Subtle signs – red flags

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Even the presence of mild chronic lung disease in patients with pulmonary hypertension is associated with worse response to targeted therapy and survival when compared to IPAH http://bit.ly/2IS7rpT

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Pulmonary hypertension (PH) in the context of chronic lung disease (*i.e.* group 3 PH) is an ongoing and unresolved challenge. Looking specifically into precapillary PH, it is evident that its presence in chronic lung disease is associated with increased dyspnoea, reduced exercise tolerance, worsened oxygenation, low diffusion capacity of the lung for carbon monoxide (D_{LCO}) and dismal prognosis. Noteably, pulmonary vascular disease is known to negatively impact clinical outcomes in chronic lung disease, even though the definition of precapillary PH may not yet be fulfilled [1]. *Vice versa*, the presence of mild or subclinical chronic lung disease may impact the course, prognosis and treatment response of patients with precapillary PH. Historically, clinical treatment trials for targeted medications in pulmonary arterial hypertension (PAH) allowed enrolment of patients with some (mild) degree of chronic lung disease, be it COPD, emphysema or interstitial lung disease. The outcome of this specific subpopulation, however, has never been focussed on. Consequently, we are lacking evidence in this subpopulation regarding the clinical disease behaviour and response to therapy.

In this issue of the *European Respiratory Journal*, Lewis *et al.* [2] set out to analyse the impact of "mild" chronic lung disease based on spirometry (forced expiratory volume in 1 s $\geqslant$60% predicted and/or forved vital capacity $\geqslant$70% predicted) and computed tomography (CT)-based radiomorphology on performance and treatment response of patients who were classified as idiopathic PAH (IPAH) or heritable PAH (HPAH) as compared to "true" IPAH/HPAH and to group 3 PH. Utilising the ASPIRE registry data, they identified a large number of PAH patients with mild lung disease or reduced D_{LCO} in isolation who fulfilled the diagnostic criteria of IPAH and who would have been eligible for participation in typical PAH clinical treatment trials. Importantly, Lewis *et al.* [2] demonstrated that in these patients, even signs of mild chronic lung disease had a drastic negative impact on outcome. The survival rates at 1 and 5 years were 95% and 70%, respectively, in patients without parenchymal lung disease compared to 78% and 22% in patients with signs of mild lung disease. Response to PAH therapy was impaired as well, at least when compared to patients with IPAH who had no signs of chronic lung disease. Lewis *et al.* [2] also highlighted a particular phenotype of patients with pre-capillary PH and low D_{LCO} with otherwise normal lung function and without evident lung disease on CT potentially related to tobacco smoke. This phenotype has been described by others before and may correspond to the previously described "vanishing pulmonary capillary syndrome" [3–5], a term that has been coined to describe a particular pulmonary vasculopathy, which involves the loss of small pulmonary vessels that seems to be directly linked to a history of (usually heavy) smoking.

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The study by Lewis *et al.* [2] highlights the necessity to take a closer look on smoking history and chronic lung disease in PAH patients, since even seemingly mild parenchymal abnormalities apparently must be taken as reds flags indicating the presence of a particularly severe, difficult-to-treat and often rapidly fatal condition. The conundrum of chronic lung disease and pulmonary vascular involvement is a field of unresolved and burning questions and high unmet medical need. Clinical trials providing convincing evidence that treating PH in the context of chronic lung disease eventually improves outcomes of patients are lacking. In contrary, some studies have indicated potentially harmful effects of PH medications in this setting [6–8], while others showed promising, albeit modest signals [9]. From the available evidence it appears undisputable that group 3 PH is pathobiologically different from PAH, and therapeutic concepts which work in PAH are not easily transferrable to group 3 PH. Since pulmonary vascular involvement is probably a feature of chronic lung disease from the very beginning, it might be a promising approach to include this aspect in the therapeutic concept as early as possible, but obviously the success of this approach remains the million dollar question.

Conflict of interest: J. Behr reports personal fees for consultancy from Actelion, Bayer and MSD, personal fees for consultancy and lectures from Boehringer Ingelheim and Roche, outside the submitted work. M.M. Hoeper reports personal fees for consultancy and lectures from Actelion, Bayer, MSD and Pfizer, personal fees for consultancy from Acceleron, all outside the submitted work.

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