, the heart remains warm and beating. If cardiac repair is necessary, the heart is arrested and cooled.

Perioperative Considerations

Lung transplantation is associated with an immediate improvement in pulmonary artery pressure with rapid normalisation of right ventricular size and septal geometry [38].

Despite the reduction in right ventricular afterload, right ventricular systolic function and left diastolic function do not improve immediately and haemodynamic instability is common in the early postoperative period. As such, patients with pulmonary arterial hypertension often require temporary inotropic, vasopressor, and inhaled nitric oxide support. Ventricular assist devices are increasingly used to support the right ventricle as it recovers.

In patients without pulmonary hypertension, ventilatory weaning usually occurs over the first few hours to days. In patients with pulmonary hypertension, haemodynamics and oxygenation are more labile, especially following single lung transplantation. A more cautious weaning approach is adopted with the continuation of neuromuscular paralysis, sedation, and ventilatory support for 24–48 h postoperatively. Thereafter, paralysis and sedation are gradually reversed and weaning follows.

Within the first 72 h post-transplant, primary graft dysfunction is a significant concern in patients with pulmonary arterial hypertension, and is associated with increased risk of death [39]. Risk factors for primary graft dysfunction include intraoperative hemorrhage or cardiovascular complications, ischemia-reperfusion lung injury, and the use of cardiopulmonary bypass in the context of severe right ventricular dysfunction. Ischaemia-reperfusion injury is more prevalent following single lung transplantation, when there is a preponderance of blood flow to the allograft lung in response to high pulmonary vascular resistance in the native lung. Any compromise to the allograft (e.g. infection, rejection) can therefore result in severe ventilation-perfusion mismatch [40]. Bilateral lung transplantation results in a lesser degree of ventilation-perfusion mismatch and these patients are easier to care for in the perioperative period.

Outcomes of Transplantation

Survival after lung and heart-lung transplantation for IPAH has historically been lower than for other major diagnostic categories of lung transplant recipients, although higher than

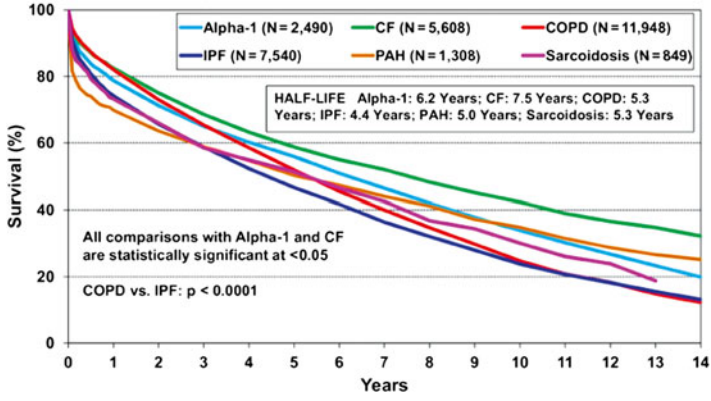

FIGURE 4.3 Kaplan-Meier survival by diagnosis for adult lung transplants performed between January 1990 and June 2010 [35]. (*Alpha-1* α_1-antitrypsin deficiency emphysema, *CF* cystic fibrosis, *COPD* chronic obstructive pulmonary disease, *IPF* idiopathic pulmonary fibrosis, *PAH* pulmonary arterial hypertension)

for idiopathic pulmonary fibrosis. Recent data suggests that although patients with IPAH undergoing transplantation have an increased 3 month mortality, their long term outcomes are comparable with patients with other diagnoses [35, 41].

The ISHLT registry reports 1-, 3-, 5-, and 10-year survival of 66 %, 57 %, 47 %, and 27 %, respectively, in pulmonary arterial hypertension patients undergoing lung transplantation [42]. These compare with baseline survival rates of 79, 64, 53, and 30 % for all lung transplant procedures [35] (Fig. 4.3).

ISHLT registry data demonstrates improved survival amongst all patients receiving bilateral rather than single lung transplant [35] and this is especially the case for IPAH. To date, there have been no direct comparisons of lung transplant versus heart-lung transplant in this population. In patients with Eisenmenger's syndrome secondary to ventricular septal defect, there appears to be a survival benefit with combined heart-lung transplant over bilateral lung transplant with simultaneous closure of the defect.

The incidence of postoperative obliterative bronchiolitis appears to be higher in patients with IPAH and the process

onsets sooner than for other conditions necessitating transplantation [43]. Recurrence of IPAH after transplantation has not been reported.

