Update in Pulmonary Arterial Hypertension 2007

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This article summarizes recent advances in the field of pulmonary arterial hypertension (PAH), a severe condition characterized by a progressive remodeling of small pulmonary arteries leading to elevated pulmonary vascular resistance and right ventricular failure (1, 2). Epidemiology, genetics, pathophysiology, and treatment will be the main focus of this update.

EPIDEMIOLOGY OF PAH: CONTEMPORARY REGISTRIES IN DEVELOPED AND DEVELOPING COUNTRIES

Contemporary Registries in Developed Countries

Until recently, information relating to the epidemiology of PAH has been derived from a single National Institutes of Health (NIH) registry conducted in the United States in the early 1980s, in which 187 patients with idiopathic PAH were described and followed for up to 5 years (3, 4). Prompted by the rapid evolution of knowledge in the field of PAH and the absence of any new multicenter registry since the 1980s, prospective registries were initiated in France (5), Scotland (6), and the United States (7). In the French registry, around half of 674 PAH cases occurred in patients with comorbid conditions (connective tissue diseases, congenital heart diseases, portal hypertension, HIV infection, and exposure to drugs and toxins, such as fenfluramine derivatives) (5). The other half had no identifiable risk factor, corresponding to idiopathic (sporadic) or familial PAH (5). Patients managed in referral centers in France in 2002/2003 were detected late in the course of the disease, with a majority of patients displaying severe functional and hemodynamic compromise: at diagnosis, 12, 63, 24, and 1% of patients were in New York Heart Association (NYHA) functional classes IV, III, II, and I, respectively (5). The lowest estimate of prevalence of PAH in France was 15 cases per million adult inhabitants (5). Of note, there was wide variation in PAH prevalence in the French dataset, with higher prevalence (25 cases per million) in the Paris area, the region with the largest pulmonary vascular center (5). In Scotland, "administrative" hospitalization data as well as "expert" information from the Scottish Pulmonary Vascular Unit were evaluated (6). When analyzing national hospitalization records, a prevalence of 52 PAH cases per million was obtained, but the robustness of PAH diagnosis was questionable (6, 8). Conversely, expert data based on gold-standard diagnostic procedures indicated a prevalence of 26 cases per million (6). These contemporary studies provide an estimate of the minimum (French expert centers) and near-maximum (Scottish hospitalization records) prevalence of PAH, confirming that PAH is a rare but certainly underestimated condition (8).

A United States–based registry from a single large referral center in Chicago established that patients with PAH are referred late to specialized centers in the United States, with 80% in NYHA class III or IV (7). This registry also emphasized that medical management is often inappropriate, with an excessive use of oral calcium channel blockers in patients with PAH showing no acute vasodilator response (7, 9). Finally, it was apparent from this registry that referral of patients with PAH with connective tissue diseases (mainly systemic sclerosis) was increasing, whereas referral of HIV-infected patients remained low (7). This latter feature is markedly different from the French registry (5) and presumably indicates the underappreciation of PAH in HIV-infected patients in the United States. This single tertiary center registry may not reflect national trends in the United States, which might be better analyzed through data provided by the Registry to Evaluate Early and Long-Term Disease Management (REVEAL) registry, a multicenter, observational, industry-sponsored United States–based registry currently enrolling patients.

