Pulmonary Arterial Hypertension

Simon Stewart

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Pulmonary Arterial Hypertension: a pocketbook guide

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Foreword

Effective therapies and increased awareness mean that general practitioners, doctors in training and nurses, as well as specialists in cardiology, respiratory medicine, rheumatology and HIV and liver medicine, need a working knowledge of the basic principles of screening and management of pulmonary arterial hypertension. I am, therefore, delighted to write the foreword for this compact volume, which, in the tradition of the very best travel guides, is packed with essential and accessible information. Rare diseases are often overlooked or forgotten, but advances in the field of pulmonary arterial hypertension mean that a hitherto rapidly fatal disease is now, for many patients, a controllable condition. A quick flick through the pages of this book is an immediate reminder of the importance of screening, early diagnosis and management. The book outlines the most salient points in respect of the pathophysiology, epidemiology, classification and clinical features of pulmonary arterial hypertension and emphasizes the need for specialist opinion and care. The known causes of pulmonary hypertension are many and ever growing and a patient may present to one of many specialities. An enhanced awareness of the condition and willingness to work across specialty boundaries, to investigate early with relevant tests, to share care and refer appropriately for further specialist advice and management will undoubtedly improve the quality and quantity of life for our patients.

I believe even the most senior specialist could learn something from this book's pages and that a comprehensive up-to-date volume such as this is an essential part of any doctor or nurse's tool kit that may encounter this disease.

Professor Carol Black

Specialist commentary

Pulmonary arterial hypertension: a historical perspective

The field of pulmonary hypertension has seen an explosion of interest over the past few years, driven largely by the development of a range of effective therapeutic agents, and concomitantly, uncovering of some of the molecular and genetic defects underpinning the development of this fascinating and challenging condition. As a result of this increased awareness of the condition, patients are increasingly being appropriately recognized, diagnosed and treated, leading to vastly improved outcomes when compared to the very poor prognosis suggested by historical data.

Pulmonary hypertension as a clinical entity was first recognized in the 1800s, but it was not until the second half of the last century that its real clinical impact started to be recognized. The term ‘primary pulmonary hypertension’ (PPH) became synonymous with a rare condition of young women, often recognized shortly after childbirth. It was also synonymous with a very poor prognosis, with no known effective treatment, a fact highlighted by D’Alanso and colleagues in their landmark study of the natural history of the condition published in 1991.

In 1981, a team at Stamford University in California, led by Norman Shumway performed the first successful lung transplant (in this case a heart-lung transplant). The recipient was a young woman with primary pulmonary hypertension, and for the first time an effective treatment for this condition was found. It soon became apparent that transplantation had limited applicability because of the uncertain availability of suitable donor organs and, as a result, patients often died waiting. In 1985, faced with this problem, Tim Higenbottam at Papworth Hospital in Cambridge used continuous intravenous prostacyclin to bridge a young woman with PPH to heart-lung transplantation. Prostacyclin (or epoprostenol as it is known in the United States) became the mainstay of therapy for this otherwise lethal condition, and in the pivotal NIH study was definitively shown to improve survival in these patients.

Today, we have available a range of effective therapeutic strategies to treat patients with all forms of pulmonary hypertension. As recognition of the disease increases, specialist pulmonary hypertension services will need to interface more and more with community and other specialist clinicians, to enable these patients to have access to the best care available in a timely fashion. In this way, appropriate assessment and treatment will continue to improve the outlook for these patients, who, once faced with a devastating disease and little prospect of effective treatment, can now achieve very significant gains in both their prognosis and quality of life.

Dr Keith McNeil

1
Introduction

An uncommon but devastating disease

Pulmonary arterial hypertension (PAH) is an uncommon but life-threatening disease. PAH is a particularly sinister condition that is, in most forms, likely to be diagnosed late and is associated with progressive clinical deterioration and premature death.[1–3]

The underlying processes that lead to the development of PAH are complex and the disease remains clinically silent until the right side of the heart begins to fail, initially only on exertion, but in later stages of the disease, at rest. Definitive diagnosis requires specialist skills. Invasive diagnostic procedures are necessary to determine the underlying aetiology and associated disease states. Due to the non-specific nature of the early symptom manifestations, diagnosis is commonly not confirmed until up to 3 years from the initial symptom presentation, when disease pathophysiology is well developed.[1–3]

In recent years there has been increasing interest in the causes, consequences and treatment of PAH. Pulmonary hypertension is defined haemo-dynamically, as a mean pulmonary arterial pressure of >25 mmHg at rest or 30 mmHg with exercise.[1,2] Pulmonary arterial hypertension is diagnosed by excluding other causes of PH, particularly left heart disease. Much attention has focussed on two specific forms of PAH that typify the clinical quandaries that surround this condition, and which have benefited from the introduction of effective treatment strategies. The first of these is idiopathic (formerly referred to as *primary*) PAH,[1–3] and the related familial PAH.[4] The other is PAH related to collagen vascular disease (predominantly systemic sclerosis, otherwise known as scleroderma).[5,6]

Without treatment, the prognosis for patients with significant PAH is poor. The reported median life expectancy of idiopathic PAH is 2.8 years from diagnosis.[7] Similarly, 2-year survival rates in PAH associated with collagen vascular disease are reported to be as low as 40–55%.[8] As such, PAH is a leading cause of death in individuals with PAH complicating systemic sclerosis.[5,6]

Idiopathic PAH is reported to generate 1–2 incident cases per million per annum in the USA.[9] Reports of incidence rates for PAH related to congenital heart disease,[10] collagen vascular disease[5,6,8] and other miscellaneous conditions, including HIV infection[11] and portal hypertension,[12] are slightly higher.[1,2] However, it is important to note that these figures emanate from specialist centres most interested in monitoring the disease, and there are few data to describe the incidence and prognostic impact of PAH within whole populations.

Given the rapid and expanding interest in the detection and management of PAH, particularly with the availability of more effective treatments, it is increasingly important for clinicians to be able to recognize this condition and direct patients to centres with experience in its assessment and treatment. Recognizing the potential for PAH in patients

with a suspicious clinical profile is only the first step. In order to substantially improve health outcomes associated with such a difficult and heterogeneous condition, it is important for each health care system to have a clear and practical framework to facilitate the following:

- Identification of potential cases of PAH in a cost-efficient manner
- Rapid and accurate diagnosis of PAH and any underlying conditions that will determine treatment and overall management
- Application of effective treatments likely to improve the quality of life, functional status and prognosis of affected patients.

An important step in this process has been the widespread adoption of the diagnostic scheme used to classify pulmonary hypertension, developed by the World Health Organization (WHO) initially in 1998 and recently modified in 2003.* It is clear that responsibility for attaining the best possible health outcomes in this group of patients lies beyond experts in the disease
(who have traditionally resided in Centres of Excellence in PAH) and extends to clinicians of all specialities and health professions who see many difficult and unusual cases in their clinical practice.

Aims of this pocketbook

This pocketbook is designed to address several aims (Box 1).

B***ox 1*** *Aims of the PAH pocketbook.*

- Enhance the overall 'PAH awareness' of the wider clinical community.
- Facilitate an understanding of the epidemiology, pathophysiology and clinical profile of PAH.
- Emphasize the need for active screening of high-risk patients and outline the screening and diagnostic process of identifying PAH.
- Outline the range and effectiveness of treatment options once PAH has been definitively diagnosed.
- Encourage the utilization of Centres of PAH Excellence. In addition, the application of a more inclusive and collaborative model of health care in relation to PAH to encourage wider involvement in screening and referral to centres best capable of ongoing management and measurement of treatment success.

* A new classification system was introduced at the World Symposium on Pulmonary Arterial Hypertension in Venice, 2003—Proceedings report published in the *J Am Coll Cardiol* 2004; 43 (Suppl S).

Additional PAH resources

This pocketbook does not contain definitive and exhaustive information concerning PAH rather, it attempts to encapsulate the most important aspects of its detection and management. To assist those clinicians in search of more definitive information, an Appendix lists some of the most useful websites relating to PAH. Each chapter cites the most relevant and contemporary references, which are listed at the back of the book.

2
Disease background and epidemiology of pulmonary arterial hypertension

Definition of pulmonary arterial hypertension

In normal circumstances, resting pulmonary artery systolic pressure ranges from 18 to 25 mmHg (mean pulmonary artery pressures 12–16 mmHg). Pulmonary circulation, therefore, usually operates within a 'low resistance' environment and any increase in pulmonary vascular resistance leads to pulmonary hypertension. Pulmonary arterial hypertension is defined as a mean pulmonary artery pressure >25 mmHg at rest or >30 mmHg with exercise. The severity of PAH can be further delineated on the basis of this pressure (Box 2).

