Which patients are SaPHe in sarcoidosis-associated pulmonary hypertension?

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Pre-capillary pulmonary hypertension is a rare and heterogenous complication in sarcoidosis. 6-min walking distance is a robust and consistent prognostic factor, but the role of pulmonary arterial hypertension-targeted treatments remains controversial. http://bit.ly/2J27Yps

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Pulmonary hypertension (PH) is a well described and clinically important complication in sarcoidosis. The epidemiology of sarcoidosis-associated pulmonary hypertension (SaPH) varies depending on the characteristics of the population analysed, but ranges from 3–75%, depending on method of diagnosis (*i.e.* echocardiography *versus* right heart catheterisation (RHC)) and severity of underlying sarcoidosis [1–4]. Elevation of pulmonary arterial pressure in sarcoidosis can occur *via* a number of mechanisms (figure 1) [5, 6] and, as such, SaPH has remained under group 5 (PH with unclear and/or multifactorial mechanisms) in the recent 6th World Symposium on Pulmonary Hypertension [7]. The breadth of pathophysiologic mechanisms that lead to PH is fairly unique to sarcoidosis, which makes SaPH an interesting but complicated entity.

To date, due to the relative rarity of the condition and lack of multinational registries, there have been limited published data on large cohorts of SaPH patients to allow accurate understanding of the predictors of disease behaviour, clinical outcomes, and response to treatment. Due to the paucity of information available regarding the behaviour of this condition, large cohorts of SAPH patients have recently been described in order to enrich our understanding of the condition [3, 8, 9].

In 2005, Shorr *et al.* [3] presented a large cohort (n=363) of sarcoidosis patients listed for lung transplant. Patients with PH had higher oxygen requirements, greater functional limitation, and impaired cardiac function in comparison to sarcoidosis patients listed for transplant with mean pulmonary arterial pressure (mPAP) <25 mmHg. In 2017, Boucly *et al.* [8] published their series in the *European Respiratory Journal* with haemodynamic and clinical data from 126 patients with severe SaPH of pre-capillary origin (defined as pulmonary artery wedge pressure ⩽15 mmHg, mPAP >35 mmHg, or mPAP 25–35 mmHg with cardiac index <2.5 $L{\cdot}min^{-1}{\cdot}m^{-2}$). Patients with presumed alternative aetiologies of pulmonary vascular disease, such as thromboembolic disease, HIV, connective tissue disease, congenital heart disease or exposure to drugs/toxins were excluded. This study demonstrated the importance of 6-min walk distance (6MWD) on transplant-free survival in multivariate analysis. Additionally, univariate analysis suggested the potential

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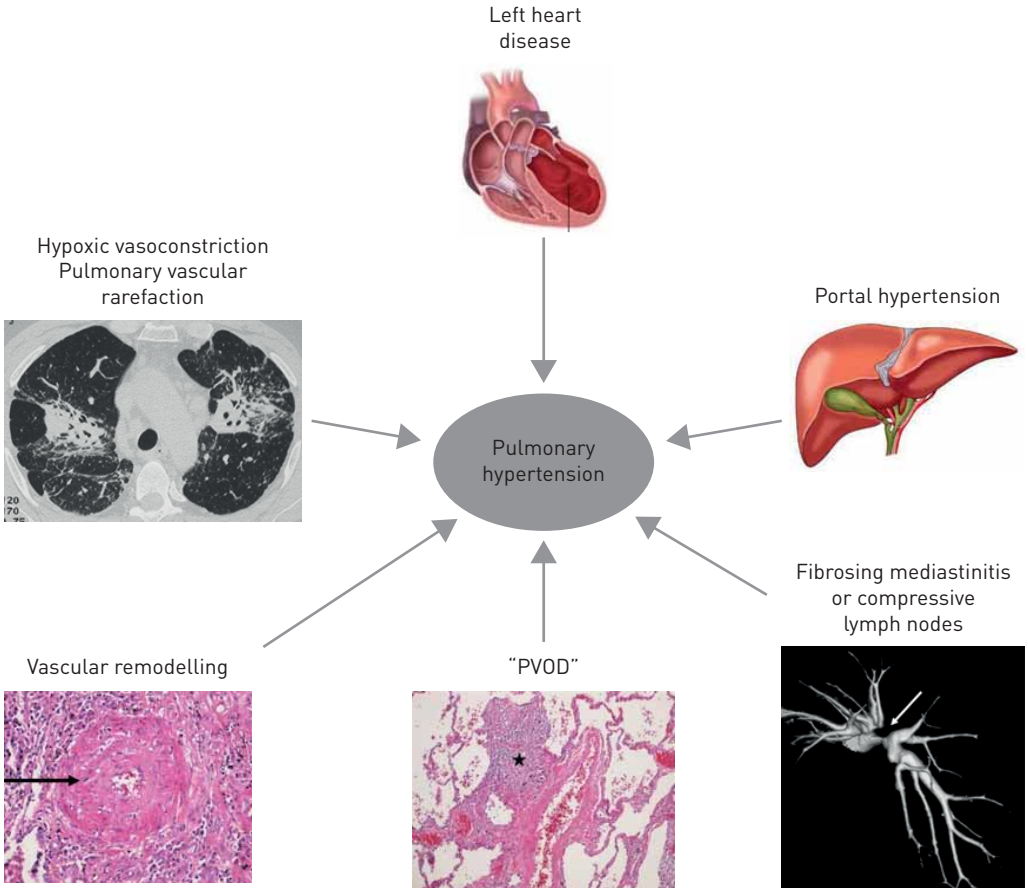

