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EDITORIAL

Beyond arterial remodelling: pulmonary venous and cardiac involvement in patients with systemic sclerosis-associated pulmonary arterial hypertension

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Pulmonary arterial hypertension (PAH) represents a heterogeneous group of disorders characterised by elevated pulmonary vascular resistance and a normal pulmonary artery wedge pressure that occurs in the absence of left heart disease, chronic lung diseases/hypoxia or chronic thromboembolic pulmonary disease [1]. Entities within the PAH group share not only similar symptoms and haemodynamic profiles but also a common therapeutic approach [2]. Unfortunately, outcome among PAH patients remains poor and a cure for the disease remains elusive [3]. One additional, although less well described, feature that favours the distinction of a PAH group is the histomorphological correlate of elevated blood pressures within the pulmonary vasculature. Indeed, PAH that is idiopathic, heritable, or associated with anorexigen exposure, HIV infection, portopulmonary hypertension and connective tissue disease (comprising mostly systemic sclerosis (SSc)-associated PAH (SSc-PAH)) appear to have a similar pulmonary arterial and arteriolar remodelling pattern. Typical PAH lesions consist mainly of widely and uniformly distributed vascular alterations, including intimal fibrosis, and endothelial and smooth muscle cell proliferation, without obvious involvement of the bronchoalveolar architecture. These histological features are markedly different from pulmonary hypertension that arises as a consequence of chronic thromboembolic disease, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis and sarcoidosis, in which vascular occlusion develops as a consequence of emboli, arteriolar rarification, interstitial scarring or obstructing granulomas, respectively. Despite similarities in pathological anatomy, clinical management and outcome among the different forms of PAH, there are, nonetheless, important differences that remain unexplained. In patients with SSc, PAH is a leading cause of mortality that requires intensive medical management. However, therapeutic responses are frequently less favourable compared to other forms of PAH [4–6]. SSc-PAH treatment with vasodilators such as continuous intravenous epoprostenol is associated with improvements in exercise capacity and cardiopulmonary haemodynamics. However, therapeutic responses using prostanoid therapy in SSc-PAH patients are often disappointing, particularly compared to those with idiopathic PAH [5–8]. Similarly, endothelin receptor antagonists seem to show less impressive effects in SSc than in other forms of PAH [9, 10]. In addition, therapeutic intervention in this population is potentially dangerous, with life-threatening acute pulmonary oedema a reported complication of vasoactive treatment in SSc-PAH [11]. Interestingly, these side-effects that occur in the context of treatment with vasodilators have been frequently described in the setting of another rare cause of pulmonary hypertension, pulmonary veno-occlusive disease (PVOD) [11, 12]. Pulmonary oedema and occult alveolar hemorrhage in treated PVOD patients is generally believed to occur as a result of fibrous intimal remodelling within small pulmonary venules that eventually leads to a post-capillary obstruction and transudation of fluid into alveoli, owing to the associated transcapillary haemodynamic gradient [12–15]. These observations have fuelled the hypothesis that venular remodelling may similarly characterise SSc-PAH and offer a potential explanation for the adverse therapeutic responses that have been previously reported in this disorder. A study by OVERBEEK *et al.* [16] in a recent issue of the *European Respiratory Journal* has shed additional light on the complex pathomechanisms of SSc-PAH. These authors analysed lung tissue from eight PAH patients with limited cutaneous SSc and compared finding to samples from 11 idiopathic PAH patients. Importantly, they found that all SSc-PAH patients displayed both arterial and venous remodelling, while venous lesions were present in only three of the 11 idiopathic PAH-patients. Of note, four of the SSc-PAH cases displayed a PVOD-like pattern, characterised by patchy capillary congestion and signs of occult alveolar haemorrhage. Similarly, our group has suggested a frequent PVOD-like involvement of the post-capillary vascular bed in the lungs of patients suffering from connective tissue disease-associated PAH [17]. Indeed, we found that six out of eight patients (four SSc, two lupus, one mixed connective tissue disease and one rheumatoid arthritis), and all four SSc-PAH patients, showed significant obstructive pulmonary vascular lesions predominantly involving the veins and pre-septal venules, as compared to five (17%) out of 29 control PAH patients. Furthermore, lesions involving the small muscular arteries

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were consistently present in PAH associated with connective tissue disease, with intimal fibrosis and intraluminal thrombosis the most frequently identified pathological changes. Importantly, neither arterial nor venous remodelling was restricted to areas of interstitial fibrosis; indeed, these pathological vascular changes were also noted in regions showing otherwise normal bronchoalveolar architecture. In addition, the degree of interstitial lung disease (if any) did not correlate with the severity of the observed pulmonary vascular disease. While complex lesions are frequently observed in most other forms of PAH, it is noteworthy that neither our group nor that of OVERBEEK *et al.* [16] has observed this histological entity in SSc-PAH. Although these morphological and clinical particularities are becoming increasingly recognised in connective tissue disease-associated PAH, they remain poorly understood.

