



EDITORIAL

More pressure on pulmonary hypertension

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The *European Respiratory Review* is structured around a “theme of the month”. I am delighted to introduce pulmonary hypertension (PH) as the first theme of the new *Review*.

PH describes a group of devastating diseases, comprising idiopathic and associated/secondary forms, which cause breathlessness, loss of exercise capacity and death due to elevated pulmonary artery pressure and subsequent right heart failure [1]. Pulmonary arterial hypertension (PAH) is defined by an elevation of the mean pulmonary artery pressure above 25 mmHg at rest and/or 30 mmHg during exercise without elevation of the pulmonary capillary wedge pressure (≤ 15 mmHg) [1]. The underlying pathophysiological mechanism is extensive pulmonary artery remodelling [2]. PH was previously classified into two categories, namely primary or secondary PH, depending on the absence or presence of identifiable causes or risk factors [1]. In the second (1998), third (2003), and fourth (2008) World Symposium on PH, a detailed clinical classification of the disease was agreed upon. The 2003 version is shown in table 1 [1]. The main subcategories share similarities in pathogenetic mechanisms, clinical presentation and therapeutic options, allowing clinicians to conduct trials using homogeneous groups of patients. Similarly, basic science specialists have attempted to describe pathophysiological mechanisms in the same homogeneous groups of patients with PH.

PAH

This includes cases without identifiable cause or risk factors, so-called idiopathic PAH (sporadic appearance) and familial PAH [1]. For these subgroups, mutations in the bone morphogenetic protein (BMP)/transforming growth factor- β superfamily (BMPR2, activin receptor-like kinase-1 and endoglin) are now known to play a crucial role [3]. However, genetic/environmental factors are likely to be the “double hit”, favouring the start of the disease [2]. The other subgroups include a number of conditions or diseases of known causes associated with the appearance of PAH [1]. Among the associated conditions, connective tissue disorders such as systemic sclerosis are major causes of PAH, with $>10\%$ of systemic sclerosis patients developing this severe life-threatening

complication [4]. All PAH forms have the localisation of remodelling lesions to the small pulmonary muscular arterioles in common [2]. In addition, they may be linked with significant venous or capillary involvement, namely pulmonary veno-occlusive disease and pulmonary capillary haemangiomatosis, conditions characterised by a certain degree of refractoriness to usual PAH therapies [1, 5].

PH WITH LEFT HEART DISEASE

This category consists predominantly of left-sided valvular or myocardial diseases, exerting mechanical strain on the pulmonary vasculature due to congestion [1]. Such conditions passively affect the pulmonary vasculature and are not usually part of the research priorities of the respiratory community. Nevertheless, studies are now focusing on this subgroup of patients who may sometimes develop severe pulmonary vascular disease.

PH ASSOCIATED WITH LUNG DISEASES AND/OR HYPOXIA

Within this category, the predominant cause is inadequate oxygenation of arterial blood as a result of either lung disease, impaired control of breathing or residence at high altitude [1]. Hypoxia-driven molecular mechanisms presumably play an important role in this group, but it remains unclear why some patients develop severe out of proportion PH [6, 7]. In addition, inflammatory mechanisms linked to the lung disease may contribute to the development of the pulmonary vascular disease [8].

PH DUE TO CHRONIC THROMBOTIC AND/OR EMBOLIC DISEASE

This category includes either chronic thromboembolic PH [9] due to proximal organised material in large pulmonary arteries, which can benefit from pulmonary endarterectomy, or more peripheral obstruction similar to those appearing in the small vessels in idiopathic PAH [9]. Abnormalities of coagulation and fibrinolysis control are assumed to represent the decisive trigger events [9].

MISCELLANEOUS

This category involves PH linked with various, mostly inflammatory, disorders. Sarcoidosis and histiocytosis X represent major conditions in this subgroup [1].

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Epidemiological data are not available for the entire field of PH. The largest and most recent national registries on PAH have been reported in 2006 in France [10] and 2007 in Scotland (UK) [11]. Prevalence rates for PAH as a whole vary among regions in France, ranging from five cases per million per year to 25 cases per million per year [10]. Data from Scotland indicate a prevalence ranging from 26 to 52 cases per million [11]. In addition, three quarters of the detected cases are in New York Heart Association functional class III or IV when diagnosed, a stage at which survival is limited despite available treatments [10]. Similar results have been reported in the USA by the Chicago group [12]. This information supports the fact that early detection should be promoted in high-risk populations, and that PH should be considered and screened for in patients displaying symptoms, such as unexplained dyspnoea. With a yearly incidence of two per million, PAH fulfils the criteria of a rare disease, with a higher appearance in females compared with males and a mean age at diagnosis of <50 yrs [10, 13]. Sex differences are also true for other categories of the disease, such as connective tissue disease-associated PAH, which is much more frequent in females compared with males [10].

