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Mechanisms of disease

Progress in the understanding and management of pulmonary arterial hypertension

A.M. Chakrabarti¹, J.A. Mitchell², S.J. Wort^{3,*}¹Royal Brompton Hospital, London, UK²National Heart and Lung Institute, Imperial College London, UK³Royal Brompton Hospital and National Heart and Lung Institute, Imperial College London, UK*Email: s.wort@imperial.ac.uk**INTRODUCTION**

In 1981 the “Patient Registry for the Characterization of Primary Pulmonary Hypertension” was set up, supported by the National Heart, Lung and Blood Institute, and recruited 194 patients across 32 clinical centres over 4 years in the United States^{1,2}. The estimated median survival of these incident cases of primary pulmonary hypertension (which approximates to what we would now term idiopathic pulmonary arterial hypertension, IPAH) was 2.8 years, with a 68% survival rate at 1 year, 48% at 3 years and 35% at 5 years¹.

Since 2000 a number of national registries have been set-up across the world to study the developing epidemiology of pulmonary arterial hypertension (PAH)³. The largest of these is the REVEAL (Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management) Registry in the United States⁴. Between 2006 and 2009, 2635 prevalent and incident cases were included in survival analysis across 55 centres. For IPAH, there was a 91% survival rate at 1 year, 74% at 3 years and 65% at 5 years⁴. The Spanish registry also recruited 866 prevalent and incident cases of IPAH between 2007 and 2008 and calculated 1-, 3- and 5-year survival rates of 87%, 75% and 65% respectively⁵. In the French registry, which also analysed prevalent and incident cases, for a sub-population of 190 patients with IPAH, hereditary PAH (HPAH) and anorexigen-associated PAH cases (which all have similar baseline characteristics and outcomes) between 2002 and 2003, a 1-year survival rate of 83% and 3-year of 58% was calculated^{6,7}. In the UK there was a focus on incident cases, and 482 patients with IPAH, HPAH, and anorexigen-associated PAH were included between 2001 and 2009 and had 1-, 3- and 5-year survival rates of 93%, 73% and 61% respectively⁸. Although there is debate about the inclusion of both prevalent and incident cases in these registries (owing to survivor bias), there is broad agreement over current survival rates across these registries.

Measurable progress has been made in the management of pulmonary arterial hypertension over the last 33 years – now, at 5 years, a larger proportion of people are living with the disease, rather than dying from it. In this review article we take a historical approach to reflect on the journey that has brought us to where we are today, focussing on the key milestones in the management of pulmonary arterial hypertension, signposted by the World Health Organisation (WHO) “World Symposia in Pulmonary Hypertension”. It will become apparent that this mirrors the developments and movements in medicine over the last 150 years: from pathology to physiology, from physiology to pharmacology, from pharmacology to cell biology, from cell biology to genetics⁹.

THE FIRST AGE: PATHOLOGY

The discovery of the pulmonary circulation has recently been reviewed in this journal¹⁰. It began with the rejection of Galen’s and Ibn Sina’s (Avicenna’s) longstanding doctrine, that the liver

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produced blood which was infused with air from the lungs and heat from the heart before being evaporated or consumed by the other organs in the body¹⁰. Ibn Al-Nafis (1213-1288) in the Arab world and Michael Servetus (1511-1553) and Realdus Columbus (1516-1559) in the European world postulated a pulmonary circulation as we understand it today¹¹. This laid the foundation for the discovery of the “motion of the heart” and the circulation of blood by William Harvey (1578-1657) and the pulmonary capillaries by Marcello Malpighi (1628-1694).

The first documented clinical case reports of pulmonary hypertension come two centuries later from Germany. In 1865, Klob found narrowing of the finer branches of the pulmonary artery in a patient who had died with progressive ankle oedema, dyspnoea and cyanosis^{12,13}. In 1891, von Romberg wrote about a 24-year-old patient with a similar clinical course in whom, on autopsy, he described “pulmonary vascular sclerosis” in addition to massive right ventricular hypertrophy¹⁴. The first clinical case series of pulmonary hypertension came from Argentina. Ayerza had described a patient with a chronic productive cough, dyspnoea, severe cyanosis and right heart failure in 1901 which he termed ‘cardíaco negro’ (black heart) due to the significant cyanosis¹⁵. His student Arrillaga published a series of 11 cases in 1913 as his doctoral thesis and the disease became known as Ayerza’s disease¹⁶. Many cases were subsequently reported across the world. The aetiology of these lesions remained unclear and although syphilis was postulated, Brenner disproved this after studying the pathology of 100 cases in the United States¹⁷. He interpreted “his pathological findings as morphologic evidence of chronic pulmonary disease, moderate pulmonary atherosclerosis and right ventricular hypertrophy”¹⁸. However, understanding of the relationship between the pulmonary and cardiac pathology could only come with physiological analysis.

