Mild parenchymal lung disease is still lung disease

To the Editor:

We read with interest the article by Lewis *et al.* [1], which reports an increased mortality in patients with idiopathic pulmonary arterial hypertension (IPAH) and mild impairment in computed tomography (CT). They also show that low diffusing capacity of the lung for carbon monoxide (D_{LCO}) was associated with worse outcomes. It is an important paper pointing out interesting issues on which we would like to comment.

PAH was originally described and classified as a pulmonary vascular disease with specific histopathological pattern: the plexogenic pulmonary arteriopathy, distinguishing it from other causes of pulmonary hypertension (PH). This morphological classification was replaced by a more clinical approach, which is still used presently, although updated classifications still bear the marks of the first attempt to categorise pulmonary vascular disease. Moreover, the term idiopathic refers to the complete absence of identifiable aetiology, including the absence of chronic lung disease (CLD), otherwise referred to CLD-associated PH [2].

Lewis reported a cohort of PAH patients presenting minor or mild lung parenchymal alterations in the group termed $IPAH_{mild\text{-}LD}$. As compared to classical IPAH, this so-called "$IPAH_{mild\text{-}LD}$" patients were characterised by older age (70 *versus* 53 years old); a male predominance (sex ratio of females to males of 3 for IPAH), high tobacco exposure (>80% current smokers), lower exertional capacity and lower D_{LCO}. Contrarily to IPAH, these patients did not respond to specific PAH therapies in terms of walking distance or quality of life, and had a very poor prognosis despite treatment. All these characteristics are highly suggestive of a CLD-PH phenotype rather than IPAH. Indeed, it has been demonstrated that there is no clear correlation between pulmonary function tests (PFTs) and severity of PH in CLD [2]. This discrepancy has been highlighted in combined pulmonary fibrosis and emphysema (CPFE), which usually associates normal or sub-normal volumes and flows on PFTs, very low D_{LCO} and frequent severe PH [3]. Interestingly, CPFE may represent 14% of the cohort of $IPAH_{mild\text{-}LD}$ reported by Lewis *et al.* [1]. We strongly believe that the association of abnormal chest CT with extremely low D_{LCO} in a senior male population exposed to cigarette smoke indicates significant intrinsic lung disease associated with PH.

Therefore, in our opinion, these patients should be considered as having CLD-PH instead of IPAH. In recent years, evidences have surfaced indicating that there exists a specific "pulmonary vascular phenotype" among patients with PH [2], with particular clinical characteristics and different prognosis, suggesting that they are not a continuum with IPAH but a different entity, closer to CLD-PH than IPAH. Patients with the pulmonary vascular phenotype exhibit a low D_{LCO}, which has been shown to be an independent prognostic marker in PAH [4]. Furthermore, Trip *et al.* [5] demonstrated that PAH patients with a D_{LCO} <45% exhibited an atypical phenotype with worse outcome and poor response to PAH-specific therapies. They were mainly older men with history of cigarette exposure. This particular phenotype was also retrieved in other cohorts and interestingly some authors noted that those patients had similarities with CPFE patients in terms of prognosis, lung function, demographic characteristics and toxic exposure [6]. Moreover, similar findings were also found in post-capillary PH, low D_{LCO} being associated with older age, male gender, poor survival, lower blood oxygenation and, again, higher cigarette smoke exposure and higher rate of CT abnormalities [7].

Conversely, it has been shown that patients with COPD and severe PH could also present analogous abnormalities with low D_{LCO} and low arterial carbon dioxide tension for a relatively mild obstructive impairment [8]. It was also recently shown that low D_{LCO} was a prognostic factor of survival in COPD with PH [9]. Similar findings were also retrieved in idiopathic pulmonary fibrosis, with the association of low D_{LCO} with severe PH as a prognostic marker [10]. The presence of a low D_{LCO} in pulmonary vascular

@ERSpublications
PAH patients with mild parenchymal disease/low D_{LCO} should be considered as group 3 patients with pulmonary vascular phenotype https://bit.ly/33awS0J

Cite this article as: Godinas L, Harari S, Barberà JA, *et al.* Mild parenchymal lung disease is still lung disease. *Eur Respir J* 2020; 56: 2003542 [https://doi.org/10.1183/13993003.03542-2020].

diseases suggests an alteration of the alveolo-capillary compartment, with diffusion capacity being determined by the blood capillary volume and the alveolar membrane diffusion components [11]. The pulmonary vascular phenotype could be due to a vanishing capillary pulmonary syndrome [12], where toxic exposure could play a major role as shown in experimental studies in mice, demonstrating that emphysema and PH development are not systematically linked and could occur independently [13]. The characterisation of this phenotype shows that it behaves more like CLD-PH than true IPAH, regarding its epidemiological, radiological, functional and clinical features. Considering this increasing amount of data concerning the pulmonary vascular phenotype in CLD, we agree with Lewis *et al.* [1] in that patients who have traits of lung disease have a phenotype different from IPAH, and therefore should not be considered as having IPAH, despite fulfilling conventional criteria. Clinical trials focused on this particular group of patients is a crucial need. Adequate and early recognition of the pulmonary vascular phenotype is not only a matter of semantics and taxonomy, it is also clinically relevant due to poor response to treatment, and would provide the possibility of avoiding inefficient or harmful treatment, and need for early referral to lung transplantation.