Screening Programs

PAH is notoriously difficult to diagnose (5). In the early stages of disease, patients are generally asymptomatic. Initial symptoms, including dyspnea, exercise intolerance, and fatigue, are often rather unimpressive, and may lead patients, relatives, and physicians to assume that they are simply "out of shape." Later, symptoms are often attributed to a more common cardiorespiratory disease. As a result, there is commonly a substantial delay of 2 or more years in the diagnosis and initiation of treatment of PAH (5). Thus, early detection of PAH is still inadequate. The implementation of screening programs targeting high-risk patient groups should help in identifying patients earlier. Recent screening programs (based on cardiac echo-Doppler evaluation followed by right-heart catheterization if PAH is suspected) have demonstrated that early diagnosis of PAH is possible in patients with HIV infection (10), systemic sclerosis (11), or sickle cell disease (12, 13). These screening programs have allowed diagnosis of patients with markedly lower mean pulmonary artery pressures and pulmonary vascular resistance, as compared with patients diagnosed with symptomatic PAH (10–13). These screening programs have also demonstrated that left-heart disease is common, emphasizing the importance of a complete evaluation, including right-heart catheterization, to properly distinguish patients with precapillary from those with postcapillary pulmonary hypertension (10–13). For instance, in a prospective multicenter study of 599 patients with systemic sclerosis, PAH was confirmed in 8%, whereas left ventricular diastolic dysfunction was found in 18% (11, 14). In that study, more than 10% of patients with systemic sclerosis with peak velocity of tricuspid regurgitation greater than 2.5 m/second had evidence of diastolic left-heart dysfunction and postcapillary pulmonary hypertension (11).

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Hemodynamics and cardiopulmonary function were evaluated in 43 patients with sickle cell disease, including 26 patients with a mean pulmonary artery pressure of 25 mm Hg or greater (pulmonary hypertension group) (13). Upon catheterization, 54% of the patients with pulmonary hypertension had PAH, whereas 46% had postcapillary pulmonary hypertension (13). Thus, determining the mechanisms of pulmonary hypertension in patients with sickle cell disease requires a complete evaluation, including right-heart catheterization. In sickle cell patients with PAH, mean pulmonary artery pressure was moderately elevated, and the cardiac output was high, in contrast to what is usually found in idiopathic PAH (13). Further investigation is warranted to assess the potential benefits and risks of using PAH-specific therapies in sickle cell disease–related pulmonary hypertension (15).

PAH in Developing Countries: Improving Awareness, Diagnosis, Prevention, and Treatment

Pulmonary hypertension is certainly much more prevalent than reported in developing countries where relatively common diseases, such as schistosomiasis, sickle cell disease, HIV infection, liver cirrhosis, and congenital heart disease, may promote pulmonary vascular disease (2, 16). In addition, hypoxia is a major risk factor for pulmonary hypertension with more than 140 million individuals living above 2,500 m worldwide, including 80 million in Asia and 35 million in South America (17). Improving awareness, diagnosis, prevention, and treatment of pulmonary hypertension in developing countries is currently supported by a World Health Organization program of the Global Alliance Against Chronic Respiratory Diseases (16, 18). Pulmonary hypertension is now being formally studied in developing countries, such as China and Brazil (19, 20).

The Complex Nature of Interactions between the Pulmonary and the Cardiovascular Systems

Pulmonary hypertension is frequently detected in patients with chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis, sarcoidosis, histiocytosis X, neuromuscular or chest wall disorders, and disorders of ventilatory control, including sleep apnea syndromes and obesity hypoventilation syndrome (21). In a majority of cases, pulmonary hypertension is mild to moderate, but sometimes it can be severe with major consequences on the right heart (21–25). In patients with COPD, a mean pulmonary artery pressure exceeding 40 mm Hg may not just be the consequence of chronic lung disease, and is likely to produce symptoms and affect clinical course (22–24). Similarly, patients with idiopathic pulmonary fibrosis may develop pulmonary hypertension, which will, in turn, impact prognosis (25). There is thus a subset of patients with respiratory diseases with "out of proportion" pulmonary hypertension that share some clinical features with idiopathic PAH (21–25). A better description of the mechanisms linking respiratory diseases and out-of-proportion pulmonary hypertension may help in understanding the clinical manifestations and devastating course that afflict some of these patients (25).