THE SECOND AGE: PHYSIOLOGY

In Germany in 1929, Forssmann introduced a catheter into his own right heart under fluoroscopic guidance¹⁹. Although rejected by his peers at the time, right heart catheterisation was taken up and refined in the United States by Courmand^{20,21} and Richards^{22,23} particularly as a means of measuring cardiac output and also pulmonary haemodynamics. The three were jointly awarded the Nobel Prize in Physiology or Medicine in 1956 “for their discoveries concerning heart catheteri[s]ation and pathological changes in the circulatory system”. Dresdale first coined the term ‘primary pulmonary hypertension’ in his paper from 1951 to describe patients with isolated elevated pulmonary artery pressures with an elevated right atrial pressure and decreased cardiac output²⁴. Wood, working in the United Kingdom, investigated pulmonary hypertension extensively using cardiac catheterisation²⁵. He related the physiological analysis to patient symptoms. With this mechanistic analysis, he developed a classification of pulmonary hypertension, including now familiar categories, such as thromboembolic disease, cor pulmonale, congenital cardiac defects, and idiopathic or primary PH. Much work was done detailing the physiological responses of the pulmonary circulation, with the notable discovery of hypoxic vasoconstriction⁹. Drugs started to be used to probe the pulmonary circulation with the demonstration that both tolazoline (an alpha-adrenergic receptor antagonist and pulmonary and systemic vasodilator)²⁶ delivered intravenously and acetylcholine²⁷ delivered to the pulmonary artery could acutely reduce pulmonary artery pressures, but there were still no treatments developed for primary pulmonary hypertension.

However, in the report, the chapter on prognosis and treatment concludes, “once established, primary pulmonary hypertension is almost always fatal... While a number of vasoactive drugs have been found to lower the pulmonary arterial pressure in acute studies, prolonged therapy has been found quite ineffective... No effective therapy is known”²⁸.

THE THIRD AGE: PHARMACOLOGY AND CELL BIOLOGY

The first treatment to successfully extend the survival of patients with pulmonary hypertension was not a drug therapy, but in fact heart-lung transplantation³¹. As understanding of the pharmacology grew, drugs that were already available at the time were used to try to treat the disease.

Attempts were made to reduce the pulmonary artery pressure and pulmonary vascular resistance using drugs that were available. Rich and Brundage found that in a subset of patients high-dose calcium channel blockers (up to 720mg/day of diltiazem or 240mg/day of nifedipine) could achieve

The First World Symposium, Geneva, 1973

The World Health Organisation convened a meeting in Geneva in 1973 to “review the hitherto scattered scientific information and to discuss the [a]etiology and pathogenesis, pathophysiology, morphology, clinical patterns, clinical physiology, and epidemiology of primary pulmonary hypertension”²⁸. This was in response to a 20-fold increase in cases of pulmonary hypertension that was reported in 1968 in Switzerland²⁹. Further study had identified an epidemic across Austria, Germany and Switzerland that had started in 1967, peaked in 1968-9 and disappeared after 1972³⁰. Although it was not possible to prove causation, there was both temporal and geographical association between these cases and the marketing of aminorex, an appetite suppressant that was available in those countries from 1965 and subsequently withdrawn in 1968.

In addition to raising the profile of this orphan disease, the 1st WHO meeting created the definition of PH that we use today with a mean pulmonary artery pressure, as measured by right heart catheterisation, exceeding 25 mm Hg indicating hypertension²⁸. The pulmonary wedge pressure was normal in the primary form. The meeting also classified pulmonary hypertension into primary, that is “pulmonary hypertension of unknown cause”²⁸ and secondary and focussed on the primary form. It also recommended establishing a central register, the fruits of which were described at the beginning of this article.

this in a sustainable manner³². At their one-year follow up they also noted regression of the right ventricular hypertrophy on echocardiography. Further study showed that at 5 years there was a significant benefit on survival as compared to those patients who did not respond to calcium channel blockade – 94% of the responders were alive, compared to 55% of the non-responders³³. Interestingly, they also anticoagulated patients on the basis of non-uniform pulmonary blood flow radiographically. Unfortunately, it was still only a minority of patients that had a vasodilator response and could therefore be treated with calcium channel blockade.

