More on idiopathic pulmonary arterial hypertension with a low diffusing capacity

To the Editor:

Pulmonary arterial hypertension (PAH) is defined by the presence of pre-capillary pulmonary hypertension (PH) in the absence of underlying causes such as lung diseases, chronic thromboembolic pulmonary hypertension (CTEPH) or other rare conditions [1, 2]. While the idiopathic form of PAH (IPAH) was originally described as a disease affecting primarily younger women [3, 4], it is now increasingly being diagnosed in elderly patients, many of whom present with cardiopulmonary comorbidities, which can make the exact diagnostic classification of such patients difficult [5–8].

In 2013, Trip *et al.* [9] described a "new" IPAH phenotype of predominantly elderly men with severe pre-capillary PH and a low diffusing capacity of the lungs for carbon monoxide (*D*LCO). Most of these patients had a smoking history but relatively well-preserved lung function, and 32% had normal findings on chest computed tomography (CT). The authors discussed the possibility that their patients may have had a variant of combined pulmonary fibrosis and emphysema (CPFE), a disease characterised by a distinct CT pattern of upper-lobe-predominant emphysema and lower-lobe-predominant fibrosis with relatively well-preserved lung function, low *D*LCO, hypoxaemia and a high prevalence of PH [10, 11]. Like the patients described by Trip *et al.* [9], patients with CPFE are typically elderly men with a history of heavy smoking. The phenotype of the patients described by Trip *et al.* [9] resembled CPFE, but the characteristic CT findings were absent, leading the authors to hypothesise that such patients may have a unique, smoking-related pulmonary vasculopathy. In a more recent paper, our group came to similar conclusions in patients with a low *D*LCO and combined pre- and post-capillary PH because of heart failure with preserved ejection fraction [12].

In the present study, we sought to obtain further data on patients with a clinical diagnosis of IPAH and a low *D*LCO, aiming to identify a well-characterised cohort of patients with pre-capillary PH, low *D*LCO (<45% of the predicted value) and absence of parenchymal lung disease. In a first step, we searched our PH clinic database for patients fulfilling the following criteria: mean pulmonary arterial pressure ⩾25 mmHg, pulmonary arterial wedge pressure ⩽15 mmHg, pulmonary vascular resistance >3 Wood units and *D*LCO <45% of the predicted value. A total of 147 out of 1518 patients (9.7%) fulfilled these criteria. In the next step, the following patients were excluded: 1) patients with clinical and radiological features of pulmonary veno-occlusive disease (PVOD; n=3); 2) patients with chronic thromboembolic pulmonary hypertension (n=12); 3) patients with connective tissue disease, sarcoidosis or Langerhans cell granulomatosis (n=42); and 4) patients with signs of parenchymal lung disease indicated by abnormal chest CT findings and/or by a total lung capacity <80% of the predicted value or a Tiffeneau index <0.7, respectively (n=90). CT scans had been rated as normal by independent radiologists and were re-reviewed by an experienced pneumologist (M.M.H.). Eventually, we identified 22 patients (1.4% of the entire population) with pre-capillary PH fulfilling the diagnostic criteria for IPAH who had no evidence of parenchymal lung disease, but a low diffusing capacity. Thirteen patients with well-characterised CPFE identified from the same database served as the control group. Descriptive statistics, chi-squared tests and two-sided t-tests were used for group comparisons. Kaplan–Meier survival estimates from the date of the first right heart catheterisation were performed for both groups and log rank statistics were used for group comparisons.

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Elderly patients with IPAH, a smoking history and a low *D*LCO may suffer from a distinct pulmonary vasculopathy http://ow.ly/sdGh30dxd0G

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TABLE 1 Patient characteristics