Laurent Godinas [1,2], Sergio Harari [3,4], Joan A. Barberà[5] and David Montani [6,7,8]
[1]Dept of Respiratory Diseases, UZ Leuven, Campus Gasthuisberg, Leuven, Belgium. [2]Laboratory of Respiratory Diseases and Thoracic Surgery (BREATHE), Dept CHROMETA, KU Leuven, Leuven, Belgium. [3]Dept of Clinical Sciences and Community Health, University of Milan, Milan, Italy. [4]Dept of Medical Sciences, Ospedale San Giuseppe, MultiMedica IRCCS, Milan, Italy. [5]Respiratory Institute, Hospital Clinic, August Pi i Sunyer Biomedical Research Institute, University of Barcelona, Barcelona, Spain. [6]Université Paris-Saclay, School of Medicine, Le Kremlin-Bicêtre, France. [7]Assistance Publique - Hôpitaux de Paris (AP-HP), Dept of Respiratory and Intensive Care Medicine, Pulmonary Hypertension National Referral Center, Hôpital Bicêtre, Le Kremlin-Bicêtre, France. [8]INSERM UMR_S 999 Pulmonary Hypertension: Pathophysiology and Novel Therapies, Hôpital Marie Lannelongue, Le Plessis-Robinson, France.

Correspondence: Laurent Godinas, Dept of Respiratory Diseases, UZ Leuven, Campus Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium. E-mail: laurent.godinas@uzleuven.be

Received: 17 Sept 2020 | Accepted: 18 Sept 2020

Acknowledgements: This article was written on behalf of the PHAROS Clinical Research Collaboration members.

Conflict of interest: L. Godinas has nothing to disclose. S. Harari has nothing to disclose. J.A. Barberà has nothing to disclose. D. Montani reports grants and personal fees from Actelion and Bayer, personal fees from GSK, Pfizer, Chiesi and Boehringer, grants, personal fees and non-financial support from MSD, non-financial support from Acceleron, outside the submitted work.

References

1 Lewis RA, Thompson AAR, Billings CG, *et al.* Mild parenchymal lung disease and/or low diffusion capacity impacts survival and treatment response in patients diagnosed with idiopathic pulmonary arterial hypertension. *Eur Respir J* 2020; 55: 2000041.
2 Nathan SD, Barbera JA, Gaine SP, *et al.* Pulmonary hypertension in chronic lung disease and hypoxia. *Eur Respir J* 2019; 53: 1801914.
3 Cottin V, Le Pavec J, Prévot G, *et al.* Pulmonary hypertension in patients with combined pulmonary fibrosis and emphysema syndrome. *Eur Respir J* 2010; 35: 105–111.
4 Chandra S, Shah SJ, Thenappan T, *et al.* Carbon monoxide diffusing capacity and mortality in pulmonary arterial hypertension. *J Heart Lung Transplant* 2010; 29: 181–187.
5 Trip P, Nossent EJ, de Man FS, *et al.* Severely reduced diffusion capacity in idiopathic pulmonary arterial hypertension: patient characteristics and treatment responses. *Eur Respir J* 2013; 42: 1575–1585.
6 Olsson KM, Fuge J, Meyer K, *et al.* More on idiopathic pulmonary arterial hypertension with a low diffusing capacity. *Eur Respir J* 2017; 50: 1700354.
7 Hoeper MM, Meyer K, Rademacher J, *et al.* Diffusion capacity and mortality in patients with pulmonary hypertension due to heart failure with preserved ejection fraction. *JACC Heart Fail* 2016; 4: 441–449.
8 Chaouat A, Bugnet A-S, Kadaoui N, *et al.* Severe pulmonary hypertension and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005; 172: 189–194.
9 Balasubramanian A, Kolb TM, Damico RL, *et al.* Diffusing capacity is an independent predictor of outcomes in pulmonary hypertension associated with COPD. *Chest* 2020; 158: 722–734.
10 Hamada K, Nagai S, Tanaka S, *et al.* Significance of pulmonary arterial pressure and diffusion capacity of the lung as prognosticator in patients with idiopathic pulmonary fibrosis. *Chest* 2007; 131: 650–656.
11 Godinas L, Amar D, Montani D, *et al.* Lung capillary blood volume and membrane diffusion in precapillary pulmonary hypertension. *J Heart Lung Transplant* 2016; 35: 647–656.
12 Hoeper MM, Vonk-Noordegraaf A. Is there a vanishing pulmonary capillary syndrome? *Lancet Respir Med* 2017; 5: 676–678.
13 Seimetz M, Parajuli N, Pichl A, *et al.* Inducible NOS inhibition reverses tobacco-smoke-induced emphysema and pulmonary hypertension in mice. *Cell* 2011; 147: 293–305.