HISTORICAL REVIEW

Diagnosis and management of pulmonary hypertension over the past 100 years

S.A. van Wolferen, K. Grünberg, A. Vonk Noordegraaf

Department of Pulmonary Diseases, Institute for Cardiovascular Research ICaR-VU, VU University Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands

Department of Pathology, Institute for Cardiovascular Research ICaR-VU, VU University Medical Center, The Netherlands

Received 11 September 2006; accepted 30 November 2006

Summary

Pulmonary hypertension is a rare disease with a poor prognosis. It was first described in the late 19th century as a clinical-pathological syndrome characterised by obstruction of the small pulmonary arteries and right ventricular hypertrophy in patients presenting with severe dyspnoea and cyanosis. After the development of right heart catheterisation in the second half of the 20th century, it was found that many diseases could cause pulmonary hypertension, which is now recognised to be high blood pressure in the arteries that supply the lungs. In the 1960s, an epidemic of pulmonary hypertension caused by appetite suppressants initiated a systematic collection of information on pulmonary hypertension, leading to the first international classification of pulmonary hypertension. Increased understanding of the pathogenesis of the various forms of pulmonary hypertension has led to novel treatments and holds promise for the future.

Introduction

In 1957, Oscar Brenner, a pathologist from Birmingham, England, wrote a review for this journal titled, The Lungs in Heart Disease. He started the introduction of his review with the following statement:

The relationship of the lungs to the heart is very close, and it is not surprising that diseases of the lung may affect the heart and diseases of the heart may affect the lungs. It is, of course, by way of the pulmonary blood vessels that this interrelationship is affected.

Although this statement seems obvious to us, it took a long time to recognise this relationship. From the late 19th century until the first half of the 20th century, several clinical-pathological case reports were published about patients with a distinctive syndrome involving obstructive lesions in the small pulmonary arteries and right ventricular hypertrophy. Right heart catheterisation, developed in the second half of the 20th century, allowed detection of...
elevated pulmonary artery pressure, thus linking pulmonary vascular disease to right ventricular hypertrophy. Pulmonary hypertension was defined as mean pulmonary artery pressure in excess of 25 mmHg at rest, or exceeding 30 mmHg with exertion. Classifications of pulmonary hypertension were made, identifying both primary pulmonary arterial hypertension, later named idiopathic pulmonary arterial hypertension (IPAH), and also various conditions associated with pulmonary hypertension12 (Table 1).

### The first clinical case reports

In 1865 the German physician Klob reported the autopsy findings of a patient who had developed progressive ankle oedema, dyspnoea and cyanosis prior to his death at age 59.2 Instead of the cardiac pathology he had expected, Klob found an impressive narrowing of the finer branches of the pulmonary artery with localised arteriosclerosis. In 1891, Romberg, a renowned German physician, described a similar clinical course in a 24-year-old patient.3 At the autopsy, other than the abnormalities in the pulmonary vessels, which he called ‘pulmonary vascular sclerosis’, he also noted massive right ventricular hypertrophy. The Argentinian physician Arrillaga was the first to describe a series of patients with pulmonary hypertension in 1913, after being made aware of the condition by his professor Ayerza.5,6 The combination of cyanosis and death by right heart failure was named Ayerza’s disease or ‘black heart disease’, due to the dark skin colour of the severely cyanotic patients. Arrillaga suggested that the cause of Ayerza’s disease was syphilis that had spread to the pulmonary arteries. Eventually, in 1935, Brenner would disprove the syphilis theory after studying 100 cases of pulmonary hypertension at the Pathology Department of Massachusetts General Hospital.9 However, at that time Brenner could not offer an alternative explanation for the pathological findings of right ventricular hypertrophy and pulmonary vascular sclerosis.