Pathologic examination of lung explant specimens from patients with end-stage idiopathic pulmonary fibrosis showed thickening of the arterial and venous wall with severe luminal narrowing in dense fibrotic zones of all patients (26). In architecturally preserved lung zones, occlusion of venules and small pulmonary veins was observed in 65% of the patients, although there were only mild changes in the muscular pulmonary arteries (26). This study points out that, in many patients with idiopathic pulmonary fibrosis, nonfibrotic lung areas demonstrate an occlusive vasculopathy, the significance of which remains undetermined. Similarly, pulmonary hypertension may be a severe life-threatening complication of sarcoidosis (27–29). Understanding the mechanisms of pulmonary hypertension is of major importance, as it may be due to cardiac disease leading to postcapillary pulmonary hypertension (28). In the absence of left-heart disease, different phenotypes can be identified according to the presence or absence of pulmonary fibrosis (29). In nonfibrotic cases, a specific and sometimes steroid-sensitive vasculopathy may contribute to pulmonary hypertension (29). In cases with fibrosis, pulmonary destruction, hypoxemia, and extrinsic pulmonary artery compression may be implicated (29). Similarly, pulmonary hypertension might be related to an intrinsic pulmonary vascular disease in histiocytosis X, in which the pulmonary circulation is involved independent of small airway and lung parenchyma injury (30).

PAH GENETICS AND PATHOBIOLOGY: THE NEED FOR MULTIPLE HITS

Germline *BMPR2* Mutations

The pathogenesis of PAH remains poorly understood (31). Heterozygous mutations of *BMPR2* coding for the bone morphogenetic protein receptor type II (BMPR-II) represent the major genetic predisposing factor for PAH (32). *BMPR2* germline mutations are detected in more than 70% of familial PAH cases tested for *BMPR2* point mutations and large size rearrangements, and are found in 11 to 40% of apparently sporadic idiopathic cases (32). Aldred and colleagues hypothesized that missing mutations in familial PAH may partly be due to mutations located in regions of the *BMPR2* gene not routinely screened by present mutation detection strategies, such as upstream regulatory elements and intronic and 3′-untranslated sequences (33). Because the genomic structure of *BMPR2* spans approximately 190 kb, direct analysis of all intronic and untranslated sequences in subjects with unknown mutations remains impractical. As a first step, the authors analyzed part of the 5′-untranslated region and promoter of the gene (33). DNA upstream of the coding region was analyzed by direct sequencing in 16 families (33). In one family, a mutation predicted to form a cryptic translational start site was identified. This mutant transcript contains a premature stop codon (33). These results further emphasize the importance of the *BMPR2* gene in familial PAH as well as the need to fully characterize the *BMPR2* promoter and noncoding regions in patients with PAH who are negative for mutations within the coding region and intron–exon junctions.

Serotonin

Germline *BMPR2* mutations have a low penetrance (32). Only 20% of *BMPR2* mutation carriers will develop PAH, suggesting that the most important consequence of *BMPR2* mutation is to cause susceptibility to "second hit(s)" corresponding to various endogenous abnormalities of other genes and gene products and/or the presence of exogenous stimuli, such as viral infection or drug exposure (34). A combination of multiple genetic defects and signal transduction abnormalities in pulmonary artery smooth muscle and endothelial cells is thus presumably required for the pathogenesis of PAH (34).

The serotonin pathway has been implicated as a major factor in PAH pathogenesis (35, 36). The pulmonary circulation has been investigated in mice deficient in BMPR-II (*BMPR2*$^{+/-}$ mice) (36). Pulmonary hemodynamics and vascular morphometry of *BMPR2*$^{+/-}$ mice were similar to wild-type littermate controls under normoxic or chronic hypoxic (2 to 3 wk) conditions (36). However, chronic infusion of serotonin caused increased pulmonary artery systolic pressure, right ventricular hypertro-

phy, and pulmonary artery remodeling in *BMPR2*$^{+/-}$ mice compared with wild-type littermates, an effect that was exaggerated under hypoxic conditions (36). *In vitro* and *in vivo* experiments suggested that serotonin inhibits bone morphogenetic protein signaling via Smad proteins and the expression of bone morphogenetic protein–responsive genes (36). These findings provide the first evidence for an interaction between BMPR-II–mediated signaling and the serotonin pathway, perturbation of which may be critical to the pathogenesis of PAH.

