11 Pulmonary Hypertension and Antiphospholipid Antibodies

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Pulmonary hypertension (PH) is defined as a mean pulmonary artery pressure greater than 25 mm Hg [1, 2]. After many years of debate, it is now agreed that PH can be classified according to three features**:** anatomical localization of vascular disorder, presence or not of any associated disease, and severity, with the magnitude of reduction of cardiac output as the best predictor survival [1] (Table 11.1). The term *primary pulmonary hypertension* (PPH) has been used extensively in literature, leading to some confusion. PPH usually means that diverse mechanisms have been ruled out, especially chronic causes of hypoxia, left ventricular failure, and repeated pulmonary embolism, and that plexogenic arteriopathy can be found on histological lung examination. PPH is a rare but life-threatening condition, whose pathophysiology has remained mysterious for a while. Advances have suggested the importance of diverse factors, such as: imbalance in vasoactive agents, that is, deficiency of nitric oxide and prostacyclin synthase versus overexpression of endothelin-1; vascular endothelial growth factor (VEGF) expression; K+ channel anomalies; genetic susceptibility; and, last but not least, clonal expansion of endothelial cells in primary but not secondary PH [2–6]. Though PPH frequently remains "unexplained," several comorbid conditions have been identified as possible etiologies, with human immunodeficiency virus (HIV) infection, prior use of anorectic agents, and connective tissue diseases (CTD) as leaders [2, 7] (Table 11.1). Whatever the "cause," severe PH may be complicated by (a) superimposed in situ

Table 11.1. Classification of pulmonary hypertension.

Arterial pulmonary hypertension (changes in precapillary arteries)
"Primary" arterial PH
Secondary arterial PH (scleroderma, MCTD and other CTD, congenital heart disease, portal hypertension, HIV, anorectic agents, cocaine, etc.)
Postcapillary pulmonary hypertension (changes in pulmonary veins)
Left-sided heart failure
Rarely: pulmonary veno-occlusive disease, pulmonary hemangiomatosis, chronic Sclerosing mediastinitis, congenital pulmonary vein anomaly
Proximal pulmonary artery involvement
Mainly: chronic thromboembolic PH
Rarely: metastatic neoplasm, parasites, miscellaneous emboli
Extrinsic vascular compression
Secondary to all chronic causes of hypoxia

thromboses affecting distal pulmonary arteries [8] and, (b) the development of plexogenic lesions, both thought to occur as a consequence of chronic endothelial injury [1, 6]. More recently, infection with human herpes virus 8 has been implicated as having a pathogenic role in the development of plexiform lesions in PPH, for a study showed the presence of the virus in plexiform lessions [9].

Mutations in the bone morphogenic protein receptor type 2 (BMPR2) have now been linked to familiar cases of PPH [10]. BMPR2 is an interesting protein to be implicated so strongly in the pathogenesis of the disease. It is a cell surface receptor belonging to the superfamily of receptors for ligands of the transforming growth factors (TGF) β family. How might the BMPR2 mutations account for the disease? PPH [10] is a disease of vascular remodeling per excellence and BMPs 2 and 7 have been shown to inhibit vascular smooth muscle cell proliferation and to induce apoptosis in some cell types in culture. It is thus tempting to suggest that PPH arises out of an impairment of control of cellular proliferation. The molecular defects in common non-familial PPH are unknown. Recent studies suggest that these forms of PPH are linked by defects in the signaling pathways involving angiopoietin-1 TIE2, BMPR1A, and BMPR2 [11], fitting in with the hypothesis that there may be impaired cellular proliferation in PPH.

This chapter will give a brief overview of PH within antiphospholipid syndrome (APS), question the possible role of antiphospholipid antibodies (aPL) in the pathophysiology of "unexplained" PPH and thromboembolic pulmonary hypertension, and then discuss practical aspects of the management.

Pulmonary Hypertension and APS

APS mainly occurs either in association with systemic lupus erythematosus (SLE), or as a primary disorder named primary APS [12]. Within these two subsets, the prevalence of PH has been estimated 1.8% and 3.5%, respectively, in a multicenter study [13]. In two other large studies performed on SLE patients, the prevalence of PH was 2% [14] and 5% [15]. Within APS, PH may result from various causes listed in Table 11.2 [16, 17].

Table 11.2. Pulmonary hypertension within APS.

APS related
Pulmonary embolism (acute/chronic)
Left-sided heart failure
Heart valve dysfunction
Myocardial infarction
Myocardiopathy
"Primary" pulmonary hypertension (?)
Miscellaneous (rare)
Portal hypertension
Pulmonary veno-occlusive disease
Not directly APS-related
Chest disorder leading to chronic hypoxia
Mainly fibrosing alveolitis
Coincidental