Characteristic	Disease		p-value
	IPAH (n=22)	CPFE (n=13)	
Age years	74±6	72±6	0.389
Gender male	16 (73)	13 (100)	0.039
Smoking habits			
Never smoked	2 (9)	1 (8)	–
Former or current smoker	20 (91)	12 (92)	–
Smoking duration pack-years	50 (35–60)	50 (40–80)	0.103
Cardiovascular comorbidities			
Coronary heart disease	17 (77)	8 (62)	0.319
Hypertension	10 (77)	21 (96)	0.096
Pulmonary function			
FVC % predicted	95±12	85±14	0.029
FEV_1 % predicted	90±11	77±15	0.007
FEV_1/FVC %	76±8	68±10	0.025
RV % predicted	98±9	101±15	0.457
TLC % predicted	94±10	84±9	0.008
RV/TLC %	42±4	44±7	0.379
FRC % predicted	98±12	95±16	0.564
D_{LCO} % predicted	30±8	22±7	0.007
D_{LCO}/V_A % predicted	33±10	27±9	0.050
Blood gas analysis (ambient air)			
P_{aO_2} mmHg	47±8	48±10	0.768
P_{aCO_2} mmHg	32±4	33±5	0.598
S_{aO_2} mmHg	83±10	83±9	0.984
Functional performance			
6-MWD m	228±108	239±82	0.789
WHO functional class			0.832
Class III	18 (82)	11 (85)	
Class IV	4 (18)	2 (15)	
Haemodynamics			
Right atrial pressure mmHg	7±3	7±6	0.966
Mean PAP mmHg	44±10	38±7	0.089
PAWP mmHg	9±4	9±4	0.895
Cardiac output $L \cdot min^{-1}$	4.2±1.3	4.7±1.0	0.274
Cardiac index $L \cdot min^{-1} \cdot m^{-2}$	2.2±0.6	2.3±0.4	0.395
PVR $dyn \cdot s \cdot cm^{-5}$	758±362	550±178	0.062
S_{vO_2} %	62±8	63±8	0.577
Drug treatment for PH			
Phosphodiesterase-5 inhibitors	22 (100)	13 (100)	–
Endothelin receptor antagonists	4 (18)	1 (8)	0.392

Data are presented as n (%), median (interquartile range, Q1–Q3) or mean±SD unless otherwise stated. IPAH: idiopathic pulmonary arterial hypertension; CPFE: combined pulmonary fibrosis and emphysema; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; TLC: total lung capacity; RV: residual volume; FRC: functional residual capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; V_A: alveolar volume; P_{aO_2}: arterial oxygen tension; P_{aCO_2}: arterial carbon dioxide tension; S_{aO_2}: arterial oxygen saturation; 6-MWD: 6-minute walk distance; WHO: World Health Organization; PAP: pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; S_{vO_2}: mixed venous oxygen saturation; PH: pulmonary hypertension.

The patients' characteristics are shown in table 1. Patients in both cohorts were mostly males of advanced age, the majority with a history of heavy smoking and with a high prevalence of hypertension and coronary heart disease. In accordance with our selection criteria, all patients in the IPAH cohort had normal chest CT findings and, except for the low diffusing capacity, normal pulmonary function test results. Still, patients in both cohorts presented with haemodynamic and functional impairment of comparable severity and a similar degree of hypoxaemia.

Medical treatments targeting PH, mostly phosphodiesterase-5 inhibitors, were used in all patients (table 1). Treatment responses after 12 weeks were variable in both cohorts. In patients with IPAH, the 6-min walk

distance declined by −10±105 m; P_{aO_2} dropped by −0.3±6.8 mmHg. The corresponding changes in the CPFE cohort were −19±65 m and −2.1±5.1 mmHg. The World Health Organization functional class improved in only one patient (IPAH), deteriorated in two (both IPAH) and remained unchanged in the remaining patients. No patients developed pulmonary oedema while receiving treatment for PH.

The mortality was high in both groups. Survival rates at 1, 2 and 4 years in the IPAH cohort were 80%, 67% and 38%. The respective survival rates in the CPFE cohort were 64%, 42% and 42%. The difference between both groups was not statistically significant (p=0.894).