FIGURE 1 Multifactorial mechanisms lead to pulmonary hypertension (PH) in sarcoidosis, including hypoxic vasoconstriction, pulmonary vascular rarefaction, parenchymal destruction, left heart disease with post-capillary PH, portal hypertension from liver disease, pulmonary vascular remodelling, changes resembling pulmonary veno-occlusive disease (PVOD), and extrinsic vascular compression due to fibrosing mediastinitis or enlarged lymph nodes.

importance of lung function (transfer coefficient of the lung (K_{CO}) and forced vital capacity (FVC)) and functional class, though these failed to remain as independent predictors. They also demonstrated a unique cohort of patients that had significant improvement with augmented immunosuppressive treatment, potentially identifying an important group of patients for whom treatment of the underlying condition may portend a better response than pulmonary arterial hypertension (PAH) treatment. With respect to PAH therapy in SaPH, limited randomised trial data are available, consisting of a single study performed utilising bosentan by Baughman *et al.* [10], which demonstrated small improvements in haemodynamics on RHC, without changes in 6MWD or in symptomatology. Of note, two patients in the bosentan-treated group had increased requirements for supplemental oxygen. The number of patients enrolled and duration of follow-up were not sufficient to detect an effect on outcomes such as transplant-free survival or hospitalisations. Other studies have evaluated inhaled iloprost, intravenous prostacyclin and other PAH therapies [11–13], which have demonstrated improvement in right heart haemodynamics, with variable responses in 6MWD, symptoms and quality of life metrics. We are currently awaiting the results of a randomised-controlled trial looking at riociguat in treating patients with SaPH [12].

In this issue of the *European Respiratory Journal*, Shlobin *et al.* [14] describe physiologic prognostic factors in the ReSAPH registry, the largest cohort yet of patients (n=159) with RHC-confirmed pre-capillary pulmonary hypertension in the setting of sarcoidosis. Both incident and prevalent patients were included in this multinational registry, with incident patients defined as having a diagnosis of PH made less than 1 year prior to entry into the registry, and prevalent patients having been diagnosed more than 1 year prior to entry. For this study, PH was defined by the 2015 European Society of Cardiology/European Respiratory Society guidelines, as mPAP ⩾25 mmHg [15]. Most SaPH patients had severe PH, with an average mPAP of 36.9±9.2 mmHg and pulmonary vascular resistance of 5.9±3.4 Wood units. The patients

in this study had comparatively less severe haemodynamics than in the French cohort reported by Boucly *et al.* [8]. Similar to the French study, though, the vast majority (66%) had Scadding stage IV changes on radiogram and marked impairments in lung function were present with reduced FVC (62.4±19.7% predicted) and severely reduced diffusing capacity of the lung for carbon monoxide (D_{LCO}) (40.0±15.9% predicted). Higher rates of transplant-free survival were observed in the prevalent group compared to the incident subgroup at all time points (1, 3 and 5 years), consistent with the known survivor bias observed in prevalent (*versus* incident) patients with group 1 PAH [16]. Transplant-free survival was associated with D_{LCO} and 6MWD, which reached statistical significance both at prespecified cut-offs and on univariate analysis. In multivariate analysis there was an association between 6MWD and survival, however they also discovered an association between lower forced expiratory volume in 1 s to FVC ratio and improved outcomes, which was a novel and interesting finding.

