Pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) are characterized by chronically elevated pulmonary vascular resistance due to distinct pathomechanisms, leading to right heart failure, progressive disability, and death if left untreated (1, 2). Clinical aspects and management of these conditions will be the main focus of this summary.

THE MANY FACES OF PULMONARY ARTERIAL HYPERTENSION

PAH is a disease of the small pulmonary arteries, characterized by intense remodeling resulting in a progressive increase in pulmonary vascular resistance (2). PAH is a condition that can occur in an idiopathic form or in association with other disease states or exposures and is believed to result from environmental or disease-inciting factors coupled with genetically determined susceptibilities (1, 2). By definition, patients with PAH do not have significant left heart disease, lung disease, or chronic thromboembolic disease (1, 2). A diagnosis of PAH requires invasive hemodynamic criteria, including a mean pulmonary artery pressure greater than 25 mm Hg at rest and a normal pulmonary capillary wedge or left ventricular end-diastolic pressure less than 15 mm Hg (2). Multiple risk factors and associated conditions that trigger and/or worsen the progression of the disease have been recognized (1, 2).

Idiopathic, Familial, and Anorexigen-associated PAH

A diagnosis of idiopathic PAH is made when no known risk factor or familial history of PAH is identified (1, 2). When PAH occurs in a familial context, germline mutations in a type II transforming growth factor (TGF)-occurs in a familial context, germline mutations in a type II factor or familial history of PAH is identified (1, 2). When PAH

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Since the 1960s, anorexigen-associated PAH has been a difficult and recurrent problem in pulmonary vascular medicine (6, 17, 22, 23). In the late 1960s, an increased incidence of severe PAH was described in Austria, Germany, and Switzerland among patients who had a history of intake of the anorexigen aminorex fumarate (22). In the early 1980s, the first descriptions demonstrated a strong association between PAH and the use of anorexigen derivatives, endothelin receptor antagonists, and phosphodiesterase type-5 inhibitors (2, 16). Prompted by the rapid evolution of knowledge in the field of PAH and the absence of a large multicenter registry since the 1980s, several epidemiological studies have been initiated with the goal to describe the disease characteristics, risk factors, and outcomes in the era of modern management (17–21).

Idiopathic PAH is the leading cause of PAH in pulmonary vascular centers, representing 39.2% of patients in the French registry (17). Anorexigen-associated PAH represents 9.5% of the population and 3.9% are familial cases (17). Thus, half of the cases correspond to idiopathic, familial, and anorexigen-associated PAH, whereas the remaining patients suffer from PAH associated with other diseases (17). As in previous studies, idiopathic PAH is seen more commonly in women, with a ratio to men of 1:6.1; the mean age at diagnosis is 52 years, older than previously (15, 17), and 80% of patients presented with New York Heart Association (NYHA) functional class III or IV at diagnosis, a situation that has not improved since the 1980s (15, 17). Interestingly, familial PAH has a similar female predominance with a ratio of women to men of 2:2:1, whereas familial cases occur earlier than idiopathic PAH (mean age at diagnosis was 37 years) (17). Nearly 70% of familial PAH cases present with NYHA functional class III or IV at diagnosis (17). Anorexigen-associated PAH mostly occurs in females with a ratio of women to men of 14.9:1, a mean age of 57 years, and in NYHA functional class III or IV in 81% of cases (17).

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Since the 1950s, a large number of familial PAH cases have been described (3, 24, 25). Genealogies provided the first characteristics of familial PAH that segregates as an autosomal dominant trait with a penetrance of 10 to 20% (24, 25). Recognition of a genetic basis enabled identification of BMPR2 conducted in the U.S. in the early 1980s (14, 15). Significant medical advances have occurred in the last 20 years that include a more systematic assessment of patients with objective parameters (such as the 6-minute walk test and acute vasodilator challenge) and availability of new treatments (such as prostacyclin derivatives, endothelin receptor antagonists, and phosphodiesterase type-5 inhibitors) (2, 16).Prompted by the rapid evolution of knowledge in the field of PAH and the absence of a large multicenter registry since the 1980s, several epidemiological studies have been initiated with the goal to describe the disease characteristics, risk factors, and outcomes in the era of modern management (17–21).