Warfarin was given to 47% of responders and 57% of non-responders and was found to be associated with an improved survival³³. Other, retrospective studies supported the theory that warfarin improved survival and so its use was recommended^{34,35}. (The database of the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) has recently been analysed to assess the question of anticoagulation in PAH³⁶. Although there were limitations in the data in this observational study, particularly with levels of anticoagulation and the percentage of patients in the anticoagulation group not on anticoagulation for the entire observation period, they did note a statistically significant survival advantage in those patients with IPAH on warfarin).

In 1976, Vane’s group isolated an enzyme from arteries that transformed prostaglandin-G₂ or H₂ to an unstable substance “prostaglandin-X” that inhibited platelet aggregation and relax certain blood vessels³⁷. This new metabolite was termed prostaglandin-I₂ or prostacyclin and found to be a potent pulmonary vasodilator in the cat and monkey³⁸. More importantly, with respect to a therapeutic use in pulmonary hypertension, there was less effect on cardiac output and aortic pressure (i.e. the systemic circulation)³⁸. Vane went on to share the Nobel Prize for Physiology or Medicine in 1982 with Bergström and Samuelsson “for their discoveries concerning prostaglandins and related biologically active substances”.

The proof of principle study was undertaken in 1982 on 7 patients with primary pulmonary hypertension³⁹. Intravenous prostacyclin was administered with an incremental dose escalation with measurements of pulmonary artery pressure by right heart catheter as each increase. There was a dose-dependent reduction in the pulmonary vascular resistance with a maintained systolic blood pressure and an increase in cardiac output. The infusion was maintained for 24-48 hours in three patients; in these the reduction in pulmonary vascular resistance was sustained for the duration of the infusion.

In the meantime, many patients were dying whilst awaiting a transplant. In the UK, a continuous infusion of prostacyclin was set up through a subcutaneously tunnelled line using a syringe pump in a young woman who was bed-bound with severe pulmonary hypertension⁴⁰. She responded with a fall in pulmonary vascular resistance, improved oxygenation and a rise in exercise tolerance. The infusion had been running for 13 months at the time of publication in 1984 and she was living independently at home.

Subsequent studies showed that the haemodynamic improvement could be maintained with continuous prostacyclin infusions in a cohort of patients (although there was a need for dose escalation)⁴¹. The first randomised controlled trial in pulmonary hypertension compared continuous intravenous prostacyclin with conventional therapy⁴². They recruited 81 patients with severe primary pulmonary hypertension in New York Heart Association (NYHA) classes III or IV. As well as physiological markers confirming a significant improvement in haemodynamics, functional tests showed a statistically and physiologically significant improvement in six-minute walk test distance. Most impressively, there was a significant difference in survival – all 8 deaths had occurred in the conventional treatment arm. To date, no other randomised controlled trial of any agent in pulmonary hypertension has demonstrated a pure survival benefit. Finally, there was proof of a successful treatment in all patients with primary pulmonary hypertension. The US Food and Drug Administration (FDA) approved its use in 1995.

The Second World Symposium, Evian, 1998

On account of “remarkable progress in the field of pulmonary hypertension.”⁴³ the second WHO meeting was held in Evian in 1998⁴³. In addition to detailing the advances in the understanding of the pathophysiology and therapeutic options, one of the key steps forward from this document were the categorisation of all pulmonary hypertension into 5 groups, based on pathophysiology, clinical presentation and treatments. There was the consequent abolition of the term ‘secondary’ pulmonary hypertension. These 5 groups have provided the framework for all subsequent categorisations at the following WHO meetings. Another important definition for both clinical and experimental use was the modification of the NYHA classification into the WHO functional classification for pulmonary hypertension (Table 1).

However, the use of continuous intravenous epoprostenol was not without complications. In the original study there were frequent minor side effects, but more importantly there were serious complications most often due to the delivery system including line sepsis, thrombotic events, and malfunctions of the drug delivery system resulting in interruptions to the infusion⁴². Furthermore, drug preparation and the need to carry a syringe pump all add to the difficulties of managing a continuous prostacyclin infusion at home. An effective subcutaneous prostacyclin analogue, treprostinil, was successfully developed, which was easier to use, but still necessitated a continuous infusion⁴⁴. Inhaled iloprost (another, longer-acting, prostacyclin analogue) was evaluated as an alternative to continuous intravenous infusions, and although there were sustained improvements in exercise capacity, pulmonary haemodynamics and clinical effectiveness, the nebulised iloprost was given every two to three hours without interruption of bed rest at night^{45,46}. Treatments that were more straightforward to administer, such as oral treatments, were clearly needed.

Due to the availability of pulmonary hypertension lung tissue from patients who had undergone transplant and the advancement in cell biology techniques, there was a significant advance in understanding the vascular biology of the pulmonary artery. In particular the pathways and agents controlling vasoconstriction and vasodilatation were explored and identified, including endothelin-1 (ET-1) and nitric oxide (NO). This understanding still forms the basis for all the treatment options available today.

