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Diffusion capacity and *BMPR2* mutations in pulmonary arterial hypertension

To the Editor:

Pulmonary arterial hypertension (PAH) is a disease in which remodelling of the small pulmonary arteries leads to an increase in pulmonary artery pressure (PAP). The most important genetic predisposing factor related to PAH is a mutation in the bone morphogenetic protein receptor type 2 gene (*BMPR2*) [1, 2]. *BMPR2* mutation carriers are known to present with disease at an earlier age and with worse haemodynamics [3]. We recently showed in a cohort of patients with idiopathic and hereditary PAH that a very low diffusion capacity for carbon monoxide (D_{LCO}) is exclusively found in some of the patients without identified *BMPR2* mutations, whereas *BMPR2* mutation carriers have a relatively preserved D_{LCO} [4]. D_{LCO} is a noninvasive marker of the quality of the alveolar capillary structure [5] and the observed difference in D_{LCO} supports the hypothesis that distinct vascular disease processes are at play in *BMPR2* mutation-related PAH and non *BMPR2* mutation-related idiopathic PAH. Until recently, insufficient availability of lung samples has prohibited the performance of a detailed comparison of the pulmonary vascular pathologies in these two disease groups [6]. Therefore, we sought, in the present study, to confirm the previously found influence of *BMPR2* mutations on diffusion capacity in a much larger multinational patient cohort.

We performed a retrospective collaborative study at the VU University Medical Center in Amsterdam, the Netherlands and the Université Paris-Sud, Assistance Publique Hôpitaux de Paris, Le Kremlin-Bicêtre, France. Patients were eligible for this study when classified in the database with idiopathic or familial PAH, and when the results from *BMPR2* mutation analysis and D_{LCO} measurements were available. Patients were diagnosed with idiopathic PAH according to current clinical guidelines [7]. Familial PAH was diagnosed when at least one family member had confirmed PAH. Patients with a family history of PAH and no mutations identified in the *BMPR2* gene were not included in this study. In total 64 patients were selected from the Dutch idiopathic and familial PAH population and 85 patients were drawn from the French population. Comorbidities of all these patients were reviewed, as was the amount of tobacco exposure. In addition, patients were reassessed for the likelihood of pulmonary veno-occlusive disease (PVOD). Patients were excluded when they had a tobacco exposure >20 pack-years or a medical history mentioning

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pulmonary embolism, tuberculosis, lobectomy, bronchiectasis, interstitial lung disease, sarcoidosis, chronic obstructive pulmonary disease (COPD) or atrial septum defect. In addition, patients with suspected portopulmonary hypertension were excluded, as were patients who had a forced expiratory volume in 1 s (FEV_1) or forced vital capacity (FVC) <60% of predicted or were highly likely to have PVOD [8].

General characteristics, medical history and smoking history were taken from the patient's clinical record. Spirometry, bodyplethysmography, and single-breath *D*LCO were measured in accordance with the European Respiratory Society guidelines [5, 9]. *D*LCO was corrected for haemoglobin level (*D*LCOc). Right heart catheterisation (RHC) was performed at the same time point as the pulmonary function test in the majority of patients. In the remaining patients RHC results closest to the pulmonary function test date were taken. Cardiac output was indexed for body surface area (CI). Total pulmonary vascular resistance (TPVR) was calculated as 80 times mean PAP (mPAP) divided by cardiac output.

From the 149 PAH patients initially selected for analysis, 45 patients were excluded after a revision of patient characteristics due to the presence of factors affecting the *D*LCO measurement or because a diagnosis other than idiopathic PAH was likely (fig. 1a). *D*LCO measurements had been performed within 3 weeks from diagnosis in 46% of patients and within 1 year from diagnosis in another 32%.