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mutations in familial as well as in apparently sporadic idiopathic PAH cases and anorexigen-associated PAH (3, 6, 26–29). Compared with noncarriers, BMPR2 mutation carriers present with a more severe hemodynamic compromise at diagnosis and come to medical attention approximately 10 years earlier, with fatal events occurring at an earlier age (3). In addition, BMPR2 mutation carriers are less likely to respond to acute vasodilator testing (3, 30). A better understanding of the mechanisms by which BMPR2 mutations define a subclass of patients with more severe disease would be critical for improving our knowledge of PAH.

The low penetrance of PAH in BMPR2 mutation carriers points to the potential requirement of additional factors, either environmental or genetic, in the pathogenesis of the disease. Additional modifier genes or proteins might be necessary for a full expression of the disease (31). Proteomics of transformed lymphocytes from a family with familial PAH showed a series of novel proteins with altered expression that could distinguish affected patients with PAH from obligate carriers. These differences provide new information highlighting proteins that may be involved in the mechanisms that differentiate those individuals with a BMPR2 mutation who develop PAH from those who do not (31). Environmental agents may trigger the occurrence of PAH in predisposed individuals. In patients with fenfluramine-associated PAH, the duration of exposure to fenfluramine derivatives in BMPR2 mutation carriers was significantly shorter than in noncarriers (6). This is in agreement with the “multiple hit” concept, with fenfluramine exposure being a trigger in genetically predisposed individuals (6).

Another genetic disorder that at times leads to PAH is hereditary hemorrhagic telangiectasia, an autosomal dominant vascular dysplasia that can involve ALK-1 mutations (a gene encoding a type I TGF-β receptor) (32). The relevance of the TGF-β superfamily in the etiology of PAH is further emphasized by a report of an endoglin germline mutation in a patient who had hereditary hemorrhagic telangiectasia and anorexigen-associated PAH (33). These observations support the hypothesis that mutations in the TGF-β superfamily may be a genetic background favoring the occurrence of pulmonary vascular remodeling.

Connective Tissue Disease–associated PAH

PAH may complicate the course of connective tissue diseases, such as systemic sclerosis (7, 8, 34), systemic lupus erythematosus (8, 35), mixed connective tissue disease (8, 35), dermatomyositis/polymyositis (8), rheumatoid arthritis (8), or primary Sjögren’s syndrome (8, 36). In the French registry, 15.3% of patients had a connective tissue disease, with systemic sclerosis and systemic lupus erythematosus representing 76 and 15% of these cases, respectively (17). Two-thirds of the systemic sclerosis cases were limited forms (17). Systemic sclerosis-associated PAH has a poor outcome and represents a leading cause of death in this patient population (7, 8, 34). Similarly, PAH complicating other connective tissue diseases has historically had a poor prognosis (8). A recent study investigated the survival and characteristics of all patients diagnosed with connective tissue–disease associated PAH in a UK pulmonary hypertension service between 2001 and 2006 (8). Survival in systemic sclerosis-associated PAH in the modern treatment era is better than in the historical series with a 1- and 3-year survival of 78 and 47% in patients without significant pulmonary fibrosis (8). In contrast, survival was much worse in the subset of patients with systemic sclerosis, interstitial lung disease, and pulmonary hypertension, with a 3-year survival rate of 28%, highlighting the dismal prognosis of this group of patients (8). Survival rates were better in patients with PAH and systemic lupus erythematosus, mixed connective tissue disease, or dermatomyositis/polymyositis (8). Interestingly, another retrospective study has shown that PAH associated with systemic lupus erythematosus or mixed connective tissue disease may be responsive to treatment combining cyclophosphamide and glucocorticosteroids (35). Patients that could benefit from such immunosuppressive therapy should be carefully selected and appear to be those who are less severe at baseline (35).

