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CORRESPONDENCE

Pulmonary arterial hypertension in systemic sclerosis: a distinctive endotheliopathy?

To the Editors:

We read with great interest the recent article by OVERBEEK *et al.* [1] on the histological differences in pulmonary vessels from patients with pulmonary arterial hypertension (PAH) related to systemic sclerosis (SSc) *versus* idiopathic PAH (IPAH). The study demonstrates that pulmonary pathological features in patients suffering from limited cutaneous SSc (lcSSc) differ from the ones seen in IPAH, in relation to the occurrence of small vessel intimal fibrosis, the presence of pulmonary veno-occlusive disease-like lesions, and the absence of plexiform lesions in the former group. OVERBEEK *et al.* [1] correctly suggest that their findings point to the presence of a distinct vasculopathy in the SSc cohort that may contribute to the lower transfer factor of the lung for carbon monoxide ($T_{L,CO}$) and, more importantly, to the worse prognosis in PAH-SSc *versus* IPAH. The authors further propose that different pathogenetic mechanisms should underlie PAH development in the two groups, and that pulmonary endothelial function should be a determinant of such dissimilar mechanisms [1].

In support of the this hypothesis, we have recently provided evidence that different degrees of pulmonary endothelial dysfunction may be present in patients suffering from IPAH and PAH related to connective tissue disease (PAH-CTD) [2]. Using first-pass lung metabolic studies at the bedside, by means of indicator dilution-type techniques, we have been studying human pulmonary endothelial function by estimating pulmonary capillary endothelium-bound enzymatic activity *in vivo* [3]. This technique allows direct and quantifiable measurements of pulmonary endothelial metabolic function, and may distinguish between functional alterations at the capillary endothelial cell level and loss of functional capillary surface area (*i.e.* perfused and metabolically active lung microvascular bed) [3].

By applying such techniques we have, in the past, provided *in vivo* evidence that pulmonary endothelial dysfunction is a feature of early systemic sclerosis, being already present prior to the development of PAH and overt interstitial lung disease [4]. Patients suffering from both lcSSc and diffused cutaneous SSc (dcSSc) demonstrated functional alterations at the capillary endothelial cell level, whereas the functional capillary surface area was reduced only in dcSSc [4]. More recently, we have extended these studies to investigate pulmonary endothelial metabolic functional patterns in subjects with IPAH and PAH-CTD, prior to receiving PAH-related treatments [2]. Approximately two-thirds of the PAH-CTD patients suffered from SSc. Indices reflecting ''true'' pulmonary endothelial dysfunction (*i.e.* functional alteration at the capillary endothelial cell level) were only present in the CTD group, supporting the intriguing hypothesis that PAH-CTD and IPAH posses different pulmonary endothelial phenotypes, and thus different metabolic functions as implied by OVERBEEK *et al.* [1]. In contrast, both groups exhibited similar functional capillary surface area reductions, mainly reflecting the PAH-related small vessel loss and remodelling. Furthermore, our study provided the first functional evidence that the reduced $T_{L,CO}$ values in PAH-CTD are related in a linear fashion to the degree of functional capillary surface area loss [2]. It should be noted that similar studies performed in patients suffering from chronic thromboembolic pulmonary hypertension revealed a different pattern, in that pulmonary endothelial metabolism was maintained, although functional capillary surface area loss was present [5].

Based on the evidence above, we feel that the study by OVERBEEK *et al.* [1] may provide a partial explanation for our findings, and the endothelial dysfunction we described may contribute to the diverse histological abnormalities that OVERBEEK *et al.* [1] have presented. Techniques that allow direct quantification of pulmonary endothelial function at the bedside might, in the future, identify varied pulmonary endothelial phenotypes in PAH patients, and assist the clinician in choosing the right treatment and monitoring its effects.

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Nonthrombotic pulmonary embolism

To the Editors:

We read with great interest the article in the *European Respiratory Journal* by JORENS *et al.* [1] on the different types of nonthrombotic pulmonary embolism. Among them, hydatid disease is of major importance as it is endemic in sheep-raising regions worldwide. We wish, therefore, to outline the management of metastatic pulmonary hydatidosis secondary to a primary hydatid cyst located in the liver according to our experience of six cases.

First, the diagnosis of hydatid pulmonary vascular obstruction should be looked for systematically in patients with a primary hepatic hydatid cyst located near the inferior vena cava and/or supra-hepatic veins, by perfusion lung scan and/or spiral thoracic computed tomography.

Secondly, once the pulmonary vascular obstruction has been diagnosed, the surgical treatment of the hepatic cyst at the origin of the embolism must be carried out as the first step. However, mobilisation of the liver may cause hydatid embolism and haemorrhagic complications when the hydatid cysts are in contact with the walls of the inferior vena cava. We suggest the following preventive measures: a wide laparotomy to control the inferior vena cava and have an extracorporeal bypass ready. These guidelines may prevent the fatal intraoperative pulmonary embolism as previously reported, and which occurred in two patients from our series [2].

Thirdly, surgery for a hydatid pulmonary vascular obstruction is quite similar to that for usual pulmonary embolism: embolectomy by arteriotomy for proximal pulmonary intra vascular hydatid cysts (five times in four patients in our series) using cardiopulmonary bypass in two cases.

Finally, chronic pulmonary arterial hypertension may worsen even after hydatid embolectomy as the vascular obstruction is also distal and associated with a granulomatous reaction and vascular fibrosis [3]. Pulmonary transplantation may be a therapeutic option because immunosuppressive treatment does not adversely affect the course of hydatid disease [4]. Recently, the use of pulmonary hypertension medical therapy, such as endothelin-1-receptor antagonists, phosphodiesterase-5-inhibitors and prostacyclin analogues, has been reported to be clinically effective [5].

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Effects of nanoparticles on lung damage in humans

To the Editors:

We read with great interest a recent article in the *European Respiratory Journal* by SONG *et al*. [1] and we would like to add some questions/comments to their paper. First, we are interested in the (estimated) total weight of the polyacrylate nanoparticles detected in the lungs and/or pleural fluids obtained from the patients. In our *in vivo* experiments, mice were exposed seven times per week to nanoparticles (carbon black [2] and latex [3]) at the weight of 50 $\mu g \cdot time^{-1} \cdot animal^{-1}$ (~83 mg in the human body), and did not die within 6 months thereafter (unpublished observation). Taken together, results