Table 1. WHO functional class (from Rich, 1998)⁴³.

Functional class	Symptoms
I	Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain or near syncope.
II	Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.
III	Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain or near syncope.
IV	Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

In 2001 the first randomised controlled trial of an oral agent to treat pulmonary hypertension was published⁴⁷. The agent was bosentan, an oral antagonist of both endothelin receptors A and B. The role of endothelin in pulmonary hypertension has recently been reviewed in this journal⁴⁸. It was tested in a group of 32 patients with either primary or scleroderma-associated pulmonary hypertension. The primary outcome of the study was a statistically significant difference in six-minute walk test distance compared with placebo in severe pulmonary arterial hypertension. On the basis of this, the Bosentan Randomised Trial of Endothelin Antagonist Therapy (BREATHE-1) was set up to investigate the effects on exercise capacity in patients in WHO functional class III or IV⁴⁹. The study took place across 27 centres in Europe, North America, Israel and Australia and randomised 213 patients who were followed-up for 16 weeks. The significant improvement in six-minute walk test was reproduced, although there was only a mean difference of 44m between the bosentan and placebo arms. Importantly, however, there was an improvement in WHO functional class in patients taking bosentan. On the basis of these studies, the FDA licensed bosentan for patients in WHO functional classes III and IV in 2001.

At the time of the 2nd WHO meeting, inhaled NO had been noted as a potent and selective pulmonary vasodilator and was being used as a short-term treatment of pulmonary hypertension⁴³. This pathway had yet to be targeted by agents that could be used in an outpatient setting. Sildenafil, a phosphodiesterase type 5 inhibitor, had been noted in a case series of infants to ameliorate the effects of inhaled NO withdrawal, by preventing cyclic guanosine monophosphate (cGMP) degradation⁵⁰. (NO increases intracellular cGMP activity by soluble guanylate cyclase, which results in smooth muscle relaxation.) Furthermore, one study found it to be as effective a pulmonary vasodilator as NO in the acute setting in patients under consideration for heart-lung transplantation in WHO functional classes III and IV⁵¹.

The first published case report of the use of sildenafil in adults to treat pulmonary hypertension was in 2000 and showed a reduction in estimated pulmonary artery pressure on echocardiography in addition to an increase in exercise capacity⁵². There was building evidence that sildenafil would be a useful therapy in pulmonary hypertension, with a small randomised controlled trial of 22 patients in WHO functional class II or III reporting a statistically significant improvement in exercise capacity as assessed by exercise time on a treadmill⁵³. However, at the time of the 3rd WHO meeting in Venice in 2004 the large Sildenafil Use in Pulmonary Arterial Hypertension (SUPER-1) randomized controlled trial was still ongoing.

The Third World Symposium, Venice, 2004

The 3rd WHO meeting in 2004 refined the classification further and primary pulmonary hypertension, as a term, was discarded in favour of idiopathic pulmonary arterial hypertension, as there are number of conditions, such as connective tissue disease, anorexigen use, portal hypertension and HIV infection that were similar to 'primary' pulmonary hypertension⁵⁴. In view of importance of accurate diagnosis, in terms of aetiology of pulmonary hypertension, and the availability of a few treatment options, one of the major steps forward at the 3rd WHO meeting was the development of a 'treatment algorithm' for severe (WHO functional class III and IV) pulmonary hypertension⁵⁵.

The SUPER-1 trial was undertaken across 53 centres internationally, randomising 278 patients from WHO functional classes II, III and IV⁵⁶. At 12 weeks there was significant improvement in six-minute walk test distance compared with placebo that was not dose-dependant. The mean improvement from baseline was 51m in 222 patients who completed 1 year of sildenafil monotherapy. Furthermore all the doses reduced the mean pulmonary artery pressure and improved WHO functional class. The FDA licensed sildenafil for use in all WHO functional classes in 2005.

The Fourth World Symposium, Dana Point, 2008

The 4th WHO meeting took place in Dana Point in 2008⁵⁷. At the time, 20 randomised controlled trials with 9 compounds had been completed, with 6 trials testing combinations of agents; approximately 5000 patients had participated⁵⁸. These studies allowed the creation of an evidence-based treatment algorithm that now encompassed all WHO functional classes of pulmonary arterial hypertension for the first time⁵⁸. A second key area of discussion and advance was the discussion about clinical trial design and the need for collaborative efforts across multiple centres. Particular focus was given to relevant endpoints, in particular 'time to clinical worsening' that had been used in a number of randomised controlled trials with different definitions. A standardised definition was developed⁵⁹.

