JACC: HEART FAILURE
VOL. 4, NO. 6, 2016

ISSN 2213-1779/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jchf.2015.12.016

Diffusion Capacity and Mortality in Patients With Pulmonary Hypertension Due to Heart Failure With Preserved Ejection Fraction

Marius M. Hoeper, MD, Katrin Meyer, MD, Jessica Rademacher, MD, Jan Fuge, MPH, Tobias Welte, MD, Karen M. Olsson, MD

ABSTRACT

OBJECTIVES This study sought to investigate the prognostic importance of a low diffusion capacity of the lung for carbon monoxide (DLCO) in patients with a catheter-based diagnosis of pulmonary hypertension due to heart failure with preserved ejection fraction (PH-HFpEF).

BACKGROUND In patients with pulmonary arterial hypertension, a low DLCO is associated with poor outcome. It is unclear whether the same is true in patients with PH-HFpEF.

METHODS This study retrospectively analyzed clinical characteristics, smoking history, lung function measurements, chest computed tomography, hemodynamics, and survival in 108 patients with PH-HFpEF. The presence of post-capillary PH was determined by right heart catheterization. Patients with moderate or severe lung function abnormalities were excluded.

RESULTS On the basis of previous studies and receiver-operating characteristic curve analysis, the study cohort was divided into patients with a DLCO <45% of the predicted value ($DLCO_{<45\%}$, low DLCO; n = 52) and patients with a DLCO ≥45% of the predicted value ($DLCO_{\geq 45\%}$; n = 56). $DLCO_{<45\%}$ was associated with male sex (odds ratio [OR]: 2.71; 95% confidence interval [CI]: 1.05 to 6.99; p = 0.039) and smoking history (OR: 5.01; 95% CI: 1.91 to 13.10; p < 0.001). There were no correlations between DLCO and other lung function parameters and hemodynamics. Compared with patients with $DLCO_{\geq 45\%}$, patients with $DLCO_{<45\%}$ had a significantly worse outcome (survival rate at 3 years 36.5% vs. 87.8%, p < 0.001 by log-rank analysis). Cox proportional hazard analysis identified $DLCO_{<45\%}$ as an independent predictor of death (hazard ratio: 6.6; 95% CI: 2.6 to 16.9; p < 0.001).

CONCLUSIONS In patients with PH-HFpEF, a low DLCO is strongly associated with mortality. (J Am Coll Cardiol HF 2016;4:441-9) © 2016 by the American College of Cardiology Foundation.

Heart failure with preserved ejection fraction (HFpEF) is characterized by normal contractility but increased wall stiffness of the left ventricle resulting in elevated left-sided filling pressures at rest and/or during exercise (1-4). HFpEF has become a leading cause of congestive heart failure that predominantly affects elderly patients (5,6). Risk factors include age, hypertension, coronary heart disease, obesity, and diabetes (5). At least 50% of patients with HFpEF develop pulmonary hypertension (PH) (2,7,8), which presents either as isolated post-capillary PH or as post-capillary PH with a pre-capillary component (9,10). The development of PH in patients with HFpEF (PH-HFpEF) is associated with increased mortality (2,7,8).

From the Department of Respiratory Medicine and German Center of Lung Research (DZL/BREATH), Hannover Medical School, Hannover, Germany. The study was funded by the German Center of Lung Research (BREATH/DZL). Dr. Hoeper has received speakers fees and honoraria for consultations from Actelion, Bayer, GlaxoSmithKline, and Pfizer. Dr. Meyer has received speakers fees from GlaxoSmithKline. Dr. Olsson has received speakers fees from Actelion, Bayer, GlaxoSmithKline, Pfizer, and United Therapeutics. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received November 12, 2015; revised manuscript received December 7, 2015, accepted December 22, 2015.