## Diagnosis of pulmonary hypertension

In 1852, Beuser in Leipzig, Germany, was the first to perform a measurement of the pulmonary artery pressure in a cat,
using mercury manometers in the same fashion as his professor, Ludwig, had done on the much more accessible systemic circulation. The first introduction of a catheter into a human pulmonary artery was performed by Forssmann. In 1929, Forssman inserted a urinary catheter into his own antecubital vein, and, guided by fluoroscopy, placed it in his right heart (Fig. 1a).\(^{13}\) Disappointed by the negative reactions of the medical profession and the lack of acceptance in cardiology, he eventually became an urologist and abandoned his experiments. Cournard and Richards further developed this technique in the 1940s. Forsmann finally received recognition for his pioneering work in 1956, when he, together with Cournard and Richards, received the Nobel Prize for the development of right heart catheterisation (Fig. 1b).\(^{14,15}\)

Non-invasive alternatives to diagnose pulmonary hypertension were sought. Although a simple chest X-ray or electrocardiogram provides clues as to whether pulmonary hypertension is present or not,\(^{16-20}\) a breakthrough came with the development of Doppler echocardiography in the late 1970s. The blood flow over the tricuspid valves appeared to predict systolic pulmonary artery pressure, while the structural information gained using this technique allowed the effect of hypertension on the right ventricle to be evaluated. However, despite these advances, right heart catheterisation is still required to confirm pulmonary hypertension.\(^{21}\)

Once pulmonary hypertension is diagnosed, further diagnostic work-up to identify possible underlying diseases is recommended.\(^{21}\) In 1957, pulmonary hypertension was already divided into 5 classes based on the underlying cause: chronic bronchitis and emphysema, left to right shunt, primary pulmonary hypertension, primary pulmonary arteriosclerosis and pulmonary embolism.\(^{1}\) At that time, primary pulmonary arteriosclerosis was regarded as the pathological counterpart of primary pulmonary hypertension. Advances in histopathology and understanding of disease pathogenesis resulted in renewed classifications in 1973 and 1998; these classifications included several other forms of pulmonary hypertension. Underlining the impact of the development of various treatment modalities in recent years, the latest WHO classification (2003) uses clinical presentation and management rather than histopathological characteristics to classify pulmonary hypertension (Table 1).

For example, WHO group 1, pulmonary arterial hypertension, now includes idiopathic pulmonary arterial hypertension, a disease with arterial involvement, and pulmonary veno-occlusive disease (PVOD), a disease with primary venous involvement. Although both diseases have distinct clinical, radiological and histological features, similar molecular pathways are involved in both diseases, hence similar treatments can be effective in both diseases.

**WHO group 1: pulmonary arterial hypertension**

**Epidemic of pulmonary hypertension caused by appetite suppressants**

In 1968, Gurtner\(^{22}\) was the first to report an epidemic of pulmonary hypertension cases in Bern, Switzerland. At the same time, an increased incidence of pulmonary hypertension was reported in Germany and Austria. Since many of these patients had used the appetite suppressing drug aminorex fumarate (Menocil), a causal relationship between the use of aminorex and the development of pulmonary hypertension was accepted.\(^{23}\) Later, fenfluramine increased the incidence of pulmonary hypertension in Europe, while the combination of fenfluramine and phentermine, which was popular in the USA, also caused an increase in pulmonary hypertension cases.\(^{24,25}\) It turned out that the use of these appetite suppressants increased the risk of developing pulmonary hypertension tenfold or more. Direct proof that appetite suppressants cause pulmonary hypertension was never obtained, as aminorex or other anorexigenic drugs failed to induce pulmonary hypertension in animal models.\(^{26}\) The strongest non-epidemiological evidence that appetite suppressants induce pulmonary hypertension is that these drugs act as a substrate for the serotonin

![Figure 1](attachment:image.png)
transporter, mimicking the action of serotonin, which is a known vasoconstrictor and smooth muscle cell mitogen. In response to the epidemic of pulmonary hypertension caused by appetite-suppressant drugs, the first WHO meeting on pulmonary hypertension was organised in 1973; later, in 1981, a National Health Registry was started by the US National Institutes of Health to collect information about the epidemiology, natural course, and histopathologic and clinical characteristics of pulmonary arterial hypertension (PAH). After 6 years of data collection, this registry proved to be very successful and became a valuable resource for systematically evaluating treatment for PAH for the centres involved in the registry. Although the unanticipated side effect of appetite suppressants caused harm to many people, the establishment of the registry in response to appetite suppressant-induced PAH resulted in a great boost to the understanding of the pathogenesis and treatment of many forms of PAH.

