Future Perspectives in Pulmonary Arterial Hypertension

Lewis J. Rubin
Division of Pulmonary and Critical Care Medicine, School of Medicine, University of California at San Diego, La Jolla, Calif., USA

Abstract
In a remarkably short interval of time, pulmonary artery hypertension (PAH) has evolved from a disease of unknown pathogenesis devoid of effective therapy to a condition whose cellular and molecular underpinnings are unfolding, and for which three treatment classes have been developed. Nevertheless, PAH remains incurable and is often refractory to medical therapy, underscoring the need for further research. This chapter will highlight some of the anticipated approaches to research in pathogenesis, diagnosis and monitoring, and novel therapies that are anticipated to yield clinical applications in the future.

The remarkable progress achieved in elucidating the pathogenesis of pulmonary arterial hypertension (PAH) over the past two decades has led to the development of disease-targeted therapies for this condition. Despite these achievements, however, the diagnosis is often established late in the course of the disease, the response to therapy is often incomplete in many patients, and survival remains poor. Accordingly, new diagnostic and treatment strategies must be developed for PAH that identify patients with early disease, optimize the treatments currently available, and capitalize on the identification of novel pathogenic pathways. This article will provide a glimpse into the future, based on recent developments in the field that hold promise for enhancing the management of PAH.

Identification of mutations in the bone morphogenetic protein receptor 2 (BMPR2) in the majority of cases of familial PAH was a major advance in the elucidation of the pathogenic sequence in PAH [1, 2]. However, fewer than 20% of individuals with a BMPR2 mutation develop familial PAH, and most individuals with PAH do not have an identifiable mutation [3]; accordingly, it is likely that other factors, including genes and external stimuli (a ‘second hit’), are needed to initiate the sequence that leads to vascular injury and the pulmonary hypertensive state. Both the role of these other factors in initiating the vascular injury and the mechanisms through which they interface with genetic abnormalities are unknown [4].

A variety of cellular abnormalities have been described that may play important roles in the development and progression of PAH [5–9]. These include altered cellular metabolism, impaired synthesis of nitric oxide, prostacyclin and endothelin, impaired potassium channel and growth factor receptor function, altered serotonin transporter regulation, increased oxidant stress, and enhanced matrix production. However, the relative importance of each of these processes is unknown, and the interactions between these various pathways need to be explored. Additionally, the intermediate steps involved in the transduction of signals related to BMPR2 are unknown; clarification of these pathways will lead to a more complete understanding of how impaired BMPR2 signaling, both inherited and acquired, leads to hypertensive pulmonary vascular disease [10–12].

Pulmonary Arterial Hypertension Therapy
Less than a decade ago, therapy for PAH was based on a limited understanding of the disease pathogenesis, largely empiric, and usually ineffective. The treatment of PAH has advanced dramatically since then, with a number well-designed and executed clinical trials demonstrating
sustained efficacy of several therapies that target specific abnormalities present in PAH [13–16]. Furthermore, the complexity of these treatments has devolved from continuous intravenous delivery to oral and inhaled modes of drug delivery. Future studies targeting newly identified alterations in endothelial and smooth muscle cell function may provide novel treatments. Several of the most promising targets are discussed below.

**Serotonin Receptor and Transporter Function**

Serotonin (5-hydroxytryptamine (5-HT)) is a potent vasoconstrictor and smooth muscle mitogen that has long been suspected to play a pathogenic role in PAH [17]. Recent work suggests that the 5-HT2B receptor may be upregulated in PAH, providing a novel therapeutic target since antagonists to this receptor have been developed. Others have shown that the serotonin transporter, a molecule that facilitates transmembrane transport of serotonin into the cell, is upregulated in PAH [9]. Interestingly, the fenfluramine anorexigen, which are known to increase the risk of developing PAH, stimulate an upregulation of the serotonin transporter in vitro, supporting a pathogenic mechanism for this system in PAH. Drugs that downregulate the serotonin transporter, such as selective serotonin reuptake inhibitors, may be worthy of study as treatment options in the future.

**Vasoactive Intestinal Polypeptide**

Vasoactive intestinal polypeptide (VIP) is a substance produced by cells from a variety of organs that exerts cellular antiproliferative effects. VIP is also a neuropeptide with potent vasodilating properties. VIP deficiency has been described in lung tissues from patients with idiopathic PAH (IPAH). In a preliminary case series, 8 patients with IPAH who were treated with inhaled VIP at daily doses of 200 μg in four single inhalations showed marked clinical and hemodynamic improvement [18]. However, a recent double-blinded trial with inhaled VIP was negative. The reasons for these discrepant findings are unclear, and may be due to dosing or delivery systems.

**Rho Kinase Inhibitors**

Rho kinase is part of a family of enzymes that is involved in the processes of cellular growth and, in particular, smooth muscle tone. Studies in animal models of pulmonary hypertension suggest that fasudil, an inhibitor of Rho kinase, may ameliorate the hemodynamic and pathologic severity of pulmonary vascular injury, as well as provide a rationale for clinical development of this agent in PAH [19, 20].