JACC: HEART FAILURE VOL. 4, NO. 6, 2016
JUNE 2016:441–9

ABBREVIATIONS AND ACRONYMS

CI = confidence interval

CT = computed tomography

DLCO = diffusion capacity for carbon monoxide

HFpEF = heart failure with preserved ejection fraction

IPAH = idiopathic pulmonary arterial hypertension

IQR = interquartile range

NT-proBNP = N-terminal fragment of pro-B-type natriuretic peptide

OR = odds ratio

PH = pulmonary hypertension

PVR = pulmonary vascular resistance

The pathogenesis of PH in patients with HFpEF is incompletely understood. It is self-evident that a rise in left-sided filling pressures and the pulmonary venous system translates directly into elevated pulmonary arterial pressures, in other words, isolated post-capillary PH. What is unclear is why some patients develop a significant pre-capillary component, as indicated by a diastolic pressure gradient >7 mm Hg and a pulmonary vascular resistance (PVR) >240 dyn·s·cm^{-5} (11). It has been hypothesized that these patients may develop an angioproliferative pulmonary vasculopathy similar to what is seen in patients with pulmonary arterial hypertension (9). Histological confirmation of this hypothesis, however, is lacking.

The diffusion capacity of the lung for carbon monoxide (DLCO) is increasingly recognized as an important diagnostic and prognostic variable in patients with pulmonary vascular disease (12). In idiopathic pulmonary arterial hypertension (IPAH), DLCO is usually normal or moderately impaired (13,14), but a subgroup of these patients presents with a low DLCO (<45% of the predicted value), and these patients have a particularly high mortality (15). Similar findings have been reported in patients with chronic lung disease and PH (16–18).

SEE PAGE 450

Little is known about the role of DLCO in patients with PH-HFpEF. In a recent study assessing predictors of mortality in these patients, a DLCO <35% of the predicted value was associated with increased mortality, whereas a DLCO ≥65% of the predicted value was associated with a survival benefit (19). Other than that, there are sparse data on the role of DLCO measurements in this patient population. The present study was conducted to further evaluate the distribution of DLCO measurements in patients with PH-HFpEF, factors associated with a low DLCO, and the prognostic importance of a low DLCO in this patient population.

METHODS

This retrospective study enrolled consecutive patients diagnosed at our center with PH-HFpEF between June 1, 2008, and December 31, 2014. Follow-up ended June 10, 2015.

Patients with a final diagnosis of PH-HFpEF were eligible for analysis if they fulfilled the following criteria: 1) a catheter-based diagnosis of post-capillary PH as indicated by a mean pulmonary artery pressure ≥25 mm Hg and a pulmonary artery wedge pressure >15 mm Hg; 2) echocardiography showing normal or near normal systolic left ventricular function as indicated by a left ventricular EF ≥50%, signs of diastolic dysfunction including left ventricular hypertrophy, abnormalities in mitral inflow patterns, an enlarged left atrium, and no more than mild valvular heart disease; 3) exclusion of significant lung or airway disease by normal or near normal pulmonary function test results including a forced vital capacity ≥70% predicted and a forced expiratory capacity in 1 s ≥60% predicted; and 4) exclusion of chronic thromboembolic pulmonary hypertension by ventilation/perfusion scintigraphy, and pulmonary angiography, if necessary. All assessments were done in stable and compensated patients who presented without clinically overt heart failure.

All patients provided written informed consent, and the study was approved by the local ethics committee.

RIGHT HEART CATHETERIZATION. All patients underwent right heart catheterization with determination of right atrial pressure; systolic, diastolic, and mean pulmonary artery pressure; and pulmonary arterial wedge pressure because of suspected severe PH. Cardiac output was determined by thermodilution. PVR, cardiac index, and diastolic pressure gradient were calculated by standard formula. Mixed venous oxygen saturation was determined from pulmonary artery blood samples. The date of PH-HFpEF diagnosis was defined as the date of the first right heart catheterization showing PH.

PULMONARY FUNCTION TESTS, DLCO MEASUREMENTS AND SMOKING STATUS. Spirometry and body plethysmography were used to determine total lung capacity, forced vital capacity, forced expiratory capacity in 1 s, and the ratio between residual volume and total lung capacity (20). DLCO was measured by the single-breath technique and corrected for hemoglobin values in accordance with recommendations from the European Respiratory Society (21). All measurements were made within 4 weeks of the right heart catheterization, usually during the same hospital stay. The patient's smoking status was assessed from medical files or by phone calls to patients or their relatives, respectively.

COMPUTED TOMOGRAPHY. Computed tomography (CT) scans were not part of the standard diagnostic assessments in the present patient population. However, the hospital's archives and medical files were searched for CT images or CT reports, which were reviewed for the presence of fibrotic or emphysematous changes. Pathological findings were graded as mild, moderate, or severe according to on-site review