Fenfluramines are anorexigens that are potent serotonin uptake inhibitors and may promote elevated serotonin circulating levels (37). More than 20% of patients displaying PAH associated with fenfluramine exposure have germline *BMPR2* mutations (37). Interestingly, *BMPR2* mutants had shorter exposure to fenfluramine derivatives, as compared with patients without mutation (37). This is in agreement with the concept that fenfluramines may act as a trigger/risk factor in genetically predisposed individuals.

Inflammation

Antiapoptotic, proliferative, and inflammatory diatheses converge to create an obstructive pulmonary vasculopathy in PAH (31, 38). There is substantial evidence from the literature that implicates dysregulated inflammation in the development of PAH (38). Severe PAH may occur in some patients displaying systemic inflammatory conditions; treatment with corticosteroids and/or immunosuppressants sometimes dramatically improves PAH complicating a range of systemic inflammatory diseases (2, 39). Autoimmunity and inflammation also contribute to idiopathic PAH pathogenesis (31, 40). Lung pathology of patients displaying severe PAH in the context of connective tissue diseases indicates that inflammation and remodeling are key contributors to pulmonary vascular disease complicating inflammatory diseases (41). Moreover, idiopathic PAH frequently reveals inflammatory infiltrates (macrophages, lymphocytes, and dendritic cells) in the range of plexiform lesions with local expression of chemokines CCL2 (MCP-1 [monocyte chemoattractant protein-1]), CCL5 (RANTES [regulated upon activation, normal T-cell expressed and secreted]), and CX3CL1 (fractalkine) seen (42–45).

Rat models of PAH have shown that a complete, intact immune system is critical to protect against pulmonary angioproliferation after a single subcutaneous injection of VEGF (vascular endothelial growth factor) receptor blocker to induce pulmonary vascular endothelial cell apoptosis (46). In contrast to euthymic rats that develop severe PAH only in combination with chronic hypoxia, athymic nude rats developed severe PAH and vascular remodeling in normoxic conditions (46). Recent studies have shown that CX3CL1 (44) and CCL2 (45) produced within the small pulmonary arteries may contribute not only to inflammatory cell recruitment but also to pulmonary artery smooth muscle cell proliferation in PAH. In addition, a complete negative feedback loop between IL-6 and bone morphogenic proteins has been shown both *in vitro* and *in vivo*, suggesting that an important consequence of *BMPR2* mutations may be poor regulation of cytokines and thus vulnerability to an inflammatory second hit (47).

PAH is characterized by increased levels of pulmonary and serum osteoprotegerin, an important regulatory molecule in vascular biology modulated by bone morphogenetic proteins, serotonin, and IL-1 (48). Recombinant osteoprotegerin stimulated proliferation and migration of pulmonary artery smooth muscle cells *in vitro*, and *BMPR2* RNA interference increased osteoprotegerin secretion (48). In addition, serotonin and IL-1 increased osteoprotegerin secretion (48). Thus, osteoprotegerin is increased in PAH and may regulate pulmonary artery smooth muscle cell proliferation and migration. In addition, activation of the transcription factor NFAT (nuclear factor of activated T cells) has been demonstrated in circulating leukocytes and in pulmonary artery wall T lymphocytes from patients with PAH versus control subjects (49). The generalized activation of NFAT in human and experimental PAH might regulate the ionic, mitochondrial, and inflammatory remodeling and be a therapeutic target and biomarker (49).