Ventricular Assist Devices

Mechanical circulatory support has a recognised role in the management of left and biventricular failure. In patients awaiting cardiac transplant, left ventricular assist devices (LVADs) have been demonstrated to reduce pulmonary vascular resistance by offloading the left heart [44], nevertheless, acute right heart failure is a not infrequent complication of LVAD implantation [45]. Right ventricular assist devices (RVADs) are effective in RV failure secondary to LV failure and their utility in acute postoperative RV failure is well described [46]. Computational modelling suggests RVAD support can effectively increase cardiac output and decrease right atrial pressure but has the unwanted consequence of increasing pulmonary artery and capillary pressures [47]. Pulsatile mechanical circulatory devices impart significant energy to the circulation, even when the devices are pneumatically driven and set to deliver the lowest possible flow rates. There is an associated risk of damage to the pulmonary microcirculation, with increased pulmonary vascular resistance and pulmonary artery pressure. In patients with pre-existing pulmonary hypertension, RVADs are most commonly used as a bridge to transplantation, although outcomes are anecdotally poor. Alveolar haemorrhage, haemoptysis, and death have been documented [23]. At present, there is insufficient evidence to fully support the use of RVADs in these patients.

Extracorporeal Life Support

Extracorporeal life support (ECLS) is commonly used for adults with acute lung injury and respiratory failure and has been successfully used to treat persistent pulmonary hypertension in neonates [48]. There is a growing body of evidence for the use of ECLS following massive pulmonary embolism

and as peri-operative support following PTE for CTEPH (when severe reperfusion oedema is a concern) [49]. ECLS is increasingly used as a bridge to lung transplantation in patients with pulmonary hypertension and in the immediate post-operative period [50, 51].

In patients with pulmonary hypertension and potentially reversible right heart failure, ECLS should be considered when maximal medical management (including targeted PH medication, fluid management, inotropes and optimised ventilation) is insufficient.

ECLS involves the use of a mechanical pump to provide prolonged cardiopulmonary bypass. Blood passes through a heat exchanger and membrane oxygenator where haemoglobin is saturated with oxygen and carbon dioxide is removed. Oxygenation is determined by flow rate, while elimination of carbon dioxide is controlled by adjusting the rate of countercurrent gas flow through the oxygenator [52].

The modality of ECLS selected depends upon specific patient requirements. Veno-venous ECLS (using large bore cannulae sited in the internal jugular or right common femoral vein) is useful for carbon dioxide removal, oxygenation, and right ventricular afterload reduction. Veno-arterial ECLS (from a large vein or the right atrium, returned to the common femoral, common carotid, or right axillary artery) is preferred for right ventricular decompression and after lung transplantation, when the left ventricle may be unable to handle a normalised preload, because it supports the cardiac output and delivers more effective oxygenation [23, 53]. In both forms of ECLS, carbon dioxide removal is superior to oxygenation.

The use of ECLS is currently limited by complications associated with cannulation (pneumothorax, vascular trauma, bleeding, infection, embolisation), systemic anticoagulation, and exsanguination resulting from circuit disruptions. The incidence of clinically relevant complications increases significantly after a period of around 2 weeks. Nevertheless, ECLS remains a potentially lifesaving intervention in patients with right ventricular failure.

The pumpless lung-assist device (LAD) (i.e. Novalung GmbH, Talheim, Germany) has a role in the management of

	VA ECLS	VV ECLS	AV ECLS (Lung Assist Device)
Arterial cannulation	☑	☒	☑
External pump	☑ Lower perfusion rates required	☑ Higher perfusion rates required	☒ Perfusion driven by cardiac output
Gas Exchange	☑ Achieves higher PaO_2	☑ Achieves lower PaO_2	☑ Achieves lower PaO_2
Cardiac Support	☑	☒	☒
Offloading of pulmonary circulation	☑	☒	☑/☒
Example indications	Cardiogenic shock, as a bridge to ventricular assist device or cardiac transplantation	Respiratory failure with preserved cardiac function e.g. ARDS, graft dysfunction post lung transplantation	Severe hypercapnia, respiratory acidosis but moderate hypoxaemia

FIGURE 4.4 Characteristics of VA ECLS, VV ECLS and the lung assist device

patients with predominantly hypercapnic respiratory failure. It operates as a low resistance arterio-venous system, and relies on the patient's cardiac output to drive blood flow. Cannulation of the main pulmonary artery trunk and the left atrium creates a septostomy-like pulmonary vascular shunt, perfused by approximately 20 % of the left ventricular output, contributing to gas exchange and hemodynamic unloading of the right ventricle. An alternative common configuration involves the cannulation of the femoral artery and contralateral femoral vein. The LAD has been successfully used as a bridge to transplantation in selected pulmonary hypertension patients with acute decline attributable to cardiogenic shock [54]. Reports suggest the LAD may be more suitable than ECLS for prolonged use [55] (Fig. 4.4).