In primary Sjögren’s syndrome, PAH is very rare insofar as fewer than 50 cases have been reported to date (36). A recent article reported nine novel PAH cases with a complete assessment, including clinical characteristics, hemodynamics, medical management, and outcomes. When compared with patients without PAH with primary Sjögren’s syndrome, patients with PAH had a significantly more frequent occurrence of Raynaud’s phenomenon, cutaneous vasculitis, and interstitial lung disease (36). They also had a more frequent occurrence of antinuclear, anti-Ro/Sjögren’s syndrome antibodies (SSA), and antinuclear factor and hypergammaglobulinemia (36). These data suggest that systemic vasculopathy, B-cell activation, and autoimmunity could play a role in the pathophysiology of primary Sjögren’s syndrome–associated PAH (36).

HIV-associated PAH

HIV-associated PAH corresponded to 6.2% of the French PAH registry (17). In addition, HIV infection was the most common condition in the 29 patients displaying two coexisting conditions known to be associated with PAH (HIV infection and portal hypertension were the most common coexisting conditions in this registry) (17). Initial studies performed in the early 1990s indicated a prevalence of 0.50% (confidence interval [CI], 0.10–0.90%) when HIV therapy combined with highly active antiretroviral treatment was not yet available (37, 38). A contemporary prospective study conducted in 7,648 consecutive HIV-positive adults concluded that the prevalence of HIV-associated PAH has not changed (0.46%, 95% CI, 0.32–0.64%) (39). However, there is now evidence that the incidence of HIV-related PAH is declining, with a stable prevalence reflecting longer survival (40, 41). Cases of hemodynamic normalization have been described in patients with HIV-associated PAH receiving antiretroviral drugs and PAH therapy, emphasizing that this condition might sometimes be reversible (41). The mechanism by which HIV infection leads to full-blown PAH in a subset of patients is unknown and it is likely that the underlying mechanisms of HIV-associated PAH are related to the indirect action of infection, possibly through the action of inflammatory mediators, growth factors, and/or pleiotropic viral proteins (42).

Portopulmonary Hypertension

Portopulmonary hypertension represented 10.4% of the patients from the French registry (17). Portopulmonary hypertension affects 1 to 6% of patients with advanced liver disease, but the predictors and biologic mechanism for the development of this complication are unknown (1, 43). A multicenter case-control study nested within a prospective cohort of patients with portal hypertension and recruited from tertiary care centers has indicated that female sex and autoimmune hepatitis were associated with an increased risk of portopulmonary hypertension, whereas hepatitis C infection was associated with a decreased risk in patients with advanced liver disease (43). The severity of liver disease was not related to the risk of portopulmonary hypertension (43). Hormonal and immunologic factors may therefore be integral to the development of
portopulmonary hypertension. In a retrospective study of 154 patients displaying portopulmonary hypertension, the prognosis appeared to be mainly related to the presence and severity of cirrhosis and to cardiac function (9).

**PAH and Schistosomiasis**

Schistosomiasis is the third leading endemic parasitic disease in the world with more than 200 million individuals infected and another 600 million at risk of infection in developing countries (regions in South America, Asia, and Africa) (44, 45). Most of the cardiopulmonary manifestations of schistosomiasis appear to be related to the hepato-splenic form of the disease, which is characterized by presinusoidal obstruction by embolized worm eggs, producing portal hypertension and portosystemic shunts (45). As many as 4 to 8% of patients with chronic schistosomiasis develop hepato-splenic disease. Nevertheless, the incidence and type of pulmonary hypertension in this subpopulation is currently unclear (45). Systematic screening of patients with hepato-splenic schistosomiasis has been recently performed in Sao Paulo, Brazil (45). When echocardiographic evaluation was compatible with a diagnosis of pulmonary hypertension, right-heart catheterization was performed to confirm and characterize the disease. Interestingly, 18.5% of patients had elevated systolic pulmonary artery pressure estimates (45). Invasive hemodynamics confirmed the presence of pulmonary hypertension in 7.7% (95% CI, 3.3–16.7%) of patients, resulting in a prevalence of PAH of 4.6% (95% CI, 1.5–16.7%), whereas the remaining patients displayed postcapillary pulmonary hypertension (45). This study reinforces the role of echocardiography as a screening tool in the investigation of pulmonary hypertension together with invasive monitoring for the confirmation of a proper diagnosis. Hepato-splenic schistosomiasis may account for one of the most prevalent forms of PAH worldwide, justifying the development of further studies to evaluate the natural history and the effect of therapy in this subgroup of patients (45).