No differences were observed in mutation carriers and non-mutation carriers for age at diagnosis (41±14 *versus* 42±17 years for *BMPR2*, respectively; p=0.99), sex (74 *versus* 76% females, respectively; p=0.87) or smoking history (31 *versus* 46%, respectively; p=0.16). RHC was performed within 1 week from the *D*LCO measurement in 88% of the patients. *BMPR2* mutation carriers had a lower CI when compared with non-carriers (mean±SD: 2.4±0.7 *versus* 3.1±1.3 $L \cdot min^{-1} \cdot m^{-2}$, respectively; p=0.001) and higher TPVR (1135±367 *versus* 949±431 $dyn \cdot s^{-1} \cdot cm^{-5,}$ respectively; p=0.02). *BMPR2* mutation carriers and non-carriers had similar mPAP (55±11 *versus* 56±17 mmHg, respectively; p=0.59), similar mean right atrial pressure (8±5 *versus* 8±5 mmHg, respectively; p=0.84) and similar mixed venous oxygen saturation (62±9 *versus* 66±8%, respectively; p=0.06). Pulmonary function test results showed no differences in total lung capacity between *BMPR2* mutation carriers and non-carriers (100±13 *versus* 96±14% pred, respectively; p=0.16) or Tiffeneau index (FEV_1/FVC 79±10 *versus* 80±9%; respectively; p=0.54). However, *BMPR2* mutation carriers showed a more preserved FEV_1 (98±18 *versus* 90±15% pred, respectively; p=0.01) and FVC (102±19 *versus* 93±17% pred, respectively; p=0.03). In a subgroup analysis of patients with no smoking history (25 *BMPR2* mutation carriers *versus* 30 non-carriers), no difference in FEV_1 (98±17 *versus* 92±13% pred, respectively; p=0.23) or FVC and FVC (99±20 *versus* 96±165% pred, respectively; p=0.76) was observed. Figure 1b shows *D*LCOc according to the presence of a *BMPR2* mutation. *D*LCOc was significantly lower in *BMPR2* wild-type patients (mutation non-carriers) and this difference remained after the exclusion of current and ex-smokers (fig. 1c).

Our investigation shows that *D*LCO is more preserved in *BMPR2*-mutation carriers compared to non-carriers, despite a worse haemodynamic profile. This finding suggests either differences in ventilation/perfusion distribution or differences in alveolar–capillary structures between *BMPR2* mutation carriers and non-carriers. Disturbed airflow or ventilatory patterns are unlikely to explain the lower *D*LCO in *BMPR2* wild-type patients, as patients with emphysema and obstructive airway disease were excluded from the present study and differences between groups remained present after exclusion of current or ex-smokers. A greater reduction in *D*LCO in *BMPR2* wild-type patients may have resulted from thickening of the alveolar capillary membrane due to early interstitial fibrosis, subclinical parenchymal lung disease or occult left ventricular dysfunction [10]. However, all patients were included based on precapillary pulmonary hypertension, meticulously confirmed by RHC and patients with post-capillary pulmonary hypertension or lung parenchymal diseases, diagnosed on pulmonary function tests or high-resolution computed tomography of the chest, were excluded from the study.

Reductions in *D*LCO have been reported in PVOD, a rare form of pulmonary hypertension characterised by predominant venous involvement associated with capillary proliferation [8]. However, pulmonary venous involvement is unlikely to explain the observed differences, because patients with clinical or radiological presentation that were compatible with PVOD were carefully excluded from this study. Higher *D*LCO values in *BMPR2* mutation carriers may also follow an increased capillary blood volume. In the presence of a higher TPVR, this could result from an increased bronchial flow through bronchopulmonary anastomoses or from an increased collateral flow, through intrapulmonary collateral vessels, in *BMPR2* mutation carriers.

To conclude, we found that *D*LCO was lower in PAH patients without identified *BMPR2* mutations, a finding not related to the differences in airflow obstruction or smoking history. As such, a distinct vascular disease process is suggested in *BMPR2* mutation carriers. Further pathological studies of PAH lungs should systematically analyse pulmonary vascular characteristics in order to demonstrate whether significant pathological differences exist between *BMPR2* mutation carriers and non-carriers.