In the context of the existing literature, several important insights into SaPH emerge from this large ReSAPH study. First, the 6MWD was independently associated with outcomes in the ReSAPH study [14] and in the French cohort studied by Boucly *et al.* [8], illustrating the power of this test as a global marker of impairment and disease severity in SaPH. Yet, there was no effect on 6MWD in the only randomised trial in this patient population, raising questions as to whether PAH therapies have any meaningful benefits on clinical outcomes or prognostic variables in SaPH [10]. There were no longitudinal data in the report of Shlobin *et al.* [14] to support the notion of treatment-related improvements in 6MWD or other clinical parameters. In the study by Boucly *et al.* [8], there were statistically significant improvements during follow-up in functional class and haemodynamics, but no improvement in 6MWD in the subgroup of patients treated with PAH therapies. Baseline haemodynamic parameters and use of PAH therapy were not related to transplant-free survival in the ReSAPH study; however, the treated subgroup had worse haemodynamics, raising the possibility that PAH therapy masked any association between haemodynamic severity and outcomes. Secondly, Shlobin *et al.* [14] confirmed the long latency to time of PH diagnosis. Boucly *et al.* [8] reported a mean time to diagnosis of PH from initial diagnosis of sarcoidosis of 17 years, and Shlobin *et al.* [14] have demonstrated a mean time to diagnosis of 12.6 years. This illustrates the importance of long-term follow-up of sarcoidosis patients to monitor for this late and serious complication. Thirdly, by including all-comers with SaPH, irrespective of PH severity at the time of initial diagnosis, the Shlobin *et al.* [14] study may be more generalisable than other large cohorts of SaPH. In contrast, the study of Boucly *et al.* [8] included only severe SaPH patients in their analysis, and Shorr *et al.* [3] included only sarcoidosis patients listed for lung transplant, who are a more severely afflicted population, by definition. Despite no severity threshold being set, the mPAP at the time of diagnosis in the ReSAPH study was 36.9 mmHg, highlighting the possibility that we are missing an opportunity to identify PH in this population earlier. Particularly when combined with the knowledge that the latency between sarcoidosis diagnosis and diagnosis of SaPH is greater than a decade, there are many years in which we could diagnose PH and potentially intervene at an earlier stage for these patients. Currently we lack studies showing an improvement in patient outcomes with earlier diagnosis and treatment of PH in sarcoidosis. However, it is possible that with proper characterisation of the underlying mechanisms of PH at earlier stages of disease, PAH therapies could benefit carefully selected patients. Lastly, the demonstration of airflow obstruction as an indicator of improved prognosis is hypothesis-generating from the perspective of how the mechanism of elevated pulmonary pressure relates to outcomes. It suggests that those with a predominantly bronchocentric pattern of fibrosis and a primarily obstructive ventilatory defect from greater small airways involvement may be at lower risk in the context of pre-capillary PH, compared to those with pulmonary artery compression by mediastinal disease or direct granulomatous vascular involvement. This result certainly warrants confirmation and further exploration in relation to computed tomography (CT) imaging features.

In light of these findings, it is clear that further work is needed to better characterise the different phenotypes of sarcoidosis that lead to SaPH. It is also clear that we need better ways of identifying PH before severe functional impairment develops. Based on the consistent association between 6MWD and outcomes in SaPH in two large registry-based studies, those with markedly reduced 6MWD deserve special attention, earlier consideration for haemodynamic assessment and consideration for lung transplantation referral. Further work is necessary to understand how the use of biomarkers, cardiac magnetic resonance imaging, alveolar–arterial oxygen gradient, desaturation on exertion, stress echocardiography, CT imaging characteristics and pulmonary function abnormalities (namely airflow obstruction and K_{CO}) can be incorporated in a multi-modality risk assessment tool for SaPH, as has been the case for group 1 PAH. It will also be necessary to consider how the findings of these studies relate to the recent World Symposium on Pulmonary Hypertension task force proposal to revise the haemodynamic definition of PH from a mPAP $\geqslant$25 mmHg to >20 mmHg [7]. As our knowledge of SaPH phenotypes and prognostic factors advances, we may begin to better identify which patients might meaningfully respond to targeted treatment of their PH, which could ultimately inform the design of future randomised trials in this field.

Until that time, we lack proof as to whether PAH therapies are "SaPHe" and whether they improve patient outcomes.

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