**PAH and Sickle Cell Disease**

The acute chest syndrome and pulmonary hypertension are two major pulmonary manifestations of sickle cell disease (46–50). Three major causes of the acute chest syndrome have been proposed: pulmonary infection, embolization of bone marrow fat, and intravascular pulmonary sequestration of sickled erythrocytes, resulting in lung injury and infarction (46). A prospective evaluation of 70 consecutive adults displaying severe acute chest syndromes indicated that pulmonary pressures increase during the severe acute chest syndrome, and that pulmonary hypertension is associated with cardiac biomarker elevation and a higher risk of death (47). These data suggest that acute pulmonary hypertension and right-heart dysfunction are major coexisting conditions in the acute chest syndrome (46, 47).

Three prospective screening studies using echocardiography have shown that 20% of adults with sickle cell disease have mildly to moderately elevated pulmonary artery pressure (46, 48). Despite pulmonary artery systolic pressures that are much lower than those in idiopathic PAH, in sickle cell disease mild pulmonary hypertension is associated with an increased risk of death (46, 48). It remains to be determined if elevations in pulmonary pressures are a marker of vasculopathy and a risk factor for cardiovascular death or whether the elevations contribute directly to death due to right-heart failure (46). Hemodynamics and cardiopulmonary function have been 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) (49). Upon catheterization, 54% of the patients with pulmonary hypertension had PAH, whereas 46% had postcapillary pulmonary hypertension (49). Thus, evaluating the mechanisms of pulmonary hypertension in patients with sickle cell disease requires a complete evaluation including right-heart catheterization (1, 49). In sickle cell patients with PAH, mean pulmonary artery pressure was moderately elevated and the cardiac output was high, contrasting to what is usually found in idiopathic PAH (49). Further investigation is warranted to assess the potential benefits and risks of using PAH-specific therapies in sickle cell disease-related pulmonary hypertension (50).

**Pulmonary Veno-occlusive Disease**

Pulmonary veno-occlusive disease (PVOD) is defined by specific pathologic changes of the pulmonary veins (51, 52). A definite diagnosis of PVOD thus requires a lung biopsy or pathologic examination of pulmonary explants or postmortem lung samples. However, lung biopsy is hazardous in patients with severe pulmonary hypertension, and there is a need for noninvasive diagnostic tools in this patient population (51, 52). Patients with PVOD may be refractory to PAH-therapy and may even deteriorate with it (51, 52). PVOD has been described as idiopathic or complicating other conditions including connective tissue diseases, HIV infection, bone marrow transplantation, sarcoidosis, and pulmonary Langerhans’ cell granulomatosis (52). PVOD shares a broadly similar clinical presentation, genetic background, and hemodynamic characteristics with PAH (51). However, compared with PAH, PVOD is characterized by a higher male/female ratio, higher tobacco exposure, lower PaO2 at rest, and DLCO and oxygen saturation that nadir during the 6-minute walk test (51). High resolution computed tomography of the chest can be suggestive of PVOD in the presence of centrilobular ground-glass opacities, septal lines, and lymph node enlargement (51, 52). Similarly, occult alveolar hemorrhage is associated with PVOD (52, 53). A noninvasive diagnostic approach using high resolution computed tomography of the chest, arterial blood gases, pulmonary function tests, and bronchoalveolar lavage could be helpful in detecting patients with PVOD and avoiding a high-risk surgical lung biopsy for histological confirmation (53). PVOD is characterized by poor prognosis and the possibility of developing severe pulmonary edema with specific PAH therapy (51, 52). Lung transplantation is the treatment of choice. Cautious use of specific PAH therapy can, however, be helpful in some patients (52, 54). Of note, a recent case report indicated that treatment with the tyrosine kinase inhibitor imatinib might be beneficial in PVOD, at least in part because of the effects of imatinib on PDGF-induced vascular remodeling and vascular integrity, as previously suggested in PAH (55, 56). More data are needed to conclude the relevance of this class of drug in PVOD.