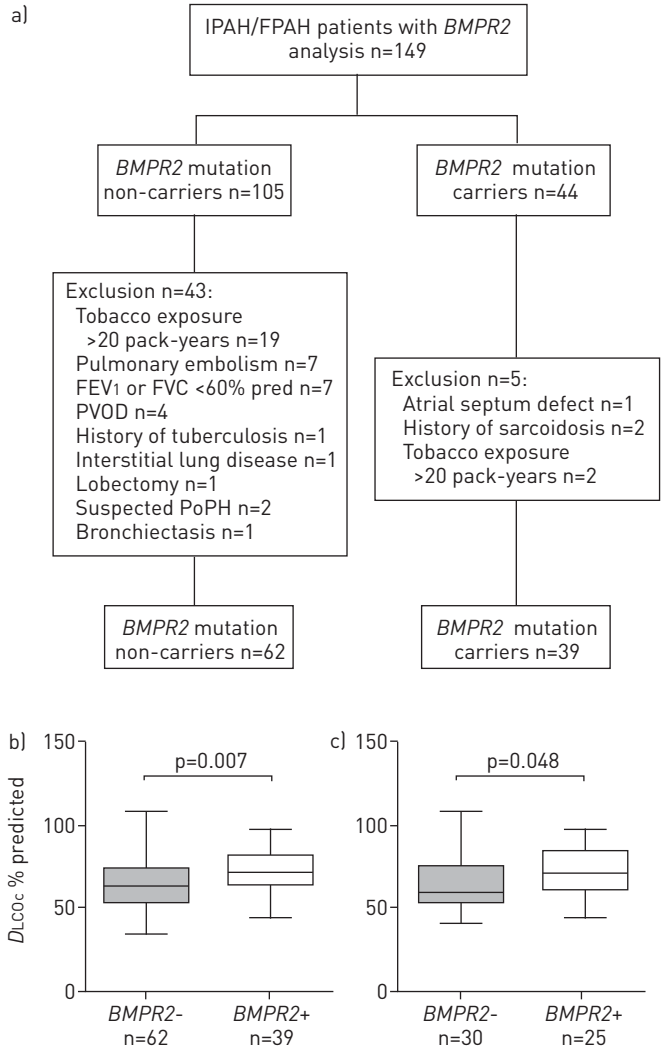

FIGURE 1 a) Inclusion flowchart of idiopathic pulmonary arterial hypertension (IPAH) and familial PAH (FPAH) patients with bone morphogenetic protein receptor type 2 (*BMPR2)* mutation analysis. In total 149 IPAH/FPAH patients with both *BMPR2* mutation analysis and a measurement of diffusion capacity were included for analysis. Factors that were considered to affect diffusion capacity were exclusion criteria as were factors that made a diagnosis other than IPAH more likely. In total 45 IPAH/FPAH patients were excluded. The selected study population consisted of 62 *BMPR2* non-carriers and 39 *BMPR2* carriers. b) Diffusion capacity for carbon monoxide corrected for haemoglobin levels (D_{LCOc}) presented as percentage of predicted according to the presence of a *BMPR2* mutation. D_{LCOc} is significantly lower in *BMPR2* non-carriers. c) The reduction in D_{LCOc} in *BMPR2* non-carriers is still present when only PAH patients without a smoking history were selected. FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; PVOD: pulmonary veno-occlusive disease; PoPH: portopulmonary hypertension; COPD: chronic obstructive pulmonary disease.

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A distinct vascular disease process is suggested in *BMPR2* mutation carriers http://ow.ly/q5XQL

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Verrucous carcinoma of the tracheobronchial tree: an underdiagnosed entity?

To the Editor:

Verrucous carcinomas, first described by ACKERMANN [1] in 1948, are rare, well-differentiated squamous cell carcinomas in the oropharynx [2], larynx [2–4] and oesophagus [5], and seem to be associated with Human papilloma virus (HPV) infections [6]. Macroscopically, they have a warty appearance and may easily be mistaken for papillomas [4]. Surprisingly, although found in the larynx, there are no descriptions of this tumour in the tracheobronchial tree.

A 74-year-old male with a history of chronic obstructive pulmonary disease and former smoking was admitted for increasing shortness of breath. On clinical investigation he had a subfebrile temperature (38.2°C) and dry rales. Chest radiography showed discrete infiltrates in the right lower lobe. Lung function testing revealed an obstructive flow–volume loop with a forced expiratory volume in 1 s (FEV_1)/forced vital capacity ratio of 32% and a FEV_1 of 1.1 L (37% predicted).

Although anti-obstructive treatment was intensified using inhaled β-adrenergics, steroids and antibiotic treatment (ampicillin/sulbactam), the dyspnoea did not improve. On bronchoscopy, the distal trachea was shown to be infiltrated by a wart-like tumour obstructing ~70% of the cross sectional area (fig. 1). The tumour was partly removed during rigid bronchoscopy and partly destroyed by Nd:YAG (neodymium-doped yttrium aluminum garnet) laser and cryotherapy.

As the features of the tumour raised the suspicion of squamous cell carcinoma, the patient was referred to the department of radiation oncology for radiation therapy. Histological examination of the tumour specimens revealed a papillary hyperplastic squamous epithelium without cell abnormalities. Ki-67 and p63 immunostaining showed a slightly increased proliferation rate in the middle layer of the epithelium. *In situ* hybridisation for the detection of HPV serotypes 1, 6, 7, 16, 18 and 31 showed evidence of previous HPV infection.

DNA image cytometry was performed in order to distinguish between hyperplastic and neoplastic lesions. Feulgen staining identified DNA contents in multiples of two in the euploid cells. In addition, stem lines at odd multiples (2.5c and 5c) could be found.