Over the course of the 5 years between the 3rd and 4th WHO meetings, 6 more agents were developed and approved by the FDA: the prostacyclin analogues treprostinil and iloprost (beraprost was not approved); the endothelin receptor antagonists sitaxentan (withdrawn in 2010 on account of fatal liver failure) and ambrisentan; the phosphodiesterase-5 inhibitors sildenafil and tadalafil.

Since Dana Point in 2008, the FDA has approved two more agents, both in 2013. The first, macitentan, was developed to improve the safety profile of the endothelin receptor antagonists, particularly with regards to liver toxicity, in addition to efficacy. The Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome (SERAPHIN) is the largest single randomised controlled trial in pulmonary arterial hypertension to date with 742 patients enrolled⁶⁰. It found a significant reduction in a composite end-point of time to clinical worsening over a median treatment period of 115 weeks. The study design was a direct response to the suggestions from Dana Point and thus set a new standard for future trials.

The second is riociguat, an oral guanylate cyclase stimulator that acts on the NO pathway. It causes vasodilatation by promoting cGMP activity through guanylate cyclase, rather than simply increasing activity by preventing breakdown with phosphodiesterase 5 inhibitors. In the Pulmonary Arterial Hypertension Soluble Guanylate Cyclase Stimulator Trial 1 (PATENT-1) there was a significant improvement in the primary endpoint of six-minute walk test distance at 12 weeks⁶¹. Interestingly, a similar benefit was also found in the Chronic Thromboembolic Pulmonary Hypertension (CTEPH) Soluble Guanylate Cyclase Stimulator Trial 1 (CHEST-1) randomised controlled trial, which assessed the role of riociguat in patients with CTEPH deemed unsuitable for pulmonary endarterectomy or with residual pulmonary hypertension post pulmonary endarterectomy⁶².

This brings us to the latest WHO meeting which took place in 2013. Table 2 summarises all the current licensed treatments. These all act via one of three pathways: the prostacyclin, endothelin and nitric oxide pathways diagrammed in Figure 1.

The Fifth World Symposium, Nice, 2013

Both of the new agents, macitentan and riociguat, were incorporated into the treatment algorithm at the 5th WHO meeting which took place in Nice in 2013⁶³. In addition to updated clinical classifications (Table 3) and management algorithms across all types of pulmonary hypertension, the meeting highlighted the deepening understanding of the complexity of pulmonary hypertension: including the intertwining of inflammatory, proliferative and disordered metabolic states⁶⁴.

There is currently a recently completed clinical trial, A Study of First-Line Ambrisentan and Tadalafil Combination Therapy in Subjects with Pulmonary Arterial Hypertension (AMBITION) investigating the role for up-front combination oral therapy at treatment initiation⁶⁵. Although yet to be published, the results were presented in the European Respiratory Congress in 2014. Combination therapy with ambrisentan and tadalafil was found to reduce the risk of clinical failure by half, prolonging the time to first clinical failure event (its primary endpoint).

Table 2. Currently licensed treatments in pulmonary arterial hypertension (adapted from Galie et al., 2013)⁶³.

Drug	Key trials	Year of FDA approval
<i>Prostacyclin Pathway</i>		
Epoprostenol	Barst et al. (1996)	1995
Iloprost	AIR	2004
Treprostinil	Simonneau et al. (2002)	2002
<i>Endothelin Pathway</i>		
Bosentan	BREATHE-1	2001
Ambrisentan	ARIES-1	2007
	ARIES-2	
Macitentan	SERAPHIN	2013
<i>Nitric Oxide Pathway</i>		
Sildenafil	SUPER-1	2005
Tadalafil	PHIRST	2009
Riociguat	PATENT-1	2013