There are many potential causes of PAH and it therefore represents a heterogeneous clinical phenomenon that requires further elucidation to ensure appropriate screening, diagnosis and management (Fig. 1).[1,2]

Diagnostic classification

In order to facilitate the detection, diagnosis and treatment of the many forms of pulmonary hypertension, including PAH, the WHO sponsored an

B***ox 2*** *Severity of PAH.*

- Mild: 25–45 mmHg
- Moderate: 46–65 mmHg
- Severe: >65 mmHg.

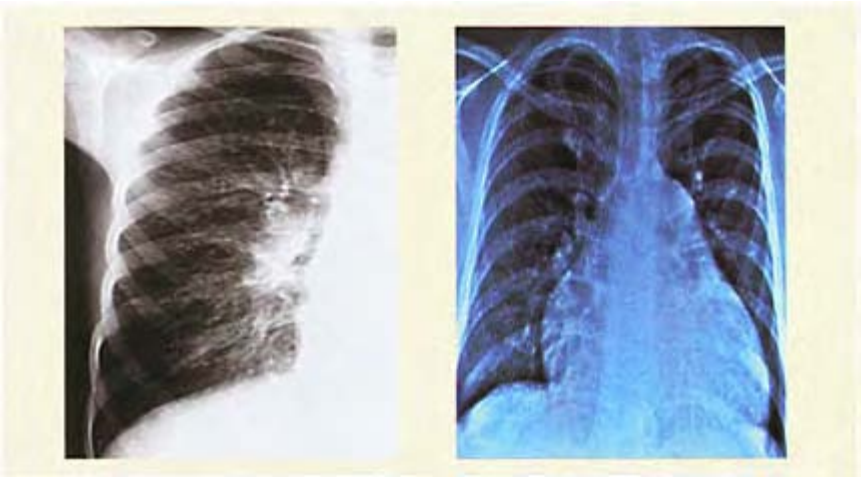

Figure 1 *Chest radiography suggestive of underlying PAH. Up to 85% of patients with PAH have an abnormal chest X-ray or 12-lead electrocardiograph (ECG).*[1] *The chest X-ray may show prominence of the main pulmonary artery, cardiomegaly, enlarged hilar vessels and diminished peripheral vessels.*

expert consensus conference in Evian, in 1998 where a formal classification system was formulated. This system was recently updated at a follow-up expert meeting in Venice, in 2003.

Table 1 shows the original classification system and the modifications recently proposed in Venice. Important modifications in the latest classification are the replacement of the term *primary pulmonary hypertension* (PPH) in favour of *idiopathic* PAH, and the recognition of *familial* PAH as a separate category. In addition, PAH is recognized as being 'related to' rather than 'secondary to' coexisting diseases such as connective tissue disease, HIV infection and portal hypertension. Changes to other categories of pulmonary hypertension clarify terminology rather than rearrange the whole classification system devised by the WHO working group in 1998.

Epidemiology

Given the inherent difficulty in detecting and providing a definitive diagnosis of PAH, it should come as no surprise that its true incidence and

Table 1 *Classification of pulmonary hypertension according to the WHO and recently proposed modifications.*

Original WHO criteria (1998)[1]	**Venice (2003) update[4]**
1. Pulmonary aterial hypertension Primary mary pulmonary Hypertension (PPH)	**1. Primary pulmonary hypertension no longer used**
■ Sporadic	■ Idiopathic PAH
■ Familial	■ Familial PAH
Related to:	**Related to:**
■ Connective tissue diseases	■ *Connective tissues diseases*
■ HIV	■ HIV drugs and toxins
■ Portal hypertension	■ *Portal hypertension*
■ Anorexigens	■ *Anorexigens*
■ Eisenmenger's syndrome	■ Congenital heart disease
■ Persistent pulmonary hypertension of the newborn	■ *Persistent pulmonary hypertension of the newborn*
	■ Significant venous and/or capillary involvement
Other forms of pulmonary hypertension	
2. Pulmonary venous hypertension (e.g. secondary to left-sided heart disease)	2. Pulmonary hypertension with left heart disease
3. Pulmonary hypertension related to disorders of the respiratory system	3. Pulmonary hypertension with lung disease and/or hypoxaemia
4. Chronic thromboembolic pulmonary hypertension (e.g. secondary to pulmonary embolism)	4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease
5. Miscellaneous disorders affecting pulmonary vasculature (e.g. sarcoidosis)	5. *Miscellaneous disorders affecting pulmonary vasculature (e.g. sarcoidosis)*

prevalence within the general population is unknown. Most data emanate from national registries and clinical trials and patients most likely to gravitate towards specialist centres. It is highly unlikely that large-scale population studies will determine the true epidemiological profile of PAH and those patients lucky enough to reach a specialist centre may be the exception rather than the rule. When considering, for example, heart failure, specialist centres typically treat younger patients in whom a differential diagnosis is less clouded by concurrent disease states and there are more severe symptoms due to advanced progression of the underlying disease state. There is little reason to presume that PAH differs from the heart failure scenario, except that in PAH there is a preponderance of younger women as opposed to younger men.[1]

This does not invalidate the type of epidemiological data published to date; it merely emphasizes the need for clinicians to resist stereotyping patients and ignoring clinical indications that a middle-aged man, for example, has developed right heart failure secondary to undiagnosed idiopathic PAH.

Incidence

Idiopathic and familial PAH have been reported to generate 1–2 cases per million each year in the USA.[13] Other causes of PAH, most notably collagen vascular disease (e.g. systemic sclerosis)[5,6] and congenital abnormalities leading to systemic to pulmonary shunts (e.g. Eisenmenger's syndrome)[10,14–16] are reported to be associated with a similar incidence rate.[13]

Recent data from the whole Scottish population suggest that the incidence of idiopathic/familial PAH over the 16-year period 1986–2001 was 4 cases per million/million (3.0 and 5.0 cases per million/annum in men and women, respectively) in those aged 16–65 years.[17] The equivalent rates for PAH-associated connective tissue disorders and congenital abnormalities during this period ranged from 1 to 3 cases per million/annum, respectively in that country. Although these data showed that incidence rates have remained fairly constant in this age group, they also show that an increasing number of older individuals (aged >65 years) are being diagnosed with PAH. Consistent with these data, contemporary reports from Australia[7] suggest that idiopathic PAH generates approximately 3–10 cases per million each year. Certainly, with an increased awareness of PAH and increased detection rates, the *reported* incidence of PAH has risen in the past decade.

Prevalence

There are very few reports of the prevalence of PAH. However, given the rise in reported incident cases and improved survival rates, most probably due to the introduction of relatively effective treatment strategies (see Chapter 5), the underlying prevalence is most likely rising. In Scotland (total population 5 million), for example, the total number of surviving men and women aged 65 years or less being actively treated for idiopathic PAH and PAH related to scleroderma is likely to be around 100 (35 cases per million) and 70 (22 cases/million).[17] Importantly, two-thirds of these cases will be women. In distinct 'high-risk' patient populations (e.g. those with systemic sclerosis), it is even harder to gauge the true prevalence of prevalence of PAH, with estimates ranging between 9 and 33%.

Prognostic implications

The reported median life expectancy of those with idiopathic PAH, registered via specialist centres with the National Institute of Health in the USA, is 2.8 years.[7]

Similarly, 2-year survival rates in those individuals with PAH associated with systemic sclerosis is reported to be as low as 40–55%.[8] As such, PAH is a leading cause of death in those with systemic sclerosis.[5,6] In both forms of the disease there is a reported preponderance of younger women.

Until recently, however, there have been few data describing survival rates in unselected population rates. Figure 2 shows long-term age- and sex-adjusted survival curves following an incident admission for PAH (including idiopathic PAH and that associated with connective tissue diseases and congenital heart disease) in Scotland during the period 1986–2001 for those aged 16–65 years old.[17]

These data are derived from the linked Scottish Morbidity Record Scheme.[18,19] Largely consistent with data from the National Institute of

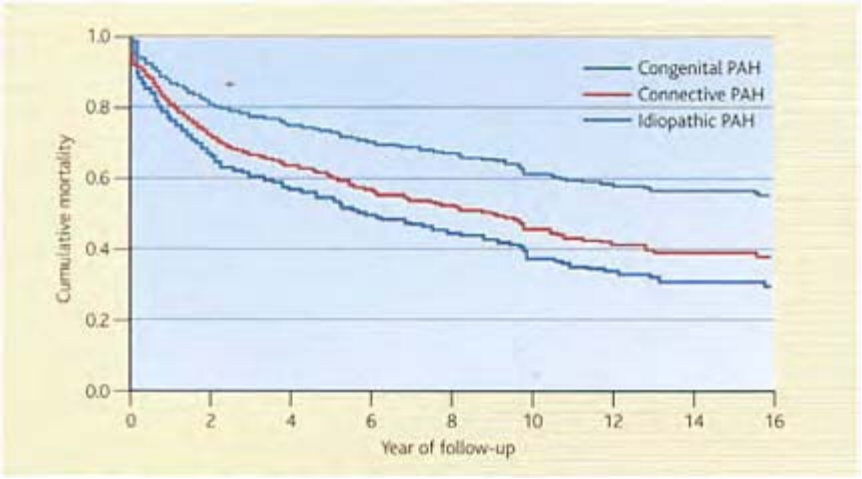

Figure 2 *Long-term survival rates in pulmonary arterial hypertension: age- and sex-adjusted Kaplan-Meier curves derived from Scottish population data (1986–2001).*[17]

Health in the USA, 1-year case fatality in those with PAH associated with collagen vascular disease was 25%, rising to 70% at 5 years. A comparison of the demographic profile of incident cases highlighted the fact that patients with connective tissue disorders are more likely to be screened for PAH and treated earlier. It should be noted, however, that patients with connective tissue-related PAH commonly have a worse prognosis than those with idiopathic PAH when presenting with the same haemodynamic profile.