Deletion of the vasoactive intestinal peptide (VIP) gene leads to spontaneous expression of moderately severe PAH in mice under normoxic conditions (50). Male VIP knockout (VIP$^{-/-}$) mice showed moderate right ventricle hypertension and hypertrophy, as well as enlarged, thickened pulmonary artery and smaller branches with increased muscularization and narrowed lumen (50). Lung pathology demonstrated perivascular inflammatory cell infiltrates (50). To explore the underlying molecular mechanisms in this model, it was examined whether absence of the VIP gene might alter the pulmonary expression of additional genes involved in the pathogenesis of PAH (51). Whole-genome microarray analysis of lungs from VIP$^{-/-}$ mice showed a wide range of significant gene expression alterations, including overexpression of genes that promote pulmonary vascular smooth muscle cell proliferation, underexpression of antiproliferative genes, and up-regulation of proinflammatory genes (51).

PAH TREATMENT AND SURVIVAL: THE VALUE OF APPROVED THERAPIES

ACCP Guidelines

No current treatments of PAH achieve a cure for this devastating condition (52). However, in less than 20 years, PAH treatment has evolved from a state of "no hope" to one in which prolonged survival and improvements in quality of life can be achieved. Current PAH treatments target the prostacyclin, NO, and endothelin-1 pathways (52). A consensus panel convened by the American College of Chest Physicians (ACCP) developed guidelines for the diagnosis and treatment of PAH that were published in 2004 (53). Updated ACCP evidence-based guidelines for clinical practice were published in 2007 (54). One of the major conclusions of these guidelines is that referral of patients with PAH to specialized centers continues to be strongly recommended due to the complexity of the diagnostic evaluation required and the treatment options available (54).

Prostacyclin

Intravenous prostacyclin is a recommended first-line therapy for unstable patients in NYHA functional class IV (52–54). How prostacyclin improves cardiac output in right-heart failure in conjunction with pulmonary hypertension has been evaluated in a dog model of acute afterload-induced right ventricular failure (55). In this model, prostacyclin improved right ventriculoarterial coupling and increased cardiac output by decreasing pulmonary arterial resistance, because of vasodilating effects, without a detectable effect on contractility (55). It is likely that clinical right ventricular failure in human PAH might be due to aggravated right ventriculoarterial decoupling, and eventually a decrease in right ventricle contractility. These observations provide a rationale for inotropic interventions added to prostacyclin therapy in patients with PAH who present with right ventricular decompensation (55).

Soluble Guanylate Cyclase Stimulators and Activators

Two novel drug classes that modulate the soluble guanylate cyclase (sGC)–cGMP signal transduction in an NO-independent manner have been recently developed (56). sGC stimulators can enhance the sensitivity of reduced sGC to low levels of

NO, whereas sGC activators can increase sGC enzyme activity even when the enzyme is oxidized and unresponsive to NO (56). Systemic administration of agonists of sGC may be associated with systemic hypotension (56, 57). In contrast, targeted drug delivery to the lungs via inhalation can result in rapid onset of action, high local bioavailability, and low metabolism, potentially avoiding or reducing systemic side effects (57). Inhalation of microparticles of sGC stimulators and activators in lambs with acute pulmonary hypertension produced dose-dependent pulmonary vasodilatation and increased transpulmonary cGMP release without significant effects on mean arterial pressure (57). Thus inhalation of microparticles containing agonists of sGC may provide an effective and novel treatment for patients with pulmonary hypertension, particularly when responsiveness to inhaled NO is impaired by oxidation of sGC (57).

Safety of Dual Endothelin Receptor Antagonist

After the approval of the dual endothelin receptor antagonist bosentan for the treatment of PAH, European authorities required a postmarketing surveillance system to obtain further data on its safety profile. A prospective, Internet-based postmarketing surveillance system was designed, which solicited reports on elevated aminotransferases, medical reasons for bosentan discontinuation, and other serious adverse events requiring hospitalization (58). Within 30 months, 4,994 patients were included, representing 79% of patients receiving bosentan in Europe. In total, 4,623 patients were naive to treatment; of these, 352 had elevated aminotransferases, corresponding to a crude incidence of 7.6% and an annual rate of 10.1% (58). Bosentan was discontinued due to elevated aminotransferases in 150 (3.2%) bosentan-naive patients (58). These real-life data complement those from randomized controlled clinical trials.