Conclusion

- All surgery for pulmonary hypertension should be performed in centres with experience and expertise in these techniques.
- Pulmonary thromboendarterectomy is the only recognised cure for chronic thromboembolic pulmonary hypertension

and should be considered for all patients with the condition.

- Assessment for pulmonary thromboendarterectomy should take precedence over the initiation of medical therapy but inoperable patients should be referred for a trial of medication.
- Atrial septostomy is currently recommended for patients with severe pulmonary arterial hypertension and intractable right heart failure but the procedure may be underutilised.
- The challenge remains to develop methods to ensure an adequate, lasting septostomy.
- Improved disease-specific medical therapy has reduced the number of patients referred for transplantation; however, bilateral lung or heart-lung transplantation remains an important option for selected patients with advanced pulmonary hypertension.
- Referral to a transplant centre is recommended for patients in NYHA functional class III or IV (irrespective of ongoing therapy), or those with rapidly progressive disease.
- At present, there is insufficient evidence to fully support the use of right ventricular assist devices in patients with advanced pulmonary hypertension.
- The development of right ventricular assist devices tailored to the circulatory characteristics of these patients may increase their utility.
- Extracorporeal life support and the lung assist device have a role in the management of life threatening cardiopulmonary failure, following pulmonary thromboendarterectomy and as a bridge to lung and heart lung transplantation.

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Chapter 5
Putting It All Together

Brendan Madden

Awareness among clinicians regarding the clinical manifestations of pulmonary hypertension, the importance of early diagnosis and the development of therapeutic strategies [1–8] has improved considerably. However on-going education is necessary to further improve our knowledge and understanding and to maximise efforts to diagnose the condition early and to define its aetiology.

Pulmonary Hypertension is receiving increasing attention in medical school curriculae and indeed in our unit we have undergraduate medical students performing specialist subject modules in pulmonary hypertension each university term. It is hoped that this will contribute to increasing future awareness among doctors and indeed many of these students have already obtained publications in this area. In addition we have developed an active post-graduate teaching programme for doctors in respiratory medicine, cardiology, intensive care, anaesthesia and cardiothoracic surgery about pulmonary hypertension. To this end local, regional and national study days have been very important. We have also

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been pioneering the use of regional study days for nurses to promote increasing awareness of pulmonary hypertension in the community and to promote training of pulmonary hypertension nurses.

Pathways for the diagnosis and investigations of patients with suspected pulmonary hypertension have been established and training of medical staff in techniques such as right heart catheterisation, echocardiographic assessment and radiological imaging have been formalised.

There has been significant advancement in our understanding of the molecular biology of the pathobiology of pulmonary arterial hypertension and this has helped to further our understanding of potential molecular targets for therapeutic Intervention.

It is possible that vascular injury can occur in patients who have a genetic predisposition e.g. bone morphogenetic protein receptor 2 (BMPR2) mutations. If such mutations occur they may lead to a loss of the inhibitory action of BMP on vascular smooth muscle growth. An insult e.g. auto immunity, toxins (not metabolised in patients with liver disease), drugs, and HIV can lead to vascular injury particularly in patients with a genetic predisposition. Endothelial cell dysfunction (e.g. abnormal production of N0, Pg 12, ET-1 etc.) and smooth muscle cell dysfunction (abnormal calcitonin and gastrin releasing peptide metabolism; KV1.5, 5-HTT) can facilitate inflammation (e.g. IL-1, IL-6, chemokines RANTES, fractalkaline and many others) and subsequently vascular remodelling resulting in plexogenic pulmonary arteriopathy.

Although standard initial agents are phosphodiesterase type 5 inhibitors these are frequently supplemented with endothelin receptor antagonists. The indication for these agents alone or in combination with other agents is coming more clearly into focus as treatment guidelines have been developed. Encouraging early experience suggests that macitentan favourably influences prognosis. Furthermore the soluble guanylate cyclase stimulator riociguat will soon become commercially available in the United Kingdom and there is already evidence supporting its use in both

pulmonary arterial hypertension and in chronic thromboembolic pulmonary hypertension. Subcutaneous treprostinil, nebulised nitric oxide and nebulised and IV prostacyclin analogues are routinely used and oral prostacyclin formulations are now available. It is becoming clear which patients with other disease processes should and should not be considered for advanced pulmonary vaso-dilator therapy. For example patients with left heart failure may experience an acute deterioration if increasing pulmonary perfusion leads to an acute on chronic elevation of left atrial filling pressure. Additionally there is no proven benefit for prescribing this type of therapy for patients with smoking related lung disease when pulmonary hypertension is proportionate to their pulmonary pathology. Furthermore the importance of diagnosis, evaluation and treatment of pulmonary hypertension at pre-operative anaesthetic assessment is now well recognised.