One of the major results of global research into the pathogenesis of PAH was the discovery of the bone morphogenetic protein receptor (BMPR)-2. A genetic mutation in this receptor was found in 50% of patients with familial pulmonary arterial hypertension and in 26% of sporadic cases of pulmonary arterial hypertension. The true incidence of defects in the BMPR-2 gene is probably much higher: recently, exonic BMPR-2 deletions and duplications were identified that account for a large proportion of BMPR-2 mutations that have remained undetected until now. Mutations in BMPR-2 result in a genetic predisposition to develop PAH; however, both in familial PAH and in sporadic PAH, a second-hit or several other triggers are required to develop PAH. These triggers include mutations or polymorphisms in other genes that have been identified and linked to PAH, such as the serotonin receptor and transporter, and exogenous factors such as appetite-suppressant drugs.

From understanding pathogenesis to developing treatments for pulmonary arterial hypertension

In pulmonary hypertension, pathologic abnormalities are present in all three layers of the pulmonary arteries, and media hypertrophy due to proliferation of smooth muscle cells is a constant feature of all forms of pulmonary hypertension. Calcium channel blockers have been shown to inhibit the contraction of pulmonary artery smooth muscle cells. Calcium channel blockers reduce right ventricular hypertrophy and improve long-term hemodynamics in PAH, but only in the small subset of patients who also show an acute hemodynamic response. A study found that survival was greatly improved in patients who showed a long-term response to calcium channel blockers; however, in patients that failed on long-term calcium channel blocker therapy, the 5-year survival rate was only 48%. Calcium channel blockers are now only recommended for patients with a positive response during acute vaso-reactivity testing and who show sustained hemodynamic improvement.

A new era in the treatment of PAH began in 1984 when epoprostenol, a natural prostacyclin, was first used with remarkable results in a patient with pulmonary hypertension. Prostacyclin was discovered as a metabolite of prostaglandin with potent anti-platelet aggregatory activity and pulmonary vasodilator activity. Endothelial cells of patients with pulmonary hypertension produce decreased amounts of prostacyclin. Barst et al. showed that patients treated with prostacyclin showed improved exercise capacity, functional status and hemodynamics compared to control patients receiving conventional treatment. In that same study, a significant difference in survival after 12 weeks was found: 8 deaths in the control group, compared to no deaths in the intravenous prostacyclin group. Since then, no long-term randomised controlled trials with intravenous prostacyclin for PAH have been conducted. However, two long-term cohort studies of patients with IPAH receiving intravenous epoprostenol showed considerable benefit compared to historical controls. In one 3-year study of 162 patients with IPAH, survival with epoprostenol was 88% at 1 year, 76% at 2 years and 63% at 3 years compared to the expected survival of 59% at 1 year, 46% at 2 years and 35% at 3 years. In another 5-year study of 178 patients with IPAH, survival with epoprostenol was 85% at 1 year, 70% at 2 years, 63% at 3 years and 55% at 5 years compared to expected survival rates of 58% at 1 year, 43% at 2 years, 33% at 3 years and 28% at 5 years. The down side of this drug is that it requires continuous intravenous administration, rendering it unsuitable for some patients and unavailable in some countries. Other, more stable prostacyclin analogues have been synthesised for different forms of administration, including oral, inhalatory and subcutaneous routes.

Continuing advances in the field of molecular biology has made targeted therapy possible for treating PAH. Giaid et al. demonstrated that the endothelial cells of patients with PAH have increased expression of endothelin-1, a small peptide that is a potent vasoconstrictor and that has mitogenic properties. Bosentan was the first endothelin receptor antagonist that showed positive results, as measured by an improvement in the walking distance during the 6-min walk test and an improvement in the time to clinical worsening in placebo-controlled trials; clinical worsening was defined as death, lung transplantation, hospitalisation for pulmonary hypertension, a lack of clinical improvement or worsening leading to discontinuation of treatment, a need for epoprostenol therapy or atrial septostomy. Sitaxsentan, an endothelin receptor antagonist with more selective properties, showed similar results. Other selective endothelin receptor antagonists are currently under investigation. Long-term survival rates of 96% at 1 year and 89% at 2 years have been reported for bosentan therapy as a first-line therapy, while additional or other therapies are used in case of clinical deterioration.