Despite the limitations of the present study (small sample sizes, single-centre setting, retrospective analysis, lack of histopathological findings), our data support the hypothesis that there is a subgroup of IPAH patients with a pulmonary phenotype characterised by an advanced age, a history of smoking, absence of parenchymal lung disease but a low diffusing capacity and marked hypoxaemia. These patients share phenotypic features with CPFE patients, except for the normal CT findings. In both cohorts, the vast majority of patients had a history of heavy smoking. It is possible that both patient groups share a common smoking-related pulmonary vasculopathy. The impaired diffusing capacity suggests involvement of capillary and post-capillary vessels as isolated pre-capillary disease is usually associated with a normal or near normal D_{LCO} [9, 13]. PVOD might be considered in these patients, but the normal chest CT findings, in particular the absence of patchy ground glass opacities and septal thickening in all IPAH patients under study, makes this diagnosis unlikely. We believe that our findings may be better explained by a loss of pulmonary capillaries. In accordance with this hypothesis, an experimental study by Seimetz *et al.* [14] showed that mice exposed to tobacco smoke developed pulmonary vascular remodelling including endothelial cell apoptosis with loss of pulmonary capillaries, which preceded the development of emphysema. A similar pulmonary vasculopathy may also be found in patients with PH because of more common smoking-related lung diseases, such as chronic obstructive pulmonary disease, emphysema and some forms of interstitial lung disease.

Future research should provide a more detailed characterisation of patients with PH or PAH and a low diffusing capacity and aim at a better understanding of their pulmonary vasculopathy, including morphometric histopathological studies. We also need to determine how these patients respond to PAH therapies. Finally, we need a term to describe these patients. Pending further data, we propose the descriptive term "smoking-related, low diffusing capacity-PH (SMOLD-PH)".

Karen M. Olsson, Jan Fuge, Katrin Meyer, Tobias Welte and Marius M. Hoeper
Dept of Respiratory Medicine and the German Centre for Lung Research (DZL/BREATH), Hannover Medical School, Hannover, Germany.

Correspondence: M.M. Hoeper, Dept of Respiratory Medicine, Hannover Medical School, Carl-Neuberg-Str. 1, 30625 Hannover, Germany. E-mail: hoeper.marius@mh-hannover.de

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References

1 Galiè N, Humbert M, Vachiery JL, *et al.* 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J* 2015; 46: 903–975.
2 Galiè N, Humbert M, Vachiery JL, *et al.* 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J* 2016; 37: 67–119.
3 Rich S, Dantzker DR, Ayres SM, *et al.* Primary pulmonary hypertension. A national prospective study. *Ann Intern Med* 1987; 107: 216–223.
4 Humbert M, Sitbon O, Chaouat A, *et al.* Pulmonary arterial hypertension in France: results from a national registry. *Am J Respir Crit Care Med* 2006; 173: 1023–1030.
5 Vachiéry JL, Adir Y, Barberà JA, *et al.* Pulmonary hypertension due to left heart diseases. *J Am Coll Cardiol* 2013; 62: Suppl. 25, D100–D108.
6 Hoeper MM, Huscher D, Ghofrani HA, *et al.* Elderly patients diagnosed with idiopathic pulmonary arterial hypertension: results from the COMPERA registry. *Int J Cardiol* 2013; 168: 871–880.
7 Rådegran G, Kjellström B, Ekmehag B, *et al.* Characteristics and survival of adult Swedish PAH and CTEPH patients 2000-2014. *Scand Cardiovasc J* 2016; 50: 243–250.
8 Frost AE, Badesch DB, Barst RJ, *et al.* The changing picture of patients with pulmonary arterial hypertension in the United States: how REVEAL differs from historic and non-US contemporary registries. *Chest* 2011; 139: 128–137.

9 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.
10 Cottin V, Nunes H, Brillet PY, *et al.* Combined pulmonary fibrosis and emphysema: a distinct underrecognised entity. *Eur Respir J* 2005; 26: 586–593.
11 Cottin V, Le Pavec J, Prevot G, *et al.* Pulmonary hypertension in patients with combined pulmonary fibrosis and emphysema syndrome. *Eur Respir J* 2010; 35: 105–111.
12 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.
13 Sun XG, Hansen JE, Oudiz RJ, *et al.* Pulmonary function in primary pulmonary hypertension. *J Am Coll Cardiol* 2003; 41: 1028–1035.
14 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.