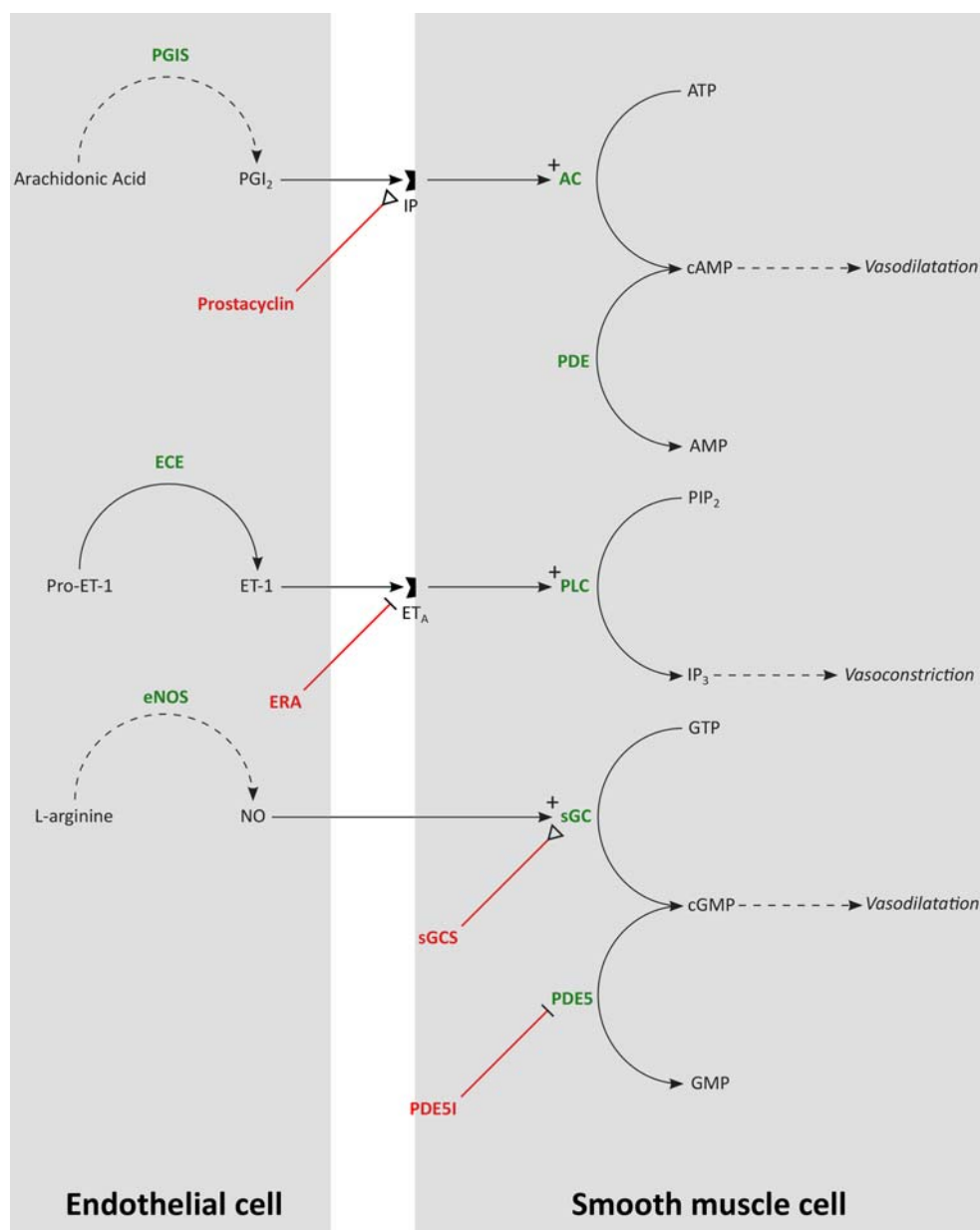


Figure 1. The three key pathways upon which currently licensed treatments for pulmonary arterial hypertension act. The prostacyclin and nitric oxide pathways cause vasodilatation and the endothelin pathway vasoconstriction. Dashed lines indicate omitted steps. Enzymes are coloured green. Therapies are coloured red. Lines ending in a triangle indicate an agonist/potentiator, lines ending in a bar indicate an antagonist/inhibitor. Abbreviations: AC, adenylate cyclase; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate (AMP); cGMP, cyclic guanosine monophosphate (GMP); ECE, endothelin converting enzyme; eNOS, endothelial nitric oxide synthase; ERA, endothelin receptor antagonist; ET-1, endothelin; ET_A, endothelin receptor type A; GTP, guanosine triphosphate; IP, prostaglandin I₂ receptor; IP₃, inositol triphosphate; PDE5I, phosphodiesterase (PDE) type 5 inhibitor; PLC, phospholipase C; NO, nitric oxide; sGCS, soluble guanylate cyclase (sGC) stimulator. Adapted from Montani et al. (2014)⁹².

Of the new agents currently in the drug development pipeline, selexipag is the most advanced. It is a highly selective oral prostacyclin receptor agonist that has the potential to have an improved safety profile compared to the prostacyclin analogues (which also act on gastrointestinal prostaglandin receptors causing a number of side effects). Preliminary studies have shown that it improves haemodynamics⁶⁶ and so the phase III Prostaglandin Receptor Agonist in Pulmonary Arterial Hypertension (GRIPHON) study has completed with preliminary results showing a significant reduction in time to first event although comprehensive analysis is still ongoing^{67,68}.

Table 3. Updated Nice 2013 classification of pulmonary hypertension (from Simonneau et al., 2013)⁹³.