A major limitation of population-derived data is the lack of specific detail collected concerning the progression of disease. As Figure 3 demonstrates, patients who exhibit more advanced symptomology as determined by a more severe WHO classification (Class IV compared with Class II and III), have a markedly worse prognosis.[7] Overall, these data reinforce two important points in relation to PAH:

- regardless of extent of disease progression and associated disease states, survival rates in PAH are extremely poor and the potential for positive effects of new modalities of

treatment are therefore high[3]

- there is a strong possibility that earlier detection and proactive management of PAH will slow the typical disease progression/deterioration

Figure 3 *Differential survival based on WHO Classification of PAH-related symptoms (Class II & III vs Class IV). Figure adapted from original data.*[7]

seen in PAH and have a positive effect on survival rates—particularly with the availability of new treatments.

Not unexpectedly, the recent Scottish data outlined above suggest that the recent interest in PAH and introduction of new more effective treatment modalities have been associated with significantly improved survival rates in recent years.[17]

3
Pulmonary arterial hypertension—increasing our understanding of disease pathophysiology

Introduction to the pathophysiology of PAH

Our understanding of the pathophysiology of PAH is still in its infancy, although significant advances have been made based on molecular science, genetics and the understanding of the clinico-pathological interactions recognized in the WHO classification scheme. Undoubtedly, the pathophysiology of PAH is complex, pivoting around the concepts of vasoconstriction, vascular remodelling and thrombosis. Vasoactive substances, growth factors, inflammatory mediators and components of the clotting/coagulation system are all involved to varying degrees.[20] This complex interplay is only just being decoded, but already there have been both real and potential therapeutic targets unearthed.

This chapter will discuss some of the underlying mechanisms and mediators responsible for (or associated with) the development of PAH, and how these interact to cause the problems encountered in clinical practice.

Vascular wall remodelling/vasconstriction and platelet activation

Mechanisms

Postmortem studies of PAH typically show histopathological changes in pulmonary resistance arteries, characterized by marked obstructive lesions.[21–23] These lesions represent proliferation of endothelial and smooth muscle cells and are the hallmark of PAH.[24] They cause progressive occlusion of the vessel lumen and provide an obvious reason for the development of PAH (see Fig. 4). These lesions also highlight the fact that

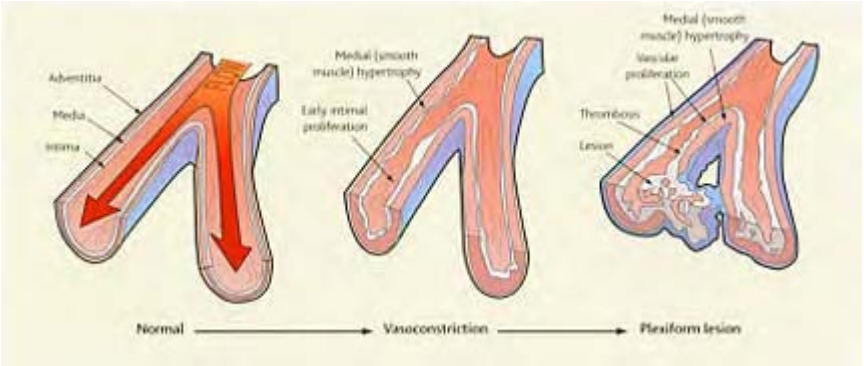

Figure 4 *Developing obstructive plexiform lesions in pulmonary arteries.*

definitive treatments for PAH will require agents with antiproliferative and/or remodelling potential, as opposed to pure vasodilator treatments.[25] PAH can however develop in the absence of these distinct lesions in the pulmonary vasculature. In this setting, it is likely there are diffuse changes in the structure of pulmonary resistance arteries, in addition to altered vasoreactivity (leading to vasoconstriction) and increased platelet activation (leading to thromboembolism) leading to progressive PAH.[26,27]

Figure 5 represents an algorithm demonstrating how all three key components of PAH (vasoconstriction, vascular wall remodelling and platelet activation/aggregation) have the potential to form a pathological triad that may lead to a cascade of vascular dysfunction, increasing pulmonary vascular resistance and progressive clinical deterioration. Standard pharmacological treatment of PAH (see Chapter 5) aims to interrupt this pathological cascade.

Vasoreactivity

Normal resting (pulmonary) arterial tone is maintained by a balance of endogenous vasodilators and vasoconstrictors. Studies of PAH have shown

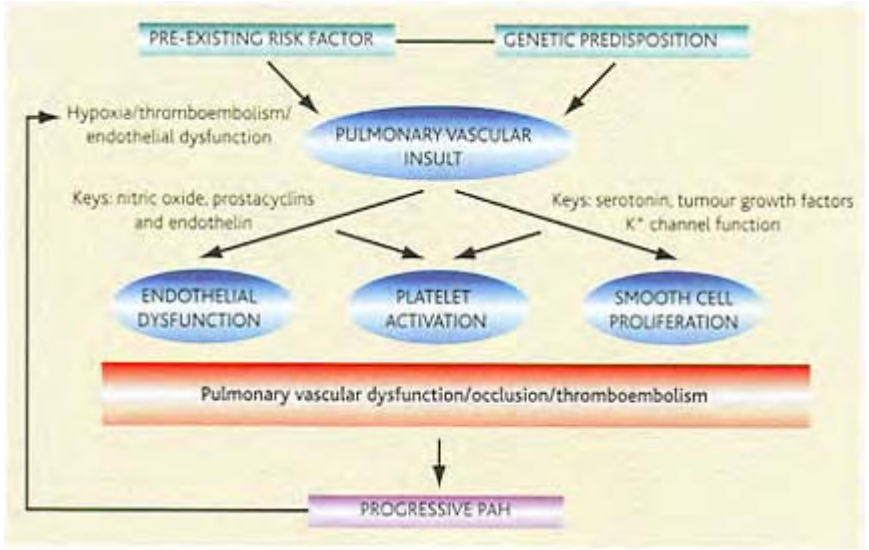

Figure 5 *Algorithm of the pathophysiology of PAH.*

that an imbalance on either side can lead to the development of pulmonary hypertension. In addition, many of these endogenous substances not only affect resting vascular tone (vasoconstriction or dilatation) but also have effects on cell (especially smooth muscle) proliferation, platelet aggregation and vascular remodelling. For example, levels of nitric oxide (NO) and prostacyclin are diminished in PAH.[24,25,28–30] Nitric oxide and prostacyclin are both potent endogenous vasodilators. Prostacyclin also has potent antiplatelet effects and inhibits smooth muscle cell proliferation. Both these agents have proven to be effective treatments for PAH—see Chapter 5.[29,31] Conversely, vasoconstrictors such as endothelin and thromboxane are present in increased concentrations in pulmonary hypertension. Endothelin, in particular, has potent proliferative effects. Thus, endothelin provides an attractive target for effective therapy in PAH.[30,32–38]

Endothelin

Endothelin is a potent and long-lasting vasoconstrictor that is 100 times more potent than noradrenaline (norepinephrine).[33] In addition to being a potent vasoconstrictor, it is directly associated with fibrosis (predominantly mediated via the ET_B receptor), vascular cell hypertrophy, inflammation and neurohormonal activation.[35,41,42] Its synthesis is triggered by numerous factors, including localized mediators such as inflammatory cytokines, and extrinsic factors such as low oxygen tension and increased arterial wall shear stress (e.g. in the presence of an obstructive plexiform lesion in the pulmonary vasculature).[35,41,42] The elevation of both plasma and tissue endothelin levels, and increased expression of endothelin receptors, are seen in pathological conditions such as