**Biomarkers**

The potential for serial measurement with a relatively noninvasive methodology makes circulating biomarkers potentially attractive surrogates in PAH. The most widely studied circulating biomarkers in PAH reflect neurohormonal activation (brain natriuretic peptide and N-terminal probrain natriuretic peptide) (57). Simple biomarkers such as hyponatremia, a well-established marker of advanced left-heart failure, which has been shown to predict poor outcome, has recently been studied in PAH (58). A neurohormonally mediated, nonosmotic release of vasopressin accounts for the decrease in sodium concentration in advanced left-heart disease (58). In PAH, hyponatremia, found on a routine chemistry panel, is strongly associated with more advanced right-heart failure, right-ventricular dysfunction, and poor survival (58). Several circulating biomarkers are
regularly reported in pulmonary hypertension. It has been shown that the extent of the vascular cell damage measured by circulating microparticles might reflect PAH severity (59, 60). Growth-differentiation factor (GDF)-15, a stress-responsive, TGF-β-related cytokine has been studied in acute pulmonary embolism and idiopathic PAH (61, 62). In these circumstances, GDF-15 appears to be a promising biomarker. Asymmetric dimethylarginine (ADMA), a potent endogenous nitric oxide synthase inhibitor, is increased in idiopathic PAH and CTEPH and is associated with an unfavorable outcome (63). Interestingly, it has been suggested that the measurement of the ADMA plasma level may be useful for estimating the degree of small-vessel arteriopathy in CTEPH (64). Further studies are needed to clarify the exact role of biomarkers in clinical practice.

Autoimmunity presumably plays a key role in some PAH cases, such as those complicating systemic lupus erythematosus (35). Circulating autoantibodies have also been regularly detected in patients with idiopathic PAH (65). Recent proteomic analysis of sera from patients with PAH and controls has allowed the description of target antigens of antifibroblast antibodies in PAH (65). Interestingly, these autoantibodies recognize cellular targets that play key roles in cell biology and maintenance of homeostasis (6). Whether such autoantibodies contribute to the genesis or the development of PAH remains an unanswered question.

Treatment of Pulmonary Arterial Hypertension

No current treatment of PAH achieves a cure for this devastating condition (16). However, in fewer than twenty years, PAH treatment has evolved from a state of hopelessness to one in which prolonged survival and improvements in quality of life can be achieved. Current PAH treatments target the prostacyclin, nitric oxide, and endothelin-1 pathways (16). Until recently, therapeutic recommendations focused on patients with moderate to severe disease in NYHA functional class III and IV (16). Indeed, in recent placebo-controlled PAH trials, the proportion of enrolled patients in NYHA functional class III and IV ranged from 60 to 100%. The effects of PAH treatment had never been explored exclusively in patients with NYHA functional class II PAH (66). The EARLY trial is a 6-month double-blind placebo-controlled study, showing that the dual endothelin receptor antagonist bosentan could be beneficial in class II patients (66). A major result of this study was the description of the natural history of class II patients, demonstrating that a proportion of subjects with mildly symptomatic disease had rapid hemodynamic and functional deterioration (66). These results provide a rationale for early intervention in PAH (67). Other endothelin receptor antagonists, including the receptor A-selective ambrisentan, have been recently studied in PAH (68).

