Pulmonary Arterial Hypertension

Mark W. Dodson, MD, PhD[a], Lynette M. Brown, MD, PhD[a,b], Charles Gregory Elliott, MD[a,b,*]

KEYWORDS

• Pulmonary hypertension • Pulmonary arterial hypertension • BMPR2 • REVEAL Registry
• Phosphodiesterase-5 inhibitors • Endothelin receptor antagonists • Prostacyclin

KEY POINTS

- Pulmonary hypertension was first described as a pathologic entity more than 100 years ago. In recent decades there have been significant advances in understanding of the causes of pulmonary hypertension, which have led to a current diagnostic classification that has important therapeutic implications.
- Pulmonary arterial hypertension (PAH) is classified as group 1 pulmonary hypertension, and is defined by specific hemodynamic criteria (mean pulmonary artery pressure $\geq$25 mm Hg, pulmonary artery occlusion pressure $\leq$15 mm Hg, and pulmonary vascular resistance $\geq$3 Wood units) in the absence of other causes of pulmonary hypertension (including hypoxemic lung disease, obstructive sleep apnea, and chronic thromboembolic disease).
- Some cases of PAH are associated with mutations in transforming growth factor-beta pathway family members, most commonly bone morphogenetic protein receptor type 2.
- In recent years, registry studies have provided important insights into factors that predict survival in patients with PAH.
- Modern treatment of PAH targets the nitric oxide, endothelin, and prostacyclin pathways. Recent data suggest that combination therapy targeting more than 1 of these pathways is beneficial.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare disease, but one that continues to cause significant morbidity and mortality despite much recent therapeutic progress. PAH is one cause of pulmonary hypertension, a broader term used to describe an increased mean pulmonary artery pressure that can occur in several different disease states; for example, because of left heart disease or parenchymal lung disease. Distinguishing PAH from other causes of pulmonary hypertension is crucial, because the modern therapies used to treat PAH are generally not beneficial, and may even be harmful, if used to treat other forms of pulmonary hypertension. This article provides a historical perspective that frames the current understanding of PAH; details the current clinical classification of the various causes of pulmonary hypertension; and then reviews the epidemiology, diagnosis, genetics, prognosis, and modern therapy for PAH.

HISTORICAL PERSPECTIVE ON PULMONARY ARTERIAL HYPERTENSION

The first recognition of what is now termed PAH dates to more than 100 years ago when Romberg[1] first described the autopsy of a patient who

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[a] Department of Medicine, Intermountain Medical Center, 5121 South Cottonwood Street, Building 2, Suite 307, Murray, UT 84107, USA; [b] Pulmonary Division, University of Utah, 24 North 1900 East, Wintrobe Building, Room 701, Salt Lake City, UT 84132, USA
* Corresponding author. Department of Medicine, Intermountain Medical Center, 5121 South Cottonwood Street, Building 2, Suite 307, Murray, UT 84107.
E-mail address: Greg.Elliott_MD@imail.org

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presented with severe right ventricular failure and cyanosis, identifying pulmonary vascular sclerosis unexplained by chronic lung disease or left heart disease. Ten years later, Abel Ayerza at the National University of Buenos Aires described patients with severe cyanosis ("cardiacos negros"), dyspnea, and chest pain.[2] The condition, which was subsequently termed Ayerza disease, was initially thought to be caused by syphilitic endarteritis.[3,4] In 1935, however, Brenner[5] refuted this concept after performing "painstaking descriptions of the pathologic changes in the pulmonary vessels" in patients with Ayerza disease.[2] Brenner[5] laid the foundation for a classification of pulmonary hypertension when he noted that "primary [pulmonary] sclerosis is not a pathologic entity, but several different conditions."[5] Brenner[5] suggested that, to diagnose what he termed primary sclerosis of the pulmonary vessels, "all factors … [that cause] secondary pulmonary vascular sclerosis must be absent" and "there must be marked hypertrophy of the right ventricle."[5]

In the 2 decades following Brenner's[5] observations, pulmonary physiologists provided new insights into the nature of pulmonary hypertension. The successful placement of a ureteral catheter into the right atrium,[6] and subsequent measurements of pulmonary artery pressures in a variety of pathologic states,[7] paved the way for the addition of physiologic observations to pathologic descriptions. In 1951, Dresdale and colleagues[8] authored the seminal description of what they termed primary pulmonary hypertension [PPH] (herein the authors use PPH when referring to a time period before 2004, when this term was abandoned in favor of PAH).[8] Dresdale and colleagues[8] defined the key clinical features as exertional weakness, dyspnea, effort syncope, and angina, combined with careful exclusion of other disorders known to cause severe pulmonary hypertension, such as mitral stenosis. Dresdale and colleagues'[8] hemodynamic and pathologic observations localized the disease to the small muscular pulmonary arteries. Dresdale and colleagues[8] also introduced the concept of vasoconstriction (vasoreactivity) by reporting the effect of tolazoline, a sympatholytic agent, in lowering pulmonary artery pressure in their patients. Subsequent investigations by Harris[9] and Wood[10] showed the variable contribution of vasoconstriction to the pathogenesis of PPH, and led to the introduction of acute vasoreactivity tests and the use of pulmonary vasodilators for the assessment and treatment of PPH.

Epidemiologists soon added insights into the link between drugs/toxins and PPH. In 1967, a sudden increase in the number of patients with pulmonary hypertension seen in cardiology departments in Switzerland, Germany, and Austria was linked to the anorexigen aminorex.[11] The number of new cases of PPH declined when aminorex was withdrawn from the European market. This increase in PPH cases motivated the World Health Organization (WHO) to convene a meeting in 1973 to review the cause, pathogenesis, morphology, physiology, and epidemiology of PPH. Participants at this first international symposium created the first classification system of pulmonary hypertension.

In the 1990s, a second epidemic of PPH followed the introduction of 2 anorexigens, fenfluramine and dexfenfluramine, into the United States and European markets. Investigation of this epidemic underscored the important role of anorexigens in the pathogenesis of PPH,[12] and, together with the demonstration that continuous infusions of epoprostenol (prostacyclin) benefited patients with PPH,[13,14] provided the impetus for the second world symposium on PPH, which was held in Evian, France, in 1998. The leaders of the Evian meeting recognized the limitations imposed by classifying pulmonary hypertension as primary or secondary in an era of rapidly advancing understanding of genetics, pathobiology, and treatment. Participants at the Evian symposium proposed a new classification system and nomenclature for pulmonary hypertension, which replaced primary pulmonary hypertension and secondary pulmonary hypertension with a system based on clinical (not pathologic) diagnoses and therapeutics.[15] The first category was renamed PAH based on a common pathology, pathophysiology, and response to therapy, especially the continuous infusion of epoprostenol. This diagnostic group was subcategorized into cases without identifiable cause, so-called primary pulmonary hypertension, which encompassed both familial and sporadic forms, and a second subgroup that included PAH related to collagen vascular diseases, congenital systemic-to-pulmonary shunts, portal hypertension, human immunodeficiency virus (HIV) infection, and exposure to certain drugs or toxins, especially anorexigens.[15]

The Evian meeting came on the eve of genetic discoveries that provided new insights into the nature of PAH. As early as 1954, Dresdale and colleagues[16] had described a mother, her son, and her sister with an apparently heritable form of PPH. Additional reports of PPH affecting multiple family members followed and established the inheritance pattern of heritable PPH as autosomal dominant with incomplete penetrance.[17] A major breakthrough occurred in 2000 with the discovery that mutations in *bone morphogenetic protein*