PAH, acute and chronic heart failure, cardiogenic shock, acute coronary syndromes and fibrotic lung disease.[35,43] Its role in connective tissue diseases is well documented, with evidence suggesting that elevated endothelin levels contribute to the vascular and fibrotic manifestations characteristic of systemic sclerosis.[5,6,44]

High plasma endothelin levels have been shown to correlate not only with severity of disease but also with prognosis for patients with both idiopathic PAH and that relating to connective tissue disease.[37,38] The growing evidence of the pathological role of endothelin in PAH has led to the development of endothelin receptor antagonists, such as bosentan, as a targeted therapeutic approach to disease pathogenesis.[25,30,32]

K^+ channel function

Abnormal K^+ channel function in pulmonary vascular smooth muscle also appears to be involved in the development of PAH. Hypoxia has been shown to selectively inhibit the function and expression of voltage-gated K^+ channels in pulmonary arterial smooth muscle cells. Via this mechanism, acute hypoxia induces membrane depolarization, and a rise in cytosolic Ca^{2+} that triggers vasoconstriction. In addition, caspace activity is inhibited, resulting in an inhibition of apoptosis, and unchecked cell proliferation resulting in vascular remodelling.[45–47]

In addition to the above, it is useful to consider the way pulmonary hypertension is now classified to give us insights into the underlying pathophysiology. In part, this classification was born from an understanding of the different contributions of various disease states to the development of pulmonary hypertension, and PAH in particular.

The genetic basis of PAH

In the original (1998) WHO classification, familial PAH was thought of as a subsection of so-called primary pulmonary hypertension.[1] The latest classification however, recognizing the identification and clarification of the gene responsible for familial PAH, classifies this as a separate entity.[13] Furthermore, it is known that the genetic defect(s) responsible for familial PAH is present in 10% of cases of idiopathic PAH.[4]

The gene defects identified as the cause of familial PAH are related to mutations in the bone morphogenetic protein receptor type 2 (BMPR2). This receptor and its ligand (bone morphogenetic protein 2) are part of the transforming growth factor beta (TGF-β) superfamily of signalling pathways. Normal activation of this receptor produces signals that inhibit proliferation, particularly of pulmonary artery smooth muscle cells. More than 40 BMPR2 gene mutations have been identified, and all lead to loss of this inhibition of cellular proliferation.[4,48–51]

In addition to the BMPR2 abnormalities, mutations in other genes have also been proposed as having a role in the development of pulmonary hypertension. Mutations in the ALK-1 receptor (activin-like kinase), also a member of the TGF-β family, have been linked to the development of PAH in patients suffering from hereditary haemorrhagic telangiectasia.[51] Likewise, genetic polymorphisms of the serotonin transporter (5-HTT) have been linked with PAH associated with hypoxia and fenfluamine use.[9,52] The role of

these and other genetic abnormalities is providing a very fruitful area of research into both the pathogenic mechanisms underlying the development of PAH and the identification of potential therapeutic targets.

Systemic sclerosis (scleroderma)

Pulmonary hypertension is recognized as a lethal complication of all forms of systemic sclerosis. Endothelin has been postulated as having a pivotal role in the pathogenesis of the pulmonary vascular disease associated with this condition, which has all the hallmarks pathologically of PAH.[5,6,44] There are, however, significant clinical differences compared to other forms of PAH, relating principally to late presentation and/or recognition of the pulmonary vascular abnormality. This occurs in the main because of the significant co-morbidities associated with the underlying condition that often dominate the clinical presentation early in the disease. As a consequence, patients with systemic sclerosis often present in advanced stages of right ventricular dysfunction and functional decline, and, as a result, treatment outcomes are generally less satisfactory when compared to idiopathic PAH for example.

PAH most commonly complicates limited systemic sclerosis (also known as CREST syndrome), and is not to be confused with the pulmonary hypertension complicating systemic sclerosis-related interstitial lung disease/pulmonary fibrosis.[5,6,44]

Other causes of PAH

As indicated in Table 1, portal hypertension,[12] human immunodeficiency virus (HIV) infection,[11,53] and anorectic agents[9,52] are external factors that can also lead to PAH. The use of appetite-suppressant drugs (amphetamine derivatives such as fenfluramine and dexfenfluramine) for more than 3 months is associated with a greater than 30-fold increased risk of developing pulmonary hypertension.[9] This complication has been linked to abnor-mal serotonin metabolism and polymorphisms in the serotonin transporter mechanism. The precise mechanisms by which portal hypertension and HIV infection lead to PAH are unknown.

Congenital abnormalities

Pulmonary vascular remodelling occurs in response to the shear stress caused by significant increases in pulmonary blood flow. This situation is most commonly encountered in congenital heart disease associated with systemic to pulmonary shunts.[15,16,54] The chronic increase in pulmonary blood flow leads to the development of PAH that is pathologically indistinguishable from idiopathic PAH. When the pulmonary arterial pressure exceeds systemic levels, reversal of the shunt occurs, with resultant cyanosis—the so-called Eisenmenger syndrome.[14]

Persistent pulmonary hypertension of the newborn (PPHN) is a rare disorder of

neonates: in Scotland (population 5 million) there were 19 reported cases during the 16-year period of 1986–2001.[17] An elevated pulmonary vascular resistance is required for an effective fetal circulation; however, if this state persists after birth, pulmonary to systemic shunting occurs through persisting fetal channels (e.g. the ductus arteriosus), thereby bypassing the lungs and resuting in systemic arterial hypoxaemia.[15,28] As in many forms of PAH, the mechanisms underlying the development of pulmonary hypertension in this setting are poorly understood. The outcome of this condition, however, has been markedly improved with the use of inhaled nitric oxide therapy.

4
Pulmonary arterial hypertension—clinical profile and diagnosis

Clinical profile

Without treatment to relieve chronic PAH, particularly in its severest form, patients typically develop progressive right ventricular hypertrophy, dilatation and associated right ventricular dysfunction—see Figure 6.[12,55–58] Without appropriate treatment, the right ventricle progressively fails, eventually resulting in death.

Many of the pathological changes associated with PAH may not produce significant and readily identifiable symptoms until the disease has pro-

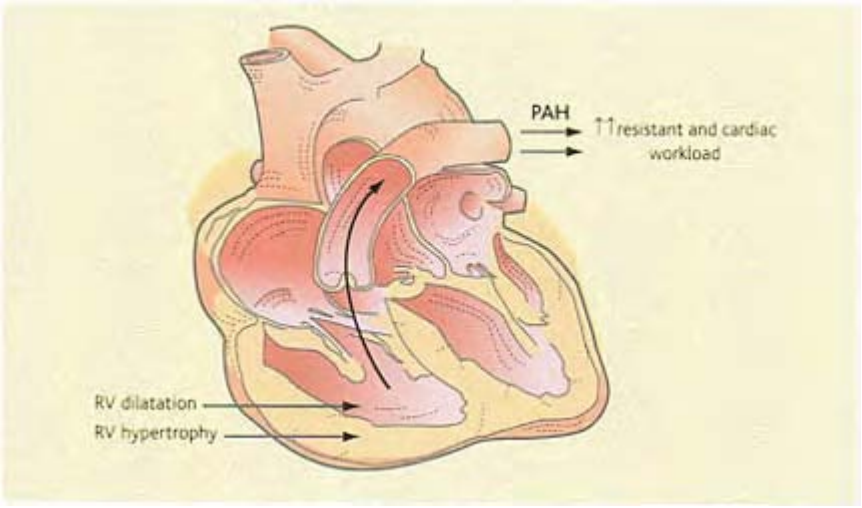

Figure 6 *Right ventricular failure secondary to pulmonary arterial hypertension.*

gressed significantly (i.e. when right heart failure has developed). In addition, the clinical profile of PAH may also be obscured by the underlying disease state (e.g. systemic sclerosis), particularly where other factors have a detrimental effect on exercise tolerance.

Symptoms

The most common symptom of PAH is progressive exertional dyspnoea. Depending on

the stage of disease and degree of right ventricular compromise, patients can also present with symptoms such as:

- presyncope and syncope
- central chest pain
- fatigue
- palpitations
- cough and occasionally haemoptysis.[1]

Signs

Physical examination is often normal in early stages of the disease process, with the classical signs of pulmonary hypertension only becoming evident as right ventricular hypertrophy and failure develop. The following signs are indicative of right ventricular hypertrophy or pre-established right heart failure secondary to chronic PAH:

- left parasternal systolic lift
- accentuated pulmonary valve closure sound (loud P2)
- tricuspid regurgitant murmur
- raised jugular venous pressure
- RV 3rd heart sound
- hepatomegaly
- peripheral oedema and ascites.