Sildenafil is a vasodilator that was first used to ameliorate the effects of inhaled nitric oxide withdrawal. Sildenafil blocks the enzyme phosphodiesterase 5, inhibiting the degradation of cyclic guanosine monophosphate (cGMP), a second messenger in the nitric oxide pathway that induces vascular relaxation. Reports of the beneficial effects of sildenafil in patients with pulmonary hypertension led to randomised clinical trials, which showed that treatment resulted in an improvement in exercise capacity, WHO functional class and mean pulmonary artery pressure.
Plexiform lesions

In the histopathological diagnosis of pulmonary hypertension, plexiform lesions were first considered a distinct feature of IPAH and were therefore a focus of investigation into the origin of cell types involved in the pathogenesis of pulmonary hypertension (Fig. 2). Early histopathological descriptions of obstructions in the small pulmonary arteries supplied evidence of the nature of the cells involved in pulmonary hypertension: in 1946, Gilmour and Evans described intimal lesions containing phenotypically altered endothelial cells, and predicted that the lesions were caused by proliferating endothelial cells. Some believed that these plexiform lesions consisted of smooth muscle cells that had transformed into myofibroblasts, but it was later shown that in IPAH, plexiform lesions consisted of monoclonal proliferation of endothelial cells. More recent studies have broadened the view of vascular plasticity, showing that phenotypic modulation of the media participates in vascular remodelling. Plexiform lesions are typically found in the idiopathic form of pulmonary hypertension, but have also been observed in other types of PAH in WHO group 1.

WHO group 2: pulmonary hypertension associated with left heart disease

Before the 1950s, mitral stenosis due to rheumatic fever was a common cause of pulmonary hypertension. However, venous congestion due to any cause may result in the characteristic histopathological features of congestive heart disease: arterialisation of the veins due to increased venous pressure, signs of congestion such as dilated and tortuous capillaries, alveoli filled with proteinaceous fluid and haemosiderin-laden macrophages, oedematous inter-lobular septa and distended lymphatics (Fig. 3). Arterial and venous adventitial fibrosis are considered characteristic and may be striking. Importantly, the pulmonary artery pressure generally rises to a greater extent than the venous pressure, causing arterial changes similar to those observed in pulmonary arterial hypertension. Many of the vascular changes are reversible when the underlying cause is treated. However, pulmonary hypertension after an acute myocardial infarction has a poor prognosis. The treatment of this type of pulmonary hypertension is focused on the underlying left heart disease. Currently, treatment specific for this type of pulmonary hypertension is lacking.

Figure 2  Plexogenic pulmonary arteriopathy featuring a plexiform lesion (upper-left centre) consisting of a number of slit-like vessels lined by cobblestone-like endothelium and surrounded by loose-textured fibrous tissue. The lesion is flanked by distended vessels, the so-called vein-like branches, which are presumed to represent widely distended branches of the feeding axial artery. At the bottom of the photo there is an axial artery showing prominent medial hypertrophy. Some alveolar iron-laden macrophages are in the upper right corner (haematoxylin and eosin stain).

Figure 3  Congestive arteriopathy featuring an axial artery (centre) with prominent medial hypertrophy, marked adventitial fibrosis and some intimal fibrosis. Some of the alveolar septae are engorged and widened. The artery in the upper left quadrant shows multiple lumina in one cross-section, representing an organised and re-canalised thrombus (elastic van Gieson stain). Note the smooth muscle hyperplasia of the bronchiole in this asthmatic patient in the lower right quadrant of the photo.
WHO group 3: pulmonary hypertension associated with lung respiratory diseases and/or hypoxia

An important discovery was the concept of hypoxic pulmonary vasoconstriction, first measured in a cat by Von Euler and Liljestrand\textsuperscript{69} in 1946, and a year later repeated in humans by Motley et al.\textsuperscript{70} in the Cournand–Richards laboratory (Fig. 4).