**Inhibitors of Growth Factor Synthesis and Promoters of Apoptosis**

PAH is characterized pathologically by uncontrolled angiogenesis and impaired apoptosis, processes that are reminiscent of malignant transformation. In support of this concept, monoclonal expansion has been demonstrated in the plexiform lesions of IPAH. Additionally, unique cellular metabolic abnormalities that result in resistance to apoptosis have been reported in cells from patients with IPAH [21]. Recently published reports in which imatinib, a tyrosine kinase inhibitor that is approved for the treatment of hematopoietic malignancies, produced improvement in an animal model of pulmonary hypertension [22] and a handful of PAH patients refractory of other available treatments [23] suggests that this novel approach may be of benefit in PAH and warrants further study. Large-scale clinical trials are now underway.

Adrenomedullin is a peptide that causes vasodilation and inhibits proliferation of pulmonary vascular smooth muscle cells [24, 25]. Both intravenous and inhaled adrenomedullin lower pulmonary vascular resistance in patients with IPAH [26, 27]. Long-term data are not available, but the substance has the potential of becoming a promising future treatment for PAH [25].

**Cell-Based Therapy**

Several recent publications have demonstrated that infusions of endothelial progenitor cells in animal models of pulmonary hypertension attenuate the injury, particularly when these cells are transfected with nitric oxide synthase, the enzyme responsible for the generation of nitric oxide from the precursor L-arginine [28]. Thus, while cell-based therapies have yet to fulfill their promise in clinical studies, particularly in cardiovascular diseases, pilot safety and efficacy trials are now underway with progenitor cell infusions in patients with severe PAH refractory to medical therapy [29].

Drugs currently marketed to treat other conditions may have effects that are beneficial in PAH as well. For example, the hydroxymethylglutaryl-coenzyme-A reductase inhibitors (statins) manifest pleiotropic effects that have been suggested to be responsible for a component of their benefit in arteriosclerotic disease [30], and these agents attenuate the pulmonary arteriopathy induced by the administration of monocrotaline to experimental animals [31, 32]. Formal clinical studies with statins may, therefore, be appropriate. Similarly, currently available platelet inhibitors (i.e. aspirin) and newer antithrombotic agents may have a role in the treatment of PAH, in light of the beneficial effects (and inherent risks) of anticoagulation with warfarin in IPAH.
As with other diseases with a complex pathogenesis, targeting a single pathway in PAH is unlikely to be uniformly successful. With the development of several pathway-specific therapies, the opportunity exists for evaluating multidrug therapy in PAH. Uncontrolled small trials have suggested that the addition of bosentan to patients failing oral or inhaled prostanoïd therapy with beraprost or iloprost, respectively, resulted in improved exercise capacity. Similarly, the addition of sildenafil to inhaled iloprost therapy resulted in potentiation of the clinical effects. Recently, randomized clinical trials have demonstrated that the addition of inhaled iloprost to background therapy with bosentan [33], or oral sildenafil to background intravenous epoprostenol therapy, resulted in further improvement in hemodynamics, exercise capacity, and time to clinical worsening [34]. The role of initial combination therapy compared with monotherapy followed by escalation to combination therapy is currently being investigated in a multicenter trial.

Unresolved questions exist regarding combination therapy for PAH include:

- Which combinations are the most potent, i.e. which pathways are the most pivotal targets for treatment, and how many should be targeted?
- What is the optimal timing for combination therapy? Should combination therapy be initiated early in the course of the disease in order to maximize the response, or should it be considered only if monotherapy fails to achieve the desired clinical response?
- What are the appropriate criteria for assessing response to therapy?

**Measuring Outcomes and Monitoring the Course of Therapy**

The development of treatments for PAH has prompted the challenge of how to best assess and monitor the efficacy of long-term therapy. Because it is believed that randomized placebo-controlled trials using survival as an end point would be unethical to perform in PAH, alternative strategies are required to measure and compare the relative effects of the available treatments. Similarly, noninvasive markers of disease severity, i.e. biomarkers, imaging studies, or physiological tests, are needed that can be widely applied to reliably monitor clinical course. Studies that assess the value of these outcome measures, alone or in combination, will enable physicians to time and select therapy in a more structured fashion. Furthermore, more attention needs to be focused on the state of right ventricular function in PAH since this is arguably the single most important determinant of outcome [35]. MRI may be particularly useful in this regard since both structure and function of the right ventricle may be assessed noninvasively and sequentially over the course of treatment [36]. Additionally, MRI may prove useful in noninvasive assessment of the pulmonary vasculature, for example in determination of operability for patients with chronic thromboembolic pulmonary hypertension.

**Conclusions**

Although major advances in our understanding of the mechanism of disease development and in the treatment of PAH have been achieved over the past decade, substantial gaps in our knowledge remain. Bringing together physicians and scientists representing multiple disciplines and expertise, all sharing an interest in PAH, affords the opportunity to develop collaborations that will narrow these gaps of knowledge in the future.

**References**