Clinical investigations

Diagnostic investigations are shown in Box 3.[59]

Routine investigations will provide evidence suggesting the diagnosis of pulmonary hypertension. For example, Figure 7 shows the pattern of right ventricular ‘strain’ seen in the ECG of a patient with right ventricular hypertrophy secondary to PAH. The majority of patients with PAH have an abnormal ECG.[1] Similarly, a chest X-ray may show proximal pulmonary

B***ox 3*** *Clinical investigations of PAH.*

Imaging:

- chest radiograph
- echocardiogram
- ventilation perfusion scan
- high-resolution computed tomography (CT) lungs.

Respiratory:

- arterial blood gases in room air

- lung function testing
- nocturnal oxygen saturation monitoring.

Cardiology:

- electrocardiography (ECG)
- six-minute walk test (6MWT)
- right heart catheterization.

Blood investigations:

- biochemistry and haematology
- thrombophilia screen
- human immunodeficiency virus (HIV).

Urine:

- β-hCG (beta-human chorionic gonadotrophin)—women.

artery enlargement and/or cardiomegaly. Both 12-lead ECG and chest X-ray represent readily available screening tools for PAH (see Chapter 6), but it must be emphasized that both tests may be substantially normal in patients with symptomatic PAH, particularly in the earlier stages of the disease, but also occasionally in later disease stages.[59]

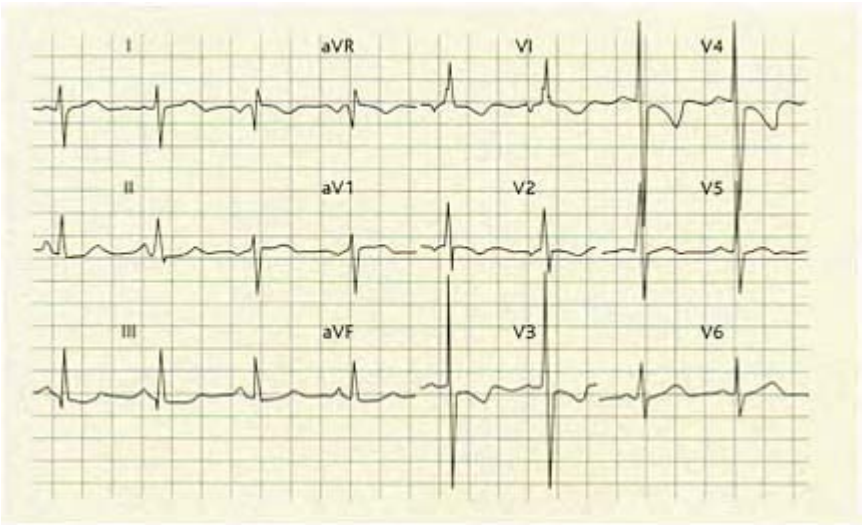

Figure 7 *12-lead ECG from a patient with right ventricular failure/hypertrophysecondary to PAH. Note the typical pattern of right ventricular strain pattern and right axis deviation, as denoted by positive R waves in leads V1, V2 and AVI.*

If pulmonary hypertension is suspected clinically, the next step is to evaluate the patient with transthoracic echocardiography. Doppler assessment of the right ventricular systolic pressure (RVSP) through measurement of the tricuspid regurgitant jet, gives an estimate of pulmonary artery pressure. In addition, there may be evidence of right ventricular hypertrophy and dysfunction.[60–62]

To confirm the diagnosis of PAH, raised left atrial pressure must be excluded by right heart catheter.[1,59] This procedure allows accurate measurement of pulmonary haemodynamics and determination of the patient's prognostic outlook.[58] Investigations used to either rule out pulmonary hypertension or confirm associated pathology (e.g. pulmonary embolism) are further described in Chapter 6.

Clinical indicators of disease progression

There are a range of non-invasive and invasive indices/parameters used to monitor disease progression in PAH. The most commonly used of these are described below.

WHO functional class

As worsening dyspnoea on exertion is the most obvious and probably most sensitive marker of the underlying disease progression associated with PAH, it has proven to be the most practical means of delineating the clinical status of affected patients. As such, the WHO adopted the NYHA functional class (first applied to heart failure)[63] to stratify the clinical status of patients with PAH, and guide appropriate management according to their response/non-response to medical treatment (Table 2).

Patients whose clinical profile is consistent with WHO Class IV usually have signs of advanced right heart failure and there is little doubt that the progression from WHO Class I to IV mirrors the evolution/progression of right-sided heart failure secondary to the underlying PAH. As can be appreciated, patients in WHO Class I with underlying PAH are unlikely to be diagnosed unless investigated for another reason. Most patients present in WHO Class III and IV and have already developed right ventricular dysfunction.

Table 2 *WHO functional classification of PAH.*[2]

WHO functional class	**Symptomatic profile**
Class 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
Class 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

Class 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
Class IV	Patients with pulmonary hypertension with inabitity 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

Six-minute walk test

In addition to asking patients about their physical limitations and classifying their responses according to an agreed formula (e.g. WHO class), it is clearly desirable to gain a more objective measure of their functional capabilities. In this respect, the easiest, most tolerated and realistic test of a patient's ability to carry out activities of daily living is the 'six-minute walk test'. This test is as simple as it sounds, only requiring an experienced supervisor to measure how far a patient can walk over a flat and unobstructed surface during the predefined time-frame of 6 min.[2,64] This simple walk test is sensitive to changes in cardiac function and can predict subsequent morbidity and mortality in PAH patients.[65] Like the WHO class, the results of this walk test may vary, so it is important to examine historical trends in patients rather than rely on a single test (i.e. using the patient as their own control following application of treatment). Improvements in right ventricular function with effective treatment can also be accurately monitored by 6MWT results. Data from this simple test can also be combined with that from the commonly used Borg dyspnoea index—a self-measure of perceived breathlessness.[66]

Haemodynamic parameters

If available, a number of haemodynamic parameters may be measured and provide concrete evidence of PAH and associative changes in cardiopulmonary function. The following parameters, often measured in Centres of Clinical Excellence, are pivotal to determining a specific cause and diagnosis of PAH, with associated decisions relating to appropriate treatment and prognostic outlook:

- pulmonary artery pressure
- cardiac index
- pulmonary vascular resistance
- right atrial pressure
- pulmonary capillary wedge pressures.

It is important to note, of course, that the definitive diagnostic tool for PAH is right heart catheterization, providing a direct measure of pulmonary pressures.[3]

Respiratory function tests

These tests may include lung volumes and carbon monoxide (CO) diffusion capacity.

Respiratory function tests often show a disproportionate reduction in carbon monoxide diffusion in the lung (DLCO—around 50% of predicted in moderate PAH), with at most a mild-to-moderate restrictive lung defect. The reduction in DLCO is greater than that seen with comparable symptomatic left heart failure and reflects the loss of effective or functioning pulmonary vasculature characteristic of PAH.[3]

5
Improving outcomes in pulmonary arterial hypertension: pharmacological and surgical treatment strategies

The evolving treatment of PAH

PAH has had an historic lack of definitive treatment options. When this is combined with its poor prognosis, it is not surprising that median survival of idiopathic PAH historically is only 2.8 years and only 1 year for patients with PAH related to scleroderma.[7,8] *It was not until* 1981 when heart-lung transplantation was introduced, that an effective treatment for PAH became available. Challenged by the limited number of organ donors, medical treatments have been sought, the most successful of which, can now postpone the need for transplantation.

Increasing interest in PAH has led to many advances in treatment, and vice versa. At the recent World Symposium on Pulmonary Arterial Hypertension (Venice 2003) the Task Force on the Medical Treatments of Pulmonary Hypertension reviewed all of the clinical trial data and provided a general guide to the management of PAH based on the strength and veracity of evidence for each of the commonly used pharmacological agents.[67] Figure 8 is based on this updated expert advice. A grading system, based on the strength of evidence for efficacy, was applied to each treatment listed in this figure. Epoprostenol[68] and bosentan[69] were the only agents awarded an 'A' (highest grade) due to the strength of their evidence-based trial data: both should be considered first-line treatment options for patients in WHO Class III and IV[70] It is also clear that using sildenafil, as adjunctive therapy in treating PAH, is the subject of much interest.[71,72] At this stage, however, its true role in this clinical context is yet to be determined, pending the completion of randomized trials. The role and purpose of these treatments are overviewed, tabulated and presented in more detail in Table 3.