Hypoxia at high altitude had long been suspected to cause death in cattle. However, it took several years before the adverse effects of chronic hypoxic vasoconstriction on remodelling of the pulmonary arterioles were recognised. In 1956, Peirson and Jensen\textsuperscript{71} concluded that atmospheric hypoxia causes increased resistance in the pulmonary circulation and failure of the right ventricle. In that same year, Canepa et al.\textsuperscript{72} demonstrated that humans living at high altitude have a modest increase in mean pulmonary artery pressure. He attributed the increase in pulmonary artery pressure to a combination of polycythemia, increased blood volume, high cardiac output and abnormal ventilation, rather than hypoxia. In 1960, the pathologists Alexander and Jensen, the cardiologists Grover and Reeves, and the physiologist Will identified the linear relationship between the severity of right ventricular hypertrophy and mean pulmonary artery pressure in cattle at high altitudes.\textsuperscript{73} Furthermore, they found that 100% oxygen reduced the mean pulmonary artery pressure in part, but not completely, indicating that a fixed change in the pulmonary vascular resistance had occurred. Indeed, the cardiologist Penaloza, the pathologist Arias-Stella, and their team at the High Altitude Research Institute in Peru presented a report at the 1962 Aspen Conference that sustained hypoxia in humans could induce anatomic narrowing of the pulmonary arterioles, and that this process was distinct from acute hypoxic vasoconstriction.\textsuperscript{74} Characteristic histological features of hypoxic pulmonary vasculopathy are medial hypertrophy of the small pulmonary arteries, muscularisation of the pulmonary arterioles and, to a lesser extent, the pulmonary veins and venules. In addition, longitudinal bundles of smooth muscle cells in the intima may develop,\textsuperscript{75,76} supporting the concept of vascular remodelling through endothelial transdifferentiation.\textsuperscript{63} An important mechanism in the pathogenesis includes an altered function of potassium-channels in hypoxia, causing decreased apoptosis and increased constriction and proliferation of smooth muscle cells.\textsuperscript{77,78}

In Brenner’s 1957 review, The Lungs in Heart Disease, chronic bronchitis and emphysema were already recognised as distinct causes of pulmonary hypertension.\textsuperscript{5} Today, it is understood that hypoxic pulmonary hypertension may complicate various other diseases such as asthma, bronchiectasis, cystic fibrosis and sleep apnoea syndrome. Although only a small percentage of patients with respiratory diseases develop pulmonary hypertension, this still constitutes a large number of patients.\textsuperscript{79} In chronic obstructive pulmonary disease (COPD), mild pulmonary hypertension develops when alveolar hypoxia is present, and treatment is focussed on supplemental oxygen to relieve hypoxic pulmonary vasoconstriction.\textsuperscript{80,81} In addition to hypoxia-induced vasoconstriction, progressive pulmonary vascular remodelling and loss of the vascular bed can also contribute to increased pulmonary vascular resistance and to advanced pulmonary hypertension in some patients. New treatments are sought for this group of patients.\textsuperscript{82}

WHO group 4: pulmonary hypertension due to chronic thrombotic and/or embolic disease

In 1953, Owen et al.\textsuperscript{83} were the first to suggest that pulmonary hypertension could be caused by recurrent silent pulmonary embolisms. Pulmonary hypertension associated with pulmonary embolism was found in 0.1–0.4% of autopsy cases,\textsuperscript{84} and prospective studies found that pulmonary hypertension occurred in ~4% of patients after a pulmonary embolism.\textsuperscript{85} Virchow’s triad, defined in 1856 and comprising endothelial damage, altered blood flow and altered blood composition, is still considered to underlie most cases of thromboembolic vasculopathy. However, the mechanisms leading to the development of chronic pulmonary hypertension after pulmonary embolism are still not entirely clear. After the first pulmonary endarterectomy, performed at the University of California at San Diego in 1971, Moser and Braunwald noted that the pulmonary vascular bed distal to the thrombotic occlusion was relatively normal, but the non-obstructed vessels showed lesions resembling IPAH.\textsuperscript{86} They suggested that although a pulmonary embolism may be the initiating event, other mechanisms such as shear stress in the non-obstructed areas induced small vessel disease and pulmonary hypertension.

