Chapter 7

Diffusion capacity and \textit{BMPR2} mutations in pulmonary arterial hypertension

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\textit{Eur Respir J} 2014; 43: 1195-8
To the editors:

Pulmonary arterial hypertension (PAH) is a disease in which remodeling 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 hemodynamics.\(^3\) We recently showed in a cohort of patients with idiopathic and hereditary PAH that a very low diffusion capacity for carbon monoxide (DLCO) is exclusively found in some of the patients without identified BMPR2 mutations, whereas BMPR2 mutation carriers have a relatively preserved DLCO.\(^4\) DLCO is a non-invasive marker of the quality of the alveolar-capillary structure\(^5\) and the observed difference in DLCO 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 (Netherlands) and the Université Paris-Sud, Assistance Publique Hôpitaux de Paris, in 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 DLCO 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 family history of PAH and no mutations identified in 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 pulmonary embolism, tuberculosis, lobectomy, bronchiectasis, interstitial lung disease, sarcoidosis, COPD or atrial septum defect. In addition, patients with suspected portopulmonary hypertension were excluded, as were patients who had a forced expiratory volume
FIGURE 7.1. (right page) **A. Inclusion flowchart of idiopathic and familial PAH (I/FPAH) patients with BMPR2 mutation analysis.** In total 149 I/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 idiopathic PAH more likely. In total 45 I/FPAH patients were excluded. The selected study population consisted of 62 BMPR2 non-carriers and 39 BMPR2 carriers. **B. Diffusion capacity corrected for hemoglobin levels (DLCOc) presented as percentage of predicted according to the presence of a BMPR2 mutation.** DLCOc is significantly lower in BMPR2 non-carriers. **C.** The reduction in DLCOc in BMPR2 non-carriers is still present when only PAH patients without a smoking history were selected.


in one second (FEV1) 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 DLCO were measured in accordance with the European Respiratory Society guidelines.⁴⁵ DLCO was corrected for hemoglobin level (DLCOc). Right heart catheterization (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 DLCO measurement or because a diagnosis other than idiopathic PAH was likely (see inclusion flowchart, FIGURE 7.1a). DLCO measurements had been performed within 3 weeks from diagnosis in 46% of patients and within one year from diagnosis in another 32%.

No differences were observed in age at diagnosis (41±14 vs. 42±17 years for BMPR2 mutation carriers and non-carriers, respectively, p = 0.99), gender (74% vs. 76% females, p = 0.87) or smoking history (31% vs. 46%, p = 0.16). RHC was performed within one week from DLCO measurement in 88% of the patients. BMPR2 mutation carriers had a lower cardiac index (CI: 2.4±0.7 vs. 3.1±1.3 L/min/m², p = 0.001) and higher TPVR (1135±367 vs. 949±431 dyn-s-cm⁻⁵, p = 0.02). BMPR2 mutation carriers and non-carriers had similar mPAP (55±11 vs. 56±17 mmHg, p = 0.59), similar mean right atrial pressure (mRAP: 8±5 vs. 8±5 mmHg, p = 0.84) and similar mixed venous oxygen saturation (SvO2: 62±9 vs.
A. Inclusion flowchart

I/FPAH patients with BMPR2 analysis
N = 149

BMPR2 mutation non carriers
N = 105

Exclusion (N=40):
19 Tobacco exposure >20 PY
7 Pulmonary embolism
7 FEV1 or FVC <60% of pred
4 PVD
1 History of tuberculosis
1 Interstitial lung disease
1 Lobectomy
2 Suspected PPH
1 Bronchiectasis
1 Severe COPD

BMPR2 mutation carriers
N = 44

Exclusion (N=5):
1 Atrial septum defect
2 History of sarcoidosis
2 Tobacco exposure >20 PY

BMPR2 mutation non carriers
N = 62

BMPR2 mutation carriers
N = 39

B. Total selection

C. Non-smoking

DLC0c (% of pred)

p 0.007

p 0.048

BMPR2-
N=62

BMPR2+
N=39

BMPR2-
N=30

BMPR2+
N=25
66±8%, p = 0.06). Pulmonary function test results showed no differences in total lung capacity (TLC: 100±13 vs. 96±14% of predicted, p = 0.16) or Tiffeneau index (FEV1/FVC: 79±10 vs. 80±9%, p = 0.54). However, BMPR2 mutation carriers showed a more preserved FEV1 (98±18 vs. 90±15% of predicted, p = 0.01) and FVC (102±19 vs. 93±17% of predicted, p = 0.03). In a subgroup analysis of patients with no smoking history (25 BMPR2 mutation carriers vs. 30 non-carriers), no difference in FEV1 or FVC was observed (FEV1: 98±17 vs. 92±13% of predicted, p = 0.23 and FVC: 99±20 vs. 96±16, p = 0.76). FIGURE 7.1b shows DLCOc according to the presence of a BMPR2 mutation. DLCOc was significantly lower in BMPR2 wild type patients (mutation non-carriers) and this difference remained after exclusion of current and ex-smokers (FIGURE 7.1c).

Our investigation shows that DLCO is more preserved in BMPR2 mutation carriers compared to non-carriers, despite a worse hemodynamic 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 DLCO 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 DLCO 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. 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 CT of the chest, were excluded from the study.

Reduction in DLCO has been reported in PVOD, a rare form of pulmonary hypertension characterized by predominant venous involvement associated with capillary proliferation. However, pulmonary venous involvement is unlikely to explain the observed differences because patients with clinical or radiological presentation compatible with PVOD were carefully excluded from this study. Higher DLCO 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 DLCO was lower in PAH patients without identified BMPR2 mutations, which finding was not related to differences in airflow obstruction or smoking history. As such, a
distinct vascular disease process is suggested in \textit{BMPR2} mutation carriers. Further pathological studies of PAH lungs should systematically analyze pulmonary vascular characteristics in order to demonstrate whether significant pathological differences exist between \textit{BMPR2} mutation carriers and non-carriers.
REFERENCES