1 Pulmonary arterial hypertension
1.1 Idiopathic PAH
1.2 Heritable PAH
1.2.1 BMPR2
1.2.2 ALK-1, ENG, SMAD9, CAV1, KCNK3
1.2.3 Unknown
1.3 Drug and toxin induced
1.4 Associated PAH
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart diseases
1.4.5 Schistosomiasis
1' Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis
1'' Persistent pulmonary hypertension of the newborn
2 Pulmonary hypertension due to left heart disease
2.1 Left ventricular systolic dysfunction
2.2 Left ventricular diastolic dysfunction
2.3 Valvular disease
2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
3 Pulmonary hypertension due to lung diseases and/or hypoxia
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental lung diseases
4 Chronic thromboembolic pulmonary hypertension
5 Pulmonary hypertension with unclear multifactorial mechanisms
5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental pulmonary hypertension

With our increasing understanding of the vascular biology in pulmonary hypertension, vasoactive targets outside of the three currently targeted pathways are being increasingly studied. The Rho signalling pathway has been shown to have effects on vasoconstriction and cell proliferation. Simvastatin, which is an indirect inhibitor of Rho kinase, was found not to be of prolonged benefit in reducing right ventricular mass when added to targeted therapy in a clinical trial of 42 patients⁶⁹. However, fasudil, a direct Rho-kinase inhibitor, has been shown to improve pulmonary haemodynamics^{70,71}, and is the most promising of the agents targeting novel vasoactive pathways, but further studies are needed to assess its effect on clinical outcomes. Interestingly, the potential effects on cell proliferation highlight the widening reach of putative new therapies beyond simple vasodilatation and the need to focus on vascular remodelling.

THE FOURTH AGE: GENETICS, THE METABOLIC THEORY AND THE FUTURE

It was known since the 1950s that familial cases of pulmonary hypertension existed^{73,74}. In the 1981 registry, 6% of patients reported a family history of pulmonary hypertension². Analysis of pedigrees suggested an autosomal dominant pattern of inheritance⁷². With the advent of genetic sequencing, mapping was undertaken in families to identify the causes of hereditary pulmonary arterial hypertension and help inform pulmonary hypertension pathology as a whole. Mutations in the gene encoding bone morphogenetic protein receptor 2 (BMPR2), a member of the transforming growth factor-beta (TGF- β) family signalling pathway, were identified as causing heritable pulmonary arterial hypertension in 2000 by two independent groups^{73,74}. Over 300 BMPR2 mutations have now been identified, accounting for 75% of patients with heritable pulmonary arterial hypertension⁷⁵. They have also been identified in 25% of patients with idiopathic pulmonary hypertension⁷⁵. As a result of this, the role of BMPR2 signalling has been extensively investigated in pulmonary arterial hypertension⁷⁶. A number of mutations in other genes have also been identified: ALK-1, SMAD9 and ENG also from the TGF- β family and CAV1 and KCNK3 which are not⁷⁵.

However, only 20% of people with BMPR2 mutations go on to develop pulmonary hypertension⁷⁷ suggesting that there are other factors that contribute to the development of disease. There is increasing evidence that inflammation and altered immunity provides a ‘second-hit’⁷⁸. Another ‘hit’ may occur via epigenetic mechanisms, such as DNA methylation, histone modification and the action of microRNAs⁷⁹ which in turn may be influenced by environmental factors, inflammation/infection, hormones or exposure to drugs. The latest “metabolic theory” also proposes a central role for altered mitochondrial metabolism, promoting a switch away from glucose oxidation towards cytosolic glycolysis and fatty acid oxidation (similar to cancer biology) which, in turn, sets a pro-proliferative, apoptosis-resistant phenotype⁸⁰. There is now a race to synthesise a unifying theory to link genetic pre-disposition with inflammation and dysregulated metabolic function. Although out of the scope of this article the reader is directed to the excellent reviews on these subjects produced at the 5th WHO Meeting^{64,75}.

With this advance in our understanding of cell proliferation, genetics, dysregulated metabolism and inflammation in PAH, trials of new treatments targeting these abnormalities are underway, although none have yet been licensed.