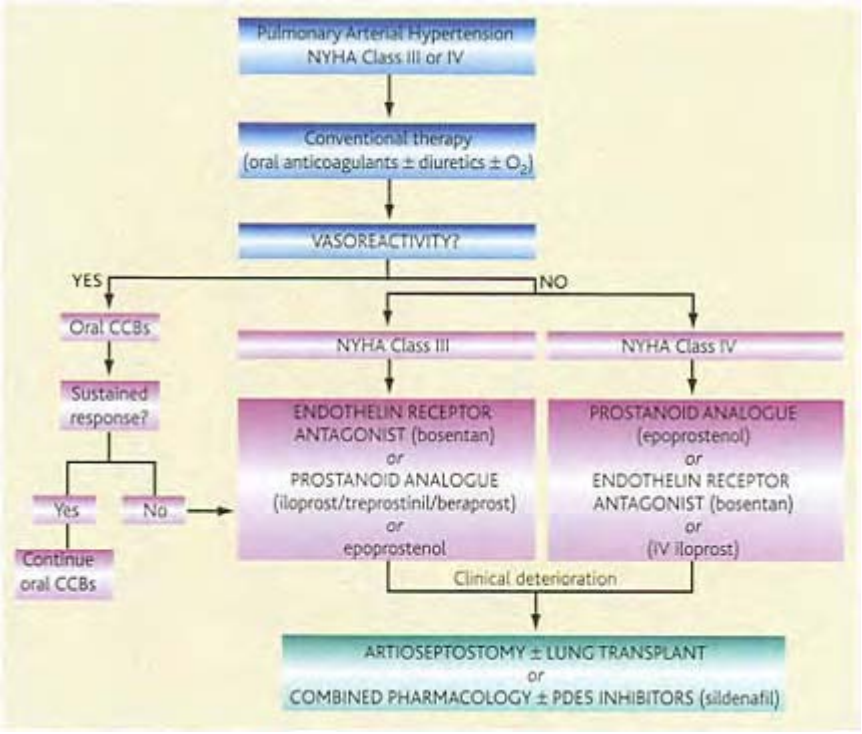

Figure 8 *Algorithm for the gold-standard treatment of patients with PAH (post Venice expert meeting in PAH, 2003).*[67] *CCB=calcium channel blocker, O_2=oxygen therapy, IV=intravenous.*

Medical management

The medical treatments summarized in Table 3 that form part of the gold standard management of PAH[67] are principally designed to directly ameliorate underlying pulmonary hypertension, reduce thromboembolic load and improve right ventricular function (primarily by reducing cardiac after-load).

Basic care of patients with pulmonary hypertension

All patients with pulmonary hypertension and right ventricular dysfunction, regardless of the cause, require standard therapy with diuretics (to reduce right ventricular preload), antiarrhythmic agents such as digoxin

Table 3 *Overview of current treatment options for PAH*

Treatment	Indication	Contraindications	Comments and references
Anticoagulation: Warfarin	Prevention of pulmonary arterial thrombosis	Caution in connective tissue disease	Associated with prolonged survival in idiopathic/familial PAH[56] There are no published data on warfarin in other forms of pulmonary hypertension
Oxygen therapy	Patients with associated lung disease. Adult nocturnal desaturation can be treated with low-concentration oxygen therapy (2 L/min)	Causes vasoconstriction and should be used with caution and closely monitored	Integral part of the management of all forms of advanced PAH[73–76]
Supportive medical therapy: diuretics; digoxin	In the presence of right heart failure. Digoxin improves cardiac output in patients who remain symptomatic on medical therapy	Digoxin should be used with caution in the elderly due to potential toxicity	Diuretics remain the gold standard for relieving the symptoms of fluid overload in right heart failure[77] ACE inhibitors and beta-blockers are superior to digoxin in treating other forms of heart failure[78,79]
Treatment	**Indication**	**Contraindications**	**Comments and references**
Calcium antagonists: diltiazem; nifedipine; amlodipine.	Reduces pulmonary artery pressure. Reduces mortality with sustained improvement of systems. Patients with right ventricular impairment should be considered for	Calcium antagonists should not be started before the performance of an acute vasodilator study. In patients who have not responded to the vasodilator challenge, oral calcium channel blocker therapy is unlikely to be beneficial and may have adverse effects.	The proportion of patients who exhibit a positive response to a provocative vasodilator test and a sustained response to calcium antagonist therapy is as low as 10%[24,80–86]

	amlodipine. Therapy should be commenced in hospital and carefully titrated according to blood pressure, oxygen saturation and exercise tolerance	In the presence of cardiac index <2.1 L/min/m^2 and/or right arterial pressure= 10 mmHg, calcium antagonists should be avoidedartery	
Treatment	**Indication**	**Contraindications**	**Comments and references**
Long-term prostaglandin therapy: epoprostenol; lloprost; (intravenous or inhalation)	Remodelling of the pulmonary vascular bed and subsequent reduction in endothelial cell injury and hypercoaguability in the following: all forms of PAH; all patients who don't respond to conventional medical therapy before transplantation	Expensive. Conventional medical therapy should be continued. Potential rebound pulmonary hypertension if withdrawn suddenly. Calcium antagonist therapy must be ceased. The dose of prostaglandin should be increased upon the return of symptoms	This form of treatment was the first to offer prognostic benefits in the management of PAH[29–32–60–87–100] Specialist care in a pulmonary vascular centre is required for this complex and technically challenging treatment
Endothelin receptor antagonist: bosentan	The treatment of idiopathic PAH or that associated with connective tissue disease in patients with WHO Class III or IV symptoms.	The following are contraindicated during bosentan therapy: pregnancy; moderate to severe hepatic impairment; cyclosporine A and glibenclamide; and hypersensitivity to bosentan	Bosentan has demonstrated an ability to improve symptoms, exercise capacity, and haemodynamic function and structure in patients with PAH. Bosentan has also been shown to delay disease progression, improve quality of life and prolong survival in PAH[32–36–69–101–110]

and/or amiodarone (to maintain sinus rhythm wherever possible) and war-farin.[56,77] Warfarin therapy has been shown to almost double 3-year survival rate in those with idiopathic PAH.[68–70] Calcium antagonists (e.g. diltiazem and nifedipine) have been shown to be effective in reducing pulmonary arterial pressures* in the approximately

*Such a response is defined as a fall of a >10 mmHg in mean pulmonary artery pressure (PAP) to <40 mmHg, associated with a stable or even increased cardiac output.

6−10% of patients who demonstrate a positive acute vasodilator response,[82,86,111] and this is associated with very significant improvements in both symptoms and survival in this small subset of patients. Most calcium antagonists, however, with the possible exception of amlodipine,[84] are contraindicated in patients who have developed significant right ventricular dysfunction secondary to PAH, because of their negative inotropic effects.[79] The clinical conundrum relating to the use of calcium antagonists in the context of advanced PAH highlights the need for specialist management and continuous monitoring.

Prostacyclin (PGI_2) analogues

Prostacyclin (or epoprostenol) was first used clinically in 1985 to bridge a patient with primary pulmonary hypertension to heart-lung transplantation and, until recently, this remained the only definitive medical treatment for PAH.[7,67] Prostacyclin is administered by continuous intravenous infusion (the half-life is only minutes) and, this, combined with the cost, has limited its widespread use. Prostacyclin has been shown to reverse the vascular endothelial abnormalities and resulting hypercoagulable state associated with PAH.[29,88] It has been shown to improve quality of life, exercise capacity and (short-term) survival in PAH patients in WHO functional Class III and IV[96] and delay (in some cases remove) the need for lung transplantation.[90,94]

In the context of the high cost, and risks of long-term continuous intravenous administration, there have been efforts to administer such therapy via inhaled, subcutaneous and oral routes. Agents such as iloprost (inhaled) and beraprost (oral), synthetic analogues of prostacyclin, have shown clinical benefit in PAH.[95,96,112] Limitations exist, however, due to the frequency of inhalation required with iloprost therapy, and the unreliable absorption of beraprost. Another PGI_2 analogue, treprostinil, is administered subcutaneously via continuous infusion.[113] However, local toxicity (mainly pain) at the infusion site may limit the dose, and therefore effectiveness, in some patients. Despite their limitations, all of these agents have proven effective in clinical use, and all provide effective treatment alternatives in selected patients.[114]

Endothelin receptor antagonists

Given the important putative role of endothelin (ET) in the pathogenesis of PAH, there is heightened interest in the therapeutic role of ET_A and ET_B receptor antagonists. Endothelin, in addition to being a potent vasoconstrictor, has been directly associated with fibrosis (predominantly mediated via the ET_B receptor), vascular cell hypertrophy, inflammation and neurohormonal activation. Bosentan, an oral ET_A and ET_B receptor antagonist, has been shown in two randomized clinical trials (including the BREATHE-1 Study) to improve clinical outcomes in patients with idiopathic PAH and in PAH associated with connective tissue disease.[69,109]

