Hypersensitivity pneumonitis and pulmonary hypertension: how the breeze affects the squeeze

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Chronic hypersensitivity pneumonitis is commonly complicated by PH, which results in increased functional limitation http://ow.ly/vGBOS

The current World Health Organization (WHO) classification of pulmonary hypertension (PH) categorises PH due to chronic lung disease under group 3 [1]. There are many reports of PH complicating the course of the more common interstitial lung diseases (ILD), such as idiopathic pulmonary fibrosis (IPF), connective tissue disease associated-ILD and conditions within WHO group 5, such as sarcoidosis. What is surprising though is the relative paucity of data on PH complicating the course of other forms of ILD. The study in this issue of the *European Respiratory Journal* by Oliveira *et al.* [2] is the largest to date of right heart catheterisation (RHC) documented PH associated with chronic hypersensitivity pneumonitis (CHP). The authors documented the presence of PH in 50% of their cohort, most of whom (22 out of 25) had group 3 PH, with the three remaining patients having evidence of group 2 PH. Similarly to IPF, they found that the presence of PH was associated with worse functional impairment [3].

This study raised a number of important issues. The first point of interest does not pertain to PH, but rather the broad spectrum of ILD. Specifically, the authors evaluated 1023 consecutive patients with ILD, of whom 95 were documented to have CHP. This equates to a prevalence of just below 10%, which is informative to the ILD community; although, this prevalence is likely to vary regionally and internationally based on many economic, environmental and cultural differences. The somewhat high prevalence of PH is in keeping with what has been described previously in IPF as is the spectrum of severity, with most patients having mild PH [3, 4]. Are the causative mechanisms for PH likely to be the same? Certainly fibrosis is common to both diseases, yet this aspect of the disease is thought to be only one component of the pathogenic process in IPF. Many other factors including comorbidities, hypoxaemia and the cytokine milieu are probably contributory to the genesis of PH in IPF. Whether all the same factors play a role in CHP is uncertain and remains to be determined. Indeed, it is also possible that elements unique to the disease may play a role. For example, the anatomic location and distribution of disease in CHP is distinctly different to that of IPF, with a more bronchiolocentric pattern to both inflammation and fibrosis. The proximity of pathological changes within the bronchovascular bundles might heighten the propensity for PH by involvement of larger more proximal vessels. This anatomic predilection might be one of the reasons for the link demonstrated in this current study between the degree of lung function impairment and PH [2]. Interestingly, a similar association in IPF, specifically between the severity of restriction and lung fibrosis with PH, has been found to be lacking [5, 6]. What of the role of the inhaled antigen itself? Is there an acute vasospastic response, akin to hypoxic vasoconstriction, that over time results in vascular remodelling? The study by Oliveira *et al.* [2] lays the foundation and hopefully provides a stimulus for further studies into the pathogenesis of PH in CHP.

An interesting confirmatory detail from this study is the limitation of echocardiography as a screening tool for PH in patients with advanced lung disease [7]. In this study over half the patients would have had an

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absent or inaccurate assessment of their pulmonary artery pressure based on echocardiogram alone. OLIVEIRA *et al.* [2] offer an ancillary scoring system upon which to base ones suspicion for PH in CHP. The greatest value of this tool appears to be in its negative predictive value. Specifically, a zero score (forced vital capacity >60%, arterial oxygen tension >70 mmHg and estimated pulmonary artery systolic pressure by echocardiography <40 mmHg) effectively rules out accompanying PH. However, this screening method remains to be validated, ideally prospectively in an independent larger cohort of CHP patients.

Is it important to be on the lookout and evaluate for PH in CHP? The same issue has perplexed clinicians with regards to IPF. The answer to this depends on what one plans to do with the information. If it is important to the patient and clinician for prognostic purposes, then this might be sufficient to warrant RHC. However, the association of PH with survival in CHP remains uncertain and was not reported in this study [2]. Therefore, although it is likely that PH complicating CHP does impact survival, at present RHC cannot be recommended for prognostic purposes alone, unless in the context of an observational study. Three of the patients had evidence of group 2 PH, and arguably discovery of this provides another target for therapy that might improve patients' functional class and quality of life. At the outset, the investigators did exclude patients with comorbidities (~27%) that could lead to PH. Therefore, in a broader cohort of CHP patients, the prevalence of occult heart failure would probably be higher. One group of patients in whom RHC does appear to be indicated are those who might progress to become lung transplant candidates, since this is important for prognostic and listing purposes, as well as to risk stratify patients in terms of their probable need for cardiopulmonary bypass during the transplant procedure.

Does the demonstrated link between PH and CHP have treatment implications? Certainly therapy for the underlying CHP is integral to not potentiating the cause of the PH. In this regard, removal of the patient from the offending antigen is essential. The role of steroids and other immunomodulating therapies is probably important for any ongoing inflammatory component, but remains uncertain in the context of more advanced fibrotic disease [8]. What of targeting the PH with pulmonary vasoactive agents? The only way this can be answered appropriately is in the context of randomised controlled clinical trials. Whether such a trial will ever be undertaken in CHP is uncertain, but appears unlikely given the prevalence of the disease. However, not all is lost in this regard since it is conceivable that CHP might be an appropriate disease to group together with other forms of pulmonary fibrosis for the implementation of clinical trials of pulmonary vasoactive agents. The inclusion of these patients will hinge on whether CHP is demonstrated to link with other forms of advanced fibrotic lung disease on a final common prognostic course. Although IPF and nonspecific interstitial pneumonia run different courses, in the advanced stages of these diseases their courses appear to converge [9]. Specifically, it has been shown that once the single breath diffusing capacity of the lung for carbon monoxide decreases below the 35% of predicted threshold, the disease prognoses are indistinguishable. Is this because a low diffusing capacity of the lung for carbon monoxide portends the presence of associated PH and at this point PH "trumps" the parenchymal lung disease as the primary driver of outcomes? Does CHP join courses with these other diseases as well, in terms of this final common pathway? If the concept holds true that PH is the driver of outcomes, then should we be implementing studies of pulmonary vasoactive agents in patients with PH from any form of pulmonary fibrosis, including CHP? If a wider net can be cast to include a variety of fibrotic entities with similar disease behaviour then this would certainly facilitate future study recruitment.

OLIVEIRA *et al.* [2] are to be commended for their work in raising the profile of PH complicating yet another form of lung fibrosis. The current study enables another tick box to be marked off to the lingering question of whether PH may complicate any of the broad spectrum of diffuse parenchymal lung diseases.

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