Perhaps the most extensively studied are the tyrosine kinase inhibitors, which inhibit platelet derived growth factor (PDGF). PDGF signalling is important in the vascular smooth muscle proliferation associated with PAH. Imatinib is a tyrosine kinase inhibitor that has been licensed for a number of years for the treatment of chronic myeloid leukaemia targeting the bcr-abl tyrosine kinase. It is also an inhibitor of the PDGF pathway. The Imatinib in Pulmonary Arterial Hypertension, a Randomised Efficacy Study (IMPRES) phase III trial found that there was a significant improvement in the primary endpoint of exercise capacity as assessed by the six-minute walk test, but that serious adverse events and discontinuations were common⁸¹. As a result of this its licensing application has been recently withdrawn⁸². A subsequent trial of Nilotinib, another tyrosine kinase inhibitor, has also been stopped early due to a high rate of serious adverse cardiac events⁸³. While the rationale behind the use of tyrosine kinase inhibitors in PAH is sound, porting agents that have been designed for use in chronic myeloid leukaemia to pulmonary hypertension has not delivered tolerable safety profiles in this disease.

Current clinical trials also include agents that are building on our understanding of the genetics to promote BMP signalling, such as tacrolimus⁸⁴ and our understanding of metabolic dysregulation to prevent the shift to glycolysis and promote mitochondrial metabolism, such as dichloroacetate⁸⁵. There are also case reports of using agents to target key inflammatory cytokines in pulmonary hypertension, such as tocilizumab, an anti-IL-6 monoclonal antibody licensed in rheumatoid arthritis^{86–88}.

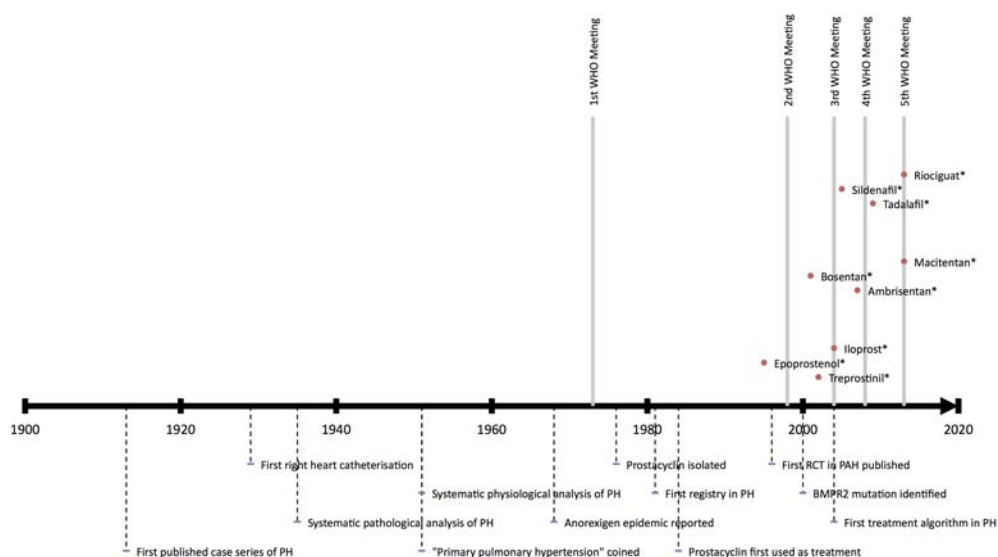


Figure 2. A timeline of key milestones in the history of pulmonary arterial hypertension. * Date of Food and Drug Administration approval. Abbreviations: BMPR2, bone morphogenetic protein receptor type 2; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; RCT, randomised controlled trial; WHO, World Health Organisation.

The Sixth World Symposium, c. 2018

At the 6th WHO meeting, we predict that discussion will expand upon the importance of the effects on inflammation, vascular remodelling, metabolic dysregulation and epigenetics in the aetiology of PAH. To this end, clinical trials of newer agents targeting these pathways will need to innovate to assess more than haemodynamics and ‘time to clinical worsening’ and may include assessment of right ventricular function and cell proliferation using novel imaging modalities, such as nuclear imaging and positron emission tomography⁸⁹. New agents targeting BMP signaling (tacrolimus) and metabolic dysregulation (dichloroacetate) may have reached phase III trials and be eagerly anticipated. While there have been some early studies in gene therapy⁹⁰, this is likely to remain some way off. There is, however, the possibility of small molecules that can act on BMP2 to potentiate its function in a subset of patients with a particular mutation, in a similar way to the mechanism of action of the cystic fibrosis drug ivacaftor in the G551D mutation of the cystic fibrosis transmembrane regulator⁹¹.

CONCLUSION

Our journey, represented as a timeline in Figure 2, has taken us from the first pathological descriptions of PAH, via the physiological measurements of the effects of PAH to the subsequent development of pharmacological agents that can improve pulmonary haemodynamics and survival. More recent understanding of the complex processes that underlie the disease have led us to consider a number of alternative targets for therapeutic agents. Whilst much progress has been made since the first descriptions in the 19th century, there is still much more progress that needs to happen in the 21st century.

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