These two studies both demonstrated that bosentan therapy was associated with highly significant improvements in 6-min walk tests (6MWTs) and haemodynamic measures when compared with placebo.[69,109] Additionally, in the BREATHE-1 study, time to clinical worsening (death, lung transplant or epoprostenol salvage therapy) was measured at 16 and 28 weeks, with a significant preservation of clinical status seen vs placebo. An

echocardiographic substudy conducted within this trial demonstrated improvement in right ventricular systolic function and left ventricular early diastolic filling, in addition to a reversal of right ventricular remodelling.[102] A similar trend was seen in the subanalysis of scleroderma patients, with bosentan preventing deterioration in exercise capacity and increasing the time to clinical worsening. These data suggest that bosentan has the potential to delay the disease progression typically seen in PAH.[105]

Early data now suggest that bosentan may also impact positively on survival in the aforementioned patient subgroups,[115] and recent Australian data have demonstrated significant improvements in quality of life indices in patients with idiopathic and scleroderma-associated PAH.[116] Dose-related liver function abnormalities were noted in all of these studies, with the abnormalities reversible with dose (down) titration or cessation of treatment. Close monitoring of liver function is recommended in all patients on bosentan therapy.[36] Endothelin receptor antagonists have rapidly become the 'cornerstone of treatment for PAH' in recent years,[117] particularly given the limitations and costs associated with prostacyclin analogues as first-line/adjunctive treat-ment for patients with Class III or IV symptoms, and potentially extending to patients in Class I and II to slow disease progression.[117]

Ongoing clinical trials

Clinical researchers continue to seek better outcomes for PAH patients. Strategies such as combination therapy (i.e. utilizing current and emerging therapies together) are an area of investigation aimed at finding further improvements in survival markers. An overview of the current research and potential future therapies is presented in Table 4.

There is much interest in the therapeutic role of sildenafil, a phosphodiesterase V inhibitor that has been shown to have beneficial haemodynamic and clinical effects.[71, 72,118] However, pending the results of ongoing clinical trials (predominantly small and non-randomized), it appears that sildenafil, in both its intravenous and oral forms[119] is likely to be used in an adjunctive role (i.e. improve clinical outcomes associated with current gold standard therapy) rather than be employed as first-line therapy for PAH.

Non-medical management

There are several non-medical options available for the management of severe pulmonary hypertension–see Table 5. These may be generic therapies for pulmonary hypertension, such as atrial septostomy,[120] or they may be specific for certain subgroups, such as pulmonary endarterectomy for patients with chronic thromboembolic pulmonary hypertension.[121–123] Transplantation of the lungs or heart and lungs remains an option for suitable patients with any form of pulmonary hypertension, when other therapies prove ineffective.[124–129]

Summary

The evidence for effective therapy improving the survival and quality of life of patients with pulmonary hypertension is compelling. Treatment is likely to be most effective if applied earlier in the course of the disease and, given the complexity of these patients and the treatments involved, this condition is best treated by experienced clinicians at centres with experience in all aspects of diagnostic assessment and management.

Table 4 *Randomized clinical trials in PAH.*

Treatment	Indication	Administration	Side effects	Combination?	RCTs	Regulatory
Epoprostenol	PAH (idiopathic, familial and connective)	IV (continuous)	Sepsis	Bosentan	3	approval USA, Canada, Europe, Japan
Iloprost	PAH (idiopathic, familial and connective)	Inhaled (6–9/day)	Short action		1	Europe, Australia
Treprostinil	PAH (idiopathic, familial and connective) + congenital	SC (Inf)	Infusion site pain		2	USA, Australia
Beraprost	PAH (idiopathic, familial and connective) + congenital	PO (QID)	Flushing, headache	Bosentan	2	USA, Canada, Europe
Bosentan	PAH (idiopathic, familial and connective)	PO (BID)	Liver enzyme increase	Epoprostenol	2	USA, Canada, Australia, Hong Kong, Singapore, Europe

RCTs=randomized controlled trials; IV=intravenous; SC=subcutaenous; Inf=infusion; PO=oral; BID=twice a day; TID=three times a day; QID=four times a day; QD=every day; GI=gastrointestinal.

Treatment	Indication	Administration	Side effects	Combination?	RCTs	Regulatory Approval
Sitaxsentan	PAH (idiopathic, familial & connective) +congenital	PO (QD)	Liver enzyme increase		1	Currently on trial
Ambrisentan	Currently on trial	PO (QD)	Liver enzyme increase	Currently on trial	Currently on trial	Currently on trial
Sildenafil	Currently on trial	PO (TID)	Visual/colour problems	Currently on trial	Currently on trial	Currently on trial
L-arginine	Currently on trial	PO (TID)	GI	Currently on trial	Currently on trial	Currently on trial

RCTs=randomized controlled trials; IV=intravenous; SC=subcutaenous; Inf=infusion; PO=oral; BID=twice a day; TID=three times a day; QID=four times a day; QD=every day; GI=gastrointestinal.

Table 5. *Surgical procedures for PAH.*

Treatment	Indication	Contraindicated	Comments/references
Atrial septostomy: palliative procedure creating a safety valve that alleviates the high pressures to which the right heart is subjected in severe disease	Considered in severe pulmonary hypertension refractory to prostaglandin therapy, particularly where associated with recurrent syncope	Atrial septostomy is not indicated in the critically ill with severe right ventricular failure or in a patient with severe left ventricular failure	Atrial septostomy should only be performed by physicians with experience in performing this procedure with low morbidity and in a PAH specialist centre[120]
Thromboendarterectomy: surgical removal of organized thrombotic material is achieved with the stripping away of pulmonary arterial endothelium, commencing proximally in the main pulmonary arteries and extending out to segmental arteries	Recommended for all age groups. Valvular disease. Coronary artery disease	Significant lung disease is contraindicated (FEV_1 30% predicted). Patients with ventriculoatrial shunts for hydrocephalus are contraindicated as they may develop distal embolic disease	The prognosis for patients with thromboembolic pulmonary hypertension is poor, with a 5-year survival of 10%[123]

FEV_1=forced expiratory volume in 1 second.

Treatment	Indication	Contramdicated	Comments/references
Lung and heart-lungtransplantation	PAH with symptomatic progressive disease that, despite optimal medical and/or surgical treatment, leaves the patient in WHO functional Class III/IV. The 6-min walk test (6MWT) is a useful tool in the assessment of when to list patients for transplantation. Those with a 6MWT of <400m should be considered for transplantation	Candidates should meet the internationally agreed guidelines for lung transplantation	Transplant organs are limited and transplants are only performed in specialist centres[124–129]

FEV_1=forced expiratory volume in 1 second.

6
Screening and management of pulmonary arterial hypertension

Introduction to screening and detection

The traditional view of PAH has been that of a rare, insidious and deadly condition, most commonly afflicting young women, and unlikely to appear on the radar of the average clinician. One of the major purposes of this pocketbook is to provide an impetus to improved recognition of this condition, by highlighting the factors given in Box 4.

B***ox 4*** *Recognition of PAH.*

- PAH is almost certainly more common than most studies from specialist centres would suggest
- most cases of PAH are only diagnosed in the advanced stages of the disease process and the prognosis thereafter is extremely poor
- there are certain 'high-risk' individuals who should be monitored for PAH, and other individuals who exhibit suspicious clinical signs and symptoms who should be assessed for the possibility of underlying PAH
- modern-day treatments offer real survival benefits to those patients with PAH fortunate enough to be accurately diagnosed and appropriately assessed and treated
- the combination of early detection and treatment of PAH with effective, more widely available treatments is likely to have a dramatic effect on the prognosis and overall impact of this condition.

The key to better outcomes for patients with PAH lies not with specialist referral centres and so-called Centres of Excellence but with those clinicians who first come into contact with patients who may be exhibiting the first signs of PAH and/or right ventricular dysfunction. Such patients need to be adequately investigated and, if there is a strong suspicion of PAH or a confirmed diagnosis, referred to the nearest specialist centre for management.[130] This chapter outlines the most effective strategies to ensure that patients who develop PAH are recognized and then rapidly access appropriate specialist care.

High-risk patient cohorts

The WHO diagnostic classification system for pulmonary hypertension provides a clear indication of those at increased risk of developing PAH.[1,67] These patients need careful monitoring to ensure that PAH is detected early. Factors/conditions strongly associated (if not causally) with the development of PAH are given in Box 5.

In addition, epidemiological studies clearly show that women are more at risk than men of developing PAH (ratio of approximately 2:1).[4,17] Other 'at-risk' groups who should be considered for a diagnosis of pulmonary hypertension include any patient (especially younger individuals) with

B***ox 5*** *High-risk candidates for PAH.*

- congenital heart disease associated with systemic-to-pulmonary shunts (e.g. Eisenmenger's syndrome)
- familial history of PAH
- acquired human immunodeficiency virus (HIV) infection
- portal hypertension/hepatic disease
- collagen vascular disease (particularly scleroderma and systemic lupus erythematosus (SLE))
- anorexic agents/toxic drugs known to be associated with the development of PAH.[67]

unexplained dyspnoea on exertion, or disproportionately low gas transfer (DLCO).