Combination therapy using drugs with different mechanisms of action to maximize clinical benefit is a currently emerging therapeutic option in PAH (16, 69). Long-term adequately powered, prospective, randomized, double-blind, placebo-controlled studies are needed to conclusively determine the effect of combination therapy in patients with PAH. PACES represents the largest double-blind placebo-controlled study of add-on combination therapy to date (addition of oral sildenafil to long-term intravenous epoprostenol). This 16-week study indicates that combination therapy is associated with significant improvements in exercise capacity, hemodynamics, and time to clinical worsening (69). Overall, these data are consistent with those from previous small and/or open studies, in which combination therapy improved endpoints in patients with PAH. Nevertheless, these results cannot be extrapolated to the most common clinical setting (that is, initiating treatment with first-line oral therapy then adding intravenous epoprostenol therapy as needed) (69).

ADVANCES IN CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

CTEPH has emerged as one of the leading causes of severe pulmonary hypertension (1, 2, 71, 71). The disease is notoriously underdiagnosed (71), and the true prevalence is still unclear (70). CTEPH is characterized by intraluminal thrombus organization and fibrous stenosis or complete obliteration of the pulmonary arteries. The consequence is an increased pulmonary vascular resistance resulting in pulmonary hypertension and progressive right-heart failure. Pulmonary endarterectomy is the treatment of choice, but not all patients with CTEPH are eligible for this surgery (70, 71). Recent research has provided evidence suggesting that the mechanistic view of CTEPH as a disease caused solely by obliteration of central pulmonary arteries due to organized thrombi may be too simplistic. Pulmonary embolism, either as a single episode or as recurrent episodes, is thought to be the initiating event followed by progressive pulmonary vascular remodeling (70). This concept might explain the clinical observation that patients with CTEPH may have severe pulmonary hypertension out of proportion to the pulmonary vascular obliteration seen on a pulmonary angiogram. Thus, treatment of CTEPH often requires a multidisciplinary approach and may involve surgery, medical treatment, or both (71).

CTEPH risk factors have been analyzed in a controlled retrospective cohort of prevalent CTEPH cases collected in three European centers offering pulmonary endarterectomy (72). Data from patients with CTEPH were compared with PAH cohorts at the participating institutions. Ventriculointerstitial-shunts and infected pacemakers, splenectomy, previous venous thromboembolism, recurrent venous thromboembolism, blood groups non-0, and lupus anticoagulant/antiphospholipid antibodies were more often associated with CTEPH (72). Thyroid replacement therapy and a history of malignancy emerged as novel CTEPH risk factors (72). Using a UK registry, the clinical importance of previously identified etiological factors and the prognostic value of a larger number of variables have been studied (73). Although univariate analysis confirmed the prognostic importance of pulmonary vascular resistance, multivariate analysis revealed that gas transfer and exercise capacity predicted pulmonary endarterectomy perioperative mortality. Cardiac index and exercise capacity independently predicted outcome in patients with nonoperable disease. The etiological importance of previously identified medical risk factors, such as previous splenectomy, has been confirmed, although these medical conditions did not influence prognosis (73).

There are few follow-up studies on long-term cardiopulmonary function after pulmonary endarterectomy. Cohort studies indicate that long-term survival after pulmonary endarterectomy is excellent, and that cardiopulmonary function can be almost normalized in most patients, highlighting the fact that surgery is the treatment of choice for eligible patients with CTEPH (74, 75). Interestingly, some CTEPH-predisposing medical conditions, such as splenectomy, permanent central intravenous lines, and certain inflammatory disorders, are predictors of poor survival in CTEPH (76). Moreover, it is noticeable that the nonsurgical CTEPH outcome has improved in recent years (75). Better overall management of nonsurgical patients is certainly the major reason explaining improved prognosis, including the use of medical therapies that have been shown to improve hemodynamics in CTEPH (75–78).
This summary has certainly omitted several significant contributions published on pulmonary hypertension in 2008, as was the case last year (79). Due to space limitation, it was not possible to extensively discuss pulmonary hypertension complicating chronic respiratory diseases and/or hypoxemia, as seen in chronic obstructive pulmonary disease and highlanders (80–85). Readers interested in cellular and molecular pathogenesis should refer to recent review articles discussing this fascinating aspect of pulmonary vascular medicine and the possible emerging therapies derived from this research (86–89).

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

References