The systemic involvement of SSc also contributes to the unique characteristics observed in SSc-PAH, as distinct from idiopathic PAH. In this issue of the *European Respiratory Journal*, MATHAI *et al*. [18] have reported their findings from a study evaluating cardiac involvement in a cohort of SSc-PAH patients. Their results may in part explain the worse outcomes observed in this population. The authors compared serum levels of N-terminal pro-brain natriuretic peptide (NT-proBNP), a circulating biomarker of neurohormonal activation produced and secreted by the myocardium, in 43 patients with idiopathic PAH and 55 SSc-PAH and correlated levels with haemodynamic parameters. They found that circulating NT-proBNP levels were significantly increased in patients with SSc-PAH compared with idiopathic PAH patients, despite less severe haemodynamic impairment, as measured by right heart catheterisation. They also showed that haemodynamic indices closely correlate to NT-proBNP levels in SSc patients and that the latter parameter predicts survival. WILLIAMS *et al*. [19] have previously shown that increased NT-proBNP serum levels in connective tissue disease-associated PAH patients closely correlated with altered haemodynamics and reliably predicted survival. In considering the main findings of these studies, one may conclude that NT-proBNP expression is the cardiac consequence of increased pulmonary arterial pressures, but is more pronounced in SSc-PAH than in idiopathic PAH, even if haemodynamics are less severe in the former. One possible explanation for this seemingly contradictory conclusion is that SSc-PAH might differ in its pathological anatomy from other forms of PAH, as already suggested above. It is known that cardiac abnormalities other than those that develop as a consequence of pulmonary hypertension may be present in SSc patients. Fibrous scarring, probably due to micro-ischaemic and/or post-inflammatory events, is frequently found in the myocardium of the left ventricle, and chronic heart failure may occur in patients with scleroderma but lacking manifest PAH [20]. Although there is increasing interest in the potential role of NT-proBNP as a biomarker in PAH, this enzyme has long been known as an indicator of left heart failure [21, 22]. Interestingly, in a recent study by VON HAEHLING *et al.* [23], serum levels of NT-proBNP and several inflammatory markers (including tumour necrosis factor-α, its receptors, and interleukin-10) from patients with right ventricular dysfunction due to chronic thrombembolic pulmonary hypertension were compared to patients with left ventricular dysfunction due to chronic heart failure. Although both groups showed significant increased levels of all markers, differences did not vary significantly between the different study groups. This finding suggests that different triggers may produce similar inflammatory signalling and pathological tissue reaction within the myocardium. One might then pose the question of whether elevated expression of NT-proBNP in SSc-PAH (as compared with idiopathic PAH) is due, at least in part, to an underlying SSc-associated heart disease that involves the right and/or left ventricle and is particularly prone to increased pressure/shear stress. It is well established that a dysregulated fibrotic reaction in lung parenchyma, oesophagus and skin is characteristic of SSc, eventually leading to interstitial pulmonary fibrosis, oesophageal dysmotility/stenosis and scleroderma [24]. This impaired pro-fibrotic response to different stimuli has been attributed, in particular, to altered transforming growth factor-β pathway signalling, which induces fibroblast-activation, reduction of extracellular matrix degrading activities and the initiation of α-smooth muscle actin expression [25, 26]. It is, therefore, conceivable that the observed fibrous remodelling within pulmonary veins and venules in SSc-PAH may develop in a similar fashion; that is, an altered fibrous reaction pattern of the post-capillary vasculature to increased downstream pressures.

However, together with fibrous interstitial and pulmonary vascular remodelling, inflammation is a key contributor in SSc-associated pulmonary disease. Indeed, OVERBEEK *et al.* [16] also observed transmural vascular inflammatory infiltrates, mainly consisting of lymphocytes, in four SSc-PAH and two idiopathic PAH cases. In two SSc-PAH patients, vasculitis was present at the venular level. This finding supports the hypothesis that inflammation and immunity may represent a possible common denominator among the various forms of PAH [27, 28]. Although there is no role for anti-inflammatory or immunosuppressive agents in most forms of PAH, beneficial effects with these forms of therapy have nevertheless been reported in small retrospective studies of patients suffering from connective tissue disease-associated PAH (systemic lupus erythematosus and mixed connective tissue disease, but not SSc) [29–31].

We have recently defined new clinical parameters for the noninvasive and early differentiation of PVOD from idiopathic PAH, an important practical issue in view of the significant risk associated with vasodilator therapy in PVOD [12, 32, 33]. Indeed, lung biopsy is not recommended in PAH patients because of the unacceptably high associated risk of death [12]. In contradistinction to PAH, PVOD patients show characteristic changes of nodular ground-glass opacities, septal lines and lymph node enlargement on high-resolution computed tomography of the chest. In addition, PVOD patients typically demonstrate lower values for partial pressure of arterial oxygen, diffusing lung capacity of carbon monoxide and oxygen saturation nadir during the 6-min walk test, when compared to idiopathic PAH patients [32]. Given these observations, it may be of considerable clinical utility to determine diagnostic and, therefore, prognostic parameters in other PAH groups with possible pulmonary venous and cardiac involvement, as is the case in SSc [34].

Considering these new possibilities in PAH management, the present work of MATHAI *et al.* [18], and the recent report by OVERBEEK *et al.* [16] in the *European Respiratory Journal* offer additional insights into the morphological characteristics of

PAH in patients with SSc. These efforts also highlight the importance of pulmonary arterial remodelling and other lesions beyond this frontier.

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STATEMENT OF INTEREST

A statement of interest for M. Humbert can be found at www.erj.ersjournals.com/misc/statements.dtl

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