Given the time involved, and range of diagnostic investigations required to accurately diagnose PAH, it is impractical to screen every patient for PAH. The key is to utilize the background information contained throughout this pocketbook to recognize those at risk, and detect the presence of PAH, prompting further investigation. For those patients most at risk of developing PAH (e.g. those with scleroderma), this means regular review and specific interrogation for specific signs and symptoms.

Detecting PAH

Figure 9 shows the various detection pathways that can be used to determine the potential of PAH and how this might lead to a definitive diagnosis of PAH through a logical series of investigations.

In addition, 'incidental' detection of PAH should not be underestimated. For example, a patient with vague symptoms and a fairly innocuous clinical profile may surprise the clinician with an electrocardiogram (ECG) similar to that shown in Figure 7. Such a patient then requires more intensive investigation (e.g. echocardiography) to determine any underlying pathology.

It follows then that the number of incidental detections of PAH could be increased if more clinicians were aware of PAH and considered it in the differential diagnosis, particularly of patients in the previously mentioned increased risk categories.

Specialist clinicians in fields outside of the PAH Centres of Excellence have an equally important role in identifying patients who would benefit from early identification and treatment. These fields include rheumatology, respiratory medicine, general cardiology and immunology, at both consultant specialist and registrar levels.

Diagnosing PAH

Currently, the definitive diagnosis of pulmonary hypertension of any form is achieved by right heart catheterization and direct measurement of

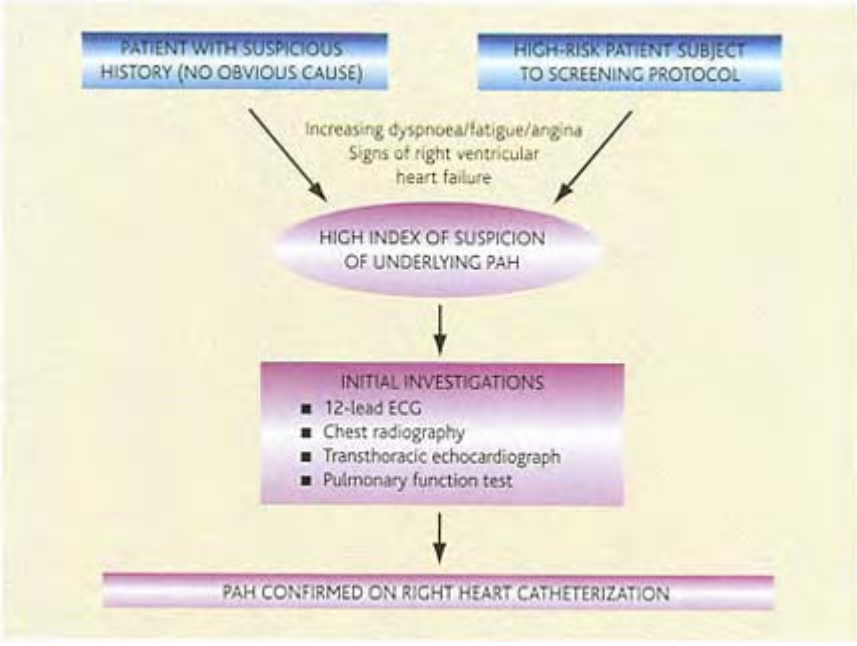

Figure 9 *Algorithm for detecting PAH.*

pulmonary artery pressures. PAH, per se, is then diagnosed by excluding raised pulmonary venous/left atrial pressure (most commonly by finding a normal pulmonary capillary wedge pressure).[61,63] Other cardiorespiratory pathology that causes exertional dyspnoea can be excluded using non-invasive means (e.g. pulmonary function tests, high-resolution CT (computed tomography) scanning and echocardiography). In the future, following more research, it is possible that selective screening with brain natriuretic peptides, which increase in the presence of elevated ventricular filling pressures secondary to PAH, may be employed to increase PAH detection rates.[131] However,

detecting patients in the latter stages of the natural history of PAH is clearly suboptimal.

Figure 10 is a 'diagnostic pathway' that shows how the two most important screening tests for PAH—transthoracic echocardiography and pulmonary function test—can be used to filter patients towards more definitive treatment and diagnosis (i.e. irrespective of whether a definitive diagnosis of PAH is made).

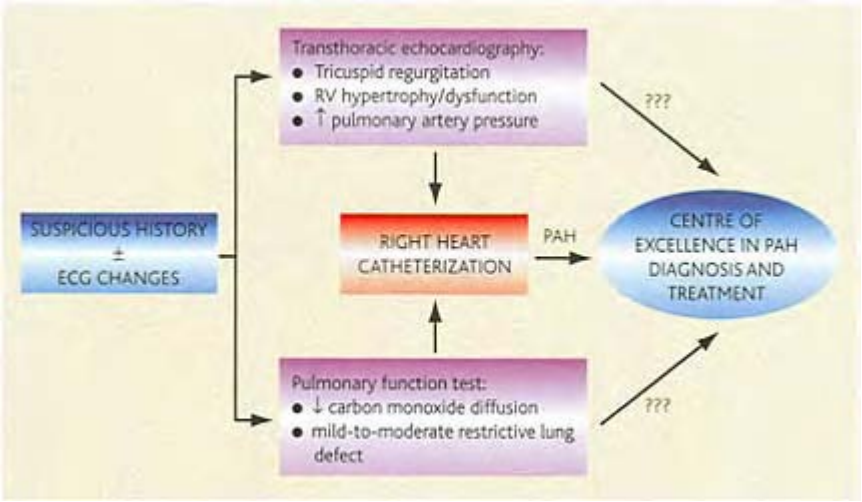

Figure 10 *Algorithm for diagnosing PAH.*

Given that there are different forms of PAH and many other causes of pulmonary hypertension per se (e.g. left-sided heart failure or valvular disease, and thromboembolic disease), there are a number of additional investigations that may be required. These include:

- ventilation perfusion scan
- high-resolution CT
- CT or magnetic resonance pulmonary angiogram
- sleep studies.

These assessments are best undertaken at a specialist centre, with physicians experienced in the diagnosis and management of the whole range of conditions associated with pulmonary hypertension.[3]

A new era of PAH management

Although the importance of the PAH Centres of Excellence should not be undermined, with the new era of effective agents available, many more clinicians now have a sound reason to diagnose PAH. The emergence of new oral agents such as bosentan, new forms of pre-existing therapy (e.g. oral prostacyclin analogues) and, potentially, completely new

treatment options (e.g. sildenafil), enables clinicians to abandon the therapeutic nihilism of past decades and offer patients effective therapies. Some of these agents allow reverse remodelling of the right ventricle and the potential to reverse the entire disease process.

APPENDIX

Informative websites: pulmonary arterial hypertension

http://www.pha-uk.com/

The Pulmonary Hypertension Association (UK) aims to provide support, understanding and information for all those people whose lives are touched by pulmonary hypertension.

h**ttp://www.pphcure.org/**

The PPH Cure Foundation (USA) provides information for the public and families affected by PPH. It is also the world's largest non-government foundation providing funding for PPH research.

h**ttp://www.phassociation.org/**

A public website, providing news and research updates on pulmonary hypertension (USA), that is dedicated to increasing advocacy and awareness of pulmonary hypertension.

h**ttp://www.phcentral.org/**

The PHCentral (USA) mission is to be the definitive internet resource for pulmonary hypertension-related information for patients, caregivers and medical professionals.

h**ttp://www.mayoclinic.org/pulmonaryhypertension-rst/**

Public information about the treatment of pulmonary hypertension at the Mayo Clinic (USA).

h**ttp://www.actelion.com/**

Actelion, the makers of bosentan (Tracleer—endotheal blockers), provides pharmaceutical information and research on drug trials (Swiss).

http://www.scleroderma.org/

The Scleroderma Foundation (USA) provides public information, education research and chat room facilities for patients and families seeking contact and support. It includes links to other related sites.

h**ttp://www.lupusnsw.org.au/ie.html**

The Lupus Association of NSW Inc. (Australia) is a community-based counselling and advocacy service with over 1100 members throughout New South Wales and Australian Capital Territory, and a permanently staffed office at North Ryde in Sydney, New South Wales.

h**ttp://www.unither.com/**

United Therapeutics, the makers of tresprostinil (Remodulin), provide information about prostacyclins.

h**ttp://www.mja.com.au/public/issues/178_11_020603/keo10709_fm.pdf**

Clinical update from Dr Anne Keough and team from the *Medical Journal of*

Australia.

h**ttp://www.ishlt.org/**

The International Society for Heart & Lung Transplantation.

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