Survival of untreated idiopathic familial PAH is extremely poor, with median survival ranging from 2 to 3 yrs [14]. This is similarly true for many other categories of PH, such as connective tissue disease-associated cases [15]. Over the past few years, various therapeutic strategies have been developed, which include different types of prostanoids, endothelin-receptor antagonists and phosphodiesterase inhibitors [16–19]. These agents were shown to relieve dyspnoea, improve exercise capacity and, not proven for all approaches, survival in these patients [16]. Nevertheless, we are still far from curing PH and further progress in drug development is urgently needed to achieve long-term survival with better quality of life.

PH has a multifactorial pathobiology. Next to vasoconstriction and *in situ* thrombosis, remodelling of all layers of the pulmonary vessel wall represents the hallmark of this disease, with proliferating resident cell types (endothelial, smooth muscle and adventitial fibroblasts), inflammatory cells and platelets, as well as circulating progenitor cells coming into close interplay [2]. Loss of endothelial function with lack of production of vasodilatory and anti-proliferative agents, such as nitric oxide and prostacyclin and their downstream cyclic nucleotides, was found to be a key event, providing a starting point for therapies based on these agents [2]. In contrast, potent vasoconstrictors, such as the endothelin-1 pathway, are known to be upregulated, again serving as a basis for novel therapeutic approaches [2]. Most importantly, going far beyond their immediate effect on vasomotor control, all these pathways have a major impact on the long-term balance of proliferation and apoptosis of the lung vascular cells, *i.e.* affect remodelling events [2, 20]. Notably, next to the resident vascular cell types involved in the remodelling, recruitment of circulating progenitor cells and different leukocyte types is controlled by these pathways and by an as yet only partially understood lung vascular chemokine system [8].

In the present issue of the *European Respiratory Review*, an update by SOUZA and JARDIM [21] will discuss novel information on several forms of pulmonary hypertension. In addition, other chapters will emphasise some important aspects of pulmonary vascular medicine, including pulmonary hypertension

TABLE 1 Diagnostic classification of pulmonary hypertension

Pulmonary arterial hypertension

Idiopathic
 Familial
 Associated with:
 Connective tissue diseases
 Congenital left-to-right shunt
 Portal hypertension
 HIV infection
 Drugs and toxins
 Other conditions[#]
 Substantial venous or capillary involvement
 Pulmonary veno-occlusive disease
 Pulmonary capillary haemangiomas
 Persistent pulmonary hypertension of the newborn

Pulmonary hypertension with left heart disease

Left-sided atrial or ventricular heart disease
 Left-sided valvular heart disease

Pulmonary hypertension associated with lung disease or hypoxaemia or both

Chronic obstructive pulmonary disease
 Interstitial lung disease
 Sleep-disordered breathing
 Alveolar hypoventilation disorders
 Chronic exposure to high altitude
 Developmental abnormalities

Pulmonary hypertension due to chronic thrombotic or embolic disease or both

Thromboembolic obstruction of proximal pulmonary arteries
 Thromboembolic obstruction of distal pulmonary arteries
 Nonthrombotic pulmonary embolism (tumour, parasites, foreign material)

Miscellaneous

Sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, and compression of pulmonary vessels (adenopathy, tumour, and fibrosing mediastinitis)

[#]: these conditions include thyroid disorders, type-1 glycogen storage disease, Gaucher's disease, hereditary haemorrhagic telangiectasia, haemoglobinopathies, myeloproliferative disorders and splenectomy. Reproduced from [1] with permission from the publisher.

complicating hereditary haemorrhagic telangiectasia [22, 23], pulmonary hypertension in high-altitude residents [24], pulmonary hypertension in children [25], chronic thromboembolic pulmonary hypertension [26], and novel therapeutic strategies such as inhaled prostaglandins [27] and soluble guanylate cyclase stimulation, an emerging option in pulmonary hypertension therapy [28].

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