It is also now accepted that patients with pulmonary hypertension should be managed within the confines of a specialist centre. It may be that patients will be seen within the specialist centre exclusively or increasingly, specialist centres are combining with satellite units to offer a joint care service. Such arrangements where protocols are unified have many advantages. Patients can be managed locally in a familiar environment by clinicians who are known to them. With clearly defined protocols for diagnosis and work up, appropriate investigations including right heart catheterisation may be performed in the satellite centre. Under joint care arrangements patients are reviewed at least 3 monthly in joint pulmonary hypertension clinics with representation from clinicians and specialist nurses from both units in attendance.

It is helpful that should a patient from the satellite clinic become acutely unwell they can be admitted locally, where they are known, and treated as appropriate with agreed protocols and discussion with the specialist centre as necessary. Often designated pulmonary hypertension centres are stand-alone cardiothoracic units and therefore will not

have local support to manage other potential issues which may co-exist in the pulmonary hypertension patient e.g. connective tissue disease, complex haematological abnormalities, rheumatological conditions and hepto-renal disorders. Additionally there may not be an obstetric service for pregnant women who have pulmonary hypertension. For these reasons joint care agreements are usually well received by patients and operate successfully. The experience of the Royal Brompton Hospital and St Georges Hospital has been excellent in this regard over the past 5 years. The development of the role of the pulmonary hypertension specialist nurse has been a significant advancement in the multidisciplinary team management of the patient with Pulmonary Hypertension.

Close communication with surgeons and anaesthetists when patients with Pulmonary Hypertension require surgical intervention is essential. This ensures that the patient is managed in an appropriate environment, that appropriate work-up and treatment strategies are defined and if required a joint discussion regarding the best approach to surgery e.g. open versus laparoscopic approach can take place. Furthermore close communication peri-operatively ensures that should a pulmonary hypertensive crisis develop appropriate information can be given to staff who have previously been made aware of potential complications. Whenever possible, patients with congenital heart disease should be managed in a congenital heart disease centre.

There are a variety of potential surgical options for selected patients who have pulmonary arterial hypertension. Initially experience was with heart and lung transplantation although driven by the well documented shortage of donor organ availability the surgical procedure of choice subsequently became bilateral lung transplantation. Some encouraging experience was reported with single lung transplantation however it was not uncommon for patients to experience often fatal pulmonary oedema peri-operatively which was multi factorial in origin reflecting exposure of the donor organ to brain stem death factors, the influence of

organ ischemic time and preservation techniques, discontinuous lymphatic circulation in the recipient, re-perfusion with the recipients blood and the significant disproportion in the recipient between the pulmonary vascular resistance of the native and transplanted lung. With bilateral lung transplantation the pulmonary vascular resistance in both lungs is equal. In addition to the shortage of donor organs, obliterative bronchiolitis post-transplantation remains a major obstacle to be overcome. Pulmonary thrombo-endarterectomy is an option for some patients with chronic thrombo-embolic pulmonary hypertension and is associated with low peri-operative mortality and significant improvement in functional capability, haemodynamics and survival. It should be performed in specialist centres. There may be some role for percutaneous pulmonary balloon angioplasty in patients who are unsuitable for this form of surgery. Atrial septostomoy which was originally developed as a treatment for transposition of the great arteries in neonates can be applied to patients who have severe idiopathic pulmonary arterial hypertension in an attempt to offload the failing right ventricle. It is however a temporary situation and may for some patients be a bridge to transplantation. The precise role for ventricular assist devices and extra corporeal life support modalities in patients with pulmonary hypertension remains to be clarified. Nevertheless it would appear that these treatments have a role should the patient develop an acute reversible condition amenable to therapeutic intervention or require them as a bridge to lung transplantation.

It is hoped that ongoing progress will continue to be made for patients who have pulmonary hypertension and that with increasing awareness, earlier diagnosis will be made. As our understanding of the pathophysiology of the condition improves and our identification of molecular biological targets grows it is logical to expect that newer, more specific drugs will be developed. Futhermore the role of combination therapy will be more clearly defined. Surgery remains an option for a small number of selected patients.

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