Pulmonary Vascular Diseases

The pulmonary circulation has fascinated researchers and clinicians for more than a century. Romberg first described the pathology of human pulmonary arterial hypertension (PAH) in 1891. In 1946, Euler and Liljestrand described the hypoxic pulmonary vasoconstriction: Whereas hypoxia dilates most systemic vascular beds, it constricts the pulmonary arteries. The physiological importance of hypoxic pulmonary vasoconstriction is now recognized as critical in the maintenance of adequate ventilation perfusion matching in all mammals, but the molecular identity of hypoxic pulmonary vasoconstriction remains unknown. The clinical syndrome of PAH was described by Dresdale in 1951, after the introduction of right heart catheterization allowed hemodynamic measurements in humans.

From 1960 to 1980, 3205 articles were published (PubMed key word pulmonary hypertension); from 1980 to 2000, the number jumped to 11 127. From 2000 until now, the number of articles has reached 9294. Despite some progress, the cause and molecular basis of PAH remains unknown. As can be seen by the number of publications, the interest of the research and clinical communities has been rapidly increasing. With the introduction of potential therapies over the past 20 years, the interest of the public, as well as that of the industry, has also been increasing. After the initial enthusiasm for the currently approved PAH therapies (parenteral prostacyclin analogues, oral endothelin-receptor antagonists, and oral phosphodiesterase type 5 inhibitors), it was realized that although these therapies alleviate symptoms in many patients, the oral therapies and possibly others do not have a significant impact on the disease in that they do not appear to reverse or modify the disease and their benefits on survival rates remain unproven.

The lack of direct and selective effects of these therapies on the primary pathology of PAH is perhaps a result of the fact that they were all originally developed for systemic cardiovascular diseases, and only when they did not appear to play a role in the treatment of diseases like heart failure or hypertension were they tested in PAH. As a result, they commonly suffer from lack of specificity to the pulmonary vessels and do not attack PAH-specific molecular mechanisms. Many of the drugs currently in use for PAH were developed in the 1980s and early 1990s, a time dominated by the vasodilator hypothesis in PAH therapeutics. A paradigm shift in the 1990s led to the proliferation hypothesis when it was realized that only a small minority of patients with PAH have active pulmonary vasoconstriction. In most cases, cellular proliferation within the vascular wall is the basis for the obliterator remodeling of the pulmonary vessels. In the new millennium, more evidence suggested that loss of microvessels might be an early event in PAH. In addition, discovery of specific genetic mutations on the bone morphogenetic protein receptor 2 in some patients with sporadic PAH and most patients with familiar PAH underlined the importance of suppressed apoptosis in the vascular wall. These findings are now driving the development of both regenerative approaches and proapoptotic cancer-like therapies in PAH. In fact, there are now several ongoing clinical trials testing novel cell-based regenerative and antiproliferative/proapoptotic therapies.

In the meantime, the field has been very dynamic and many world symposia have reclassified PAH several times, emphasizing its association with common diseases like collagen vascular diseases, congenital heart disease, viral infections, sickle cell disease, or extremely common parasites like *Schistosoma*. Because of the increased awareness, the disease is now usually diagnosed earlier, leading to another paradigm shift: PAH is not seen as a rare disease anymore. When one considers that in many PAH clinics, one of the most common referrals is the management of pulmonary hypertension in patients with increased left-sided filling pressures (for example, left ventricular diastolic dysfunction), one can understand why these clinics, now present in most tertiary care hospitals, are quite busy. Lastly, over the past few years, researchers have come to realize that the function of the right ventricle is critical in both the prognosis and management of PAH patients.

In summary, the PAH field is entering a new era that is characterized by the realizations that

(1) PAH is not a rare disease;
(2) molecular regenerative, antiproliferative, and proapoptotic therapies developed specifically for PAH mechanisms, rather than vasodilator therapies, will have a much better chance of modifying or reversing the disease; (3) the role of common entities like left ventricular diastolic dysfunction or parasitic infections needs to be better defined in PAH; and (4) the right ventricle–pulmonary circulation has to be approached as a unit in both the diagnosis of PAH and the assessment of established and experimental therapies.

Articles in the “Pulmonary Vascular Diseases” series, which will be published in Circulation biweekly, do not aim to summarize the existing knowledge about PAH; many excellent reviews have been published recently on this, including some in Circulation (2004;109:2947–2952, 2006;114:1417–1431, 2008;117:1436–1448). Rather, the objective is to facilitate the transition of researchers and clinicians to the new era in the PAH field. In the first article in the series, Ghofrani et al discuss many uncertainties and controversies that have been developing in the clinical management of PAH, a common phenomenon that characterizes many transition phases in science. In the second article, Michelakis et al will discuss emerging concepts on the molecular pathogenesis of PAH, emphasizing on their translational and immediate clinical applications. Butrous et al will then discuss the potentially most common global causes of PAH, that is, parasitic infections in the developing world, which remain completely ignored by the opinion leaders and laboratories of the developed countries. Rich et al will then discuss the assessment and management of one of the most common causes of severe pulmonary hypertension in the developed world, that is, elevated left-sided filling pressures that, when associated with normal systolic left ventricular function, mimic PAH. Lastly, Champion et al will discuss a proposed comprehensive approach to the right ventricle–pulmonary circulation unit through novel hemodynamic and imaging approaches.

Disclosures

None.

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