Surgical removal of the thromboembolic obstruction in the pulmonary arteries is the preferred treatment of chronic thromboembolic pulmonary hypertension.\textsuperscript{87} In cases in which pulmonary endarterectomy is not possible, medical therapy, similar to that used to treat PAH might be effective.\textsuperscript{88–95} These are currently under investigation in randomised controlled trials.

Monitoring therapy

The development of treatment options led to questions about how to best monitor treatment efficacy. Because the
pulmonary artery pressure and pulmonary vascular resistance are elevated in pulmonary hypertension, initial studies focussed on measuring hemodynamic changes. Later trials chose the 6-min walk test, a test of submaximal exercise capacity, as a surrogate measure of right ventricular performance. Authors of reviews discussing clinical trial end-points expressed the need for simple and accurate end-points that would better reflect treatment results. In 1987, it was suggested by Johnson and Rubin that newer imaging techniques might play an important role in non-invasively monitoring PAH. Recent technical developments in CT imaging and MRI make it possible to quantify invasively monitoring PAH. Recent technical developments in imaging techniques might play an important role in non-invasively monitoring PAH. Recent technical developments in CT imaging and MRI make it possible to quantify invasively monitoring PAH. Recent technical developments in imaging techniques might play an important role in non-invasively monitoring PAH.

A promising new option for monitoring treatment is measuring plasma brain natriuretic peptide levels. Known as a marker of left heart failure, elevated levels of this peptide were found in patients with PAH and appear to be related to right ventricular function and prognosis.

From the past to the future

In the past 100 years, incredible progress in the diagnosis and management of pulmonary hypertension has been made: we have come from recognising it as a clinical syndrome and identifying its histopathological characteristics to measuring arterial pulmonary pressure and developing several treatment modalities. These advances have improved the outlook of patients diagnosed with pulmonary hypertension over the last several decades. Early diagnosis resulting in early initiation of treatment might further improve patient outcomes. Effective screening tools are still being sought to help detect pulmonary hypertension. This is of increasing importance, as the number of patients who suffer from hypoxic pulmonary hypertension secondary to respiratory diseases like COPD is likely to rise, and because hypoxic and chronic thromboembolic pulmonary hypertension may have been under-diagnosed in the past. Much work is being done to develop clinical trials to evaluate treatment in these patients. As more therapies for pulmonary arterial hypertension are becoming available, identifying those patients who will benefit most from different combinations of therapies is an important task for the future.

Several classes of drugs targeting pulmonary vascular remodelling have shown promising results in experimental models of pulmonary hypertension. For example, blocking the epidermal growth factor receptor results in apoptosis of pulmonary vascular smooth muscle cells and improves the survival of rats with monocrotaline-induced pulmonary hypertension. Similarly, blocking platelet-derived growth factor signalling with imatinib, a tyrosine kinase inhibitor, reversed pulmonary hypertension in monocrotaline-treated rats and in a single case report. Other substances that have been tested in monocrotaline rat models of pulmonary hypertension include rho kinase inhibitors and serotonin transporter inhibitors. These drugs have been developed for other indications, and it is important to establish their long-term efficacy and safety for treatment of pulmonary hypertension in randomised controlled clinical trials.

Finally, the use of gene therapy to induce apoptosis of pulmonary vascular cells and the use of bone marrow-derived endothelial progenitor cells to replace and regenerate damaged endothelium in monocrotaline rat models may lead to novel therapeutic options in patients with pulmonary hypertension.

Statement of interest: The authors declare that there was no conflict of interest regarding the preparation of this manuscript.

References


105. Mukerjee D, St George D, Knight C, et al. Echocardiography and pulmonary function as screening tests for pulmonary...