Tyrosine Kinase Inhibitors

Platelet-derived growth factor (PDGF) has the ability to induce the proliferation and migration of smooth muscle cells and fibroblasts, and PDGF and its receptors are overexpressed in human and experimental PAH (59). Novel therapeutic agents, such as imatinib mesylate, inhibit several tyrosine kinases, including PDGF receptors α and β (59). Imatinib has been demonstrated to reverse pulmonary vascular remodeling in animal models of pulmonary hypertension (59). Four cases of clinical and hemodynamic improvements have also been reported in human PAH (60–62). Concerns have arisen about the cardiac safety of tyrosine kinase inhibitors, especially in patients with preexisting cardiac conditions (63, 64). Safety and efficacy of tyrosine kinase inhibitors are currently being evaluated in multicenter randomized trials.

Survival

The prognosis of untreated patients with PAH across all functional classes is generally poor, with a mean survival from diagnosis of less than 3 years (4). Contemporary registries indicate that survival rates have increased but remain low, emphasizing the fact that PAH is still a progressive, fatal disease (5, 7). The situation is even more dramatic in the developing world. The Beijing registry, for example, indicates that survival at the beginning of the 21st century was similar to that observed in the 1980s in the NIH registry, before the era of novel PAH therapies (19). The lack of effective treatment was presumably a major cause of poor survival in this registry (19).

The first meta-analysis of PAH trials has analyzed randomized trials of prostacyclin and analogs, endothelin receptor antagonists, and phosphodiesterase type 5 inhibitors (65). Sixteen trials involving 1,962 patients met the inclusion criteria. Up to 80% of the patients were in NYHA functional class III/IV, with a median walking distance of 330 m at baseline. Overall, the pharmacologic interventions were associated with a nonsignificant reduction in all-cause mortality (relative risk, 0.70; 95% confidence interval [CI], 0.41–1.22), a significant improvement in exercise capacity of 42.8 m (95% CI, 27.8–57.8), and an improved dyspnea status by at least one NYHA functional class (relative risk, 1.83; 95% CI, 1.26–2.66) (65). Changes in exercise capacity were not found to be predictive of survival benefit. The authors of the meta-analysis suggest that a longer follow-up period is the prerequisite for evaluating the relationship, if any, between surrogate (such as six-minute-walk distance) and hard (such as survival) endpoints (65, 66). Although PAH is a rare disease, these authors recommended additional efforts to plan and conduct large, clinically oriented clinical trials (65, 66).

Combination Therapy

Combination therapy using drugs with different mechanisms of action to maximize clinical benefit is an emerging therapeutic option in PAH (52, 54, 67, 68). Long-term, adequately powered, prospective, randomized, double-blind, placebo-controlled studies are needed to conclusively determine the effect of combination therapy in PAH. Results of several combination therapy trials should be available in the next months.

This brief summary has attempted to show that the field of PAH has experienced a tremendous increase in clinical and basic science knowledge in the past year. More developments are expected in the near future and will greatly benefit from the conclusions of the next World Symposium on Pulmonary Hypertension. After Geneva (Switzerland) in 1973, Evian (France) in 1998, and Venice (Italy) in 2003, the Fourth World Symposium on Pulmonary Hypertension will be held in Dana Point, California, in 2008 (http://www.4thworldphsymposium.com/).

Conflict of Interest Statement: M.H. has relationships with drug companies including Actelion, Bayer Schering, GlaxoSmithKline, Novartis, Pfizer, and United Therapeutics; in addition to being an investigator in trials involving these companies, his relationships include consultancy services and membership of scientific advisory boards.

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