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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.

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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).

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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

of available images or according to written reports. In accordance with a recent paper by Trip et al. (15), mild emphysema was defined by subtle emphysematous changes confined to the apical lung segments; moderate emphysema was defined by more extensive emphysematous changes, predominantly in the upper lobes; and severe emphysema was defined by extensive emphysematous changes in the upper and lower lobes of both lungs. Mild fibrosis was defined by focal reticular opacities confined to the subpleural spaces of the lower lungs; moderate fibrosis was defined by more continuous reticular opacities restricted to either upper or lower lobes; and severe fibrosis was defined by extensive fibrotic patterns affecting all parts of the lungs (15).

BLOOD GASES AND LABORATORY ANALYSIS. Experienced technicians obtained arterialized capillary blood gases from earlobes after a resting period ≥10 min while patients were breathing room air (22). The blood samples were analyzed without delay using a standard device (Radiometer, Copenhagen, Denmark).

Routine laboratory assessments were done in all patients at the time of right heart catheterization.

STATISTICAL ANALYSIS. The IBM SPSS Statistics (version 22.0, IBM Corp., Armonk, New York) and STATA (version 13.0, StataCorp, College Station, Texas) statistical software programs were used to analyze the data. Categorical variables are shown as numbers (n) and percentages (%). Continuous variables are shown as mean ± SD, unless indicated otherwise. On the basis of a previous study in patients with IPAH, a DLCO cutoff value of 45% was used to divide the study cohort into patients with a DLCO below 45 of the predicted value ($DLCO_{<45\%}$, also referred to herein as low DLCO) and patients with a DLCO equal to or above 45% of the predicted value ($DLCO_{\geq 45\%}$) (15). For comparisons of these 2 patient populations, Fisher exact test, chi-square test, Mann-Whitney *U* test, or 2-sided paired *t* test were used as appropriate.

In order to identify the DLCO level with the highest power to discriminate between survivors and nonsurvivors, receiver-operating characteristic curves were drawn and the area under the curve was calculated. The cutoff value that resulted in the highest product of sensitivity and specificity was considered the best DLCO value for prognostication. The asymptotic 95% confidence interval (CI) as well as the asymptotic p value under the null hypothesis that the true area = 0.5 were calculated using a nonparametric method.

Determinants of variables associated with a $DLCO_{<45\%}$ were identified by logistic regression analysis with the use of the following variables: sex; coronary heart disease; diabetes; and smoking status (ever smokers vs. never smokers). Associations between DLCO and clinical/hemodynamic variables were assessed by Pearson correlation analysis and 2-sided testing for significance.

Kaplan-Meier estimates on survival were made for the whole group and the 2 DLCO groups, and the survival estimates of the $DLCO_{<45\%}$ and the $DLCO_{\geq 45\%}$ group were compared by log-rank analyses.

Simple Cox regression analysis was performed to identify predictors of death. Variables with a p value of <0.1 were tested in a stepwise forward Cox regression analyses. A second Cox regression analysis was performed with the same variables except for the DLCO, which was dichotomized into the $DLCO_{<45\%}$ group and the $DLCO_{\geq 45\%}$ group. P values <0.05 were considered statistically significant for all analyses. Variables with more than 30% missing values were excluded from the regression analyses, with the exception of N-terminal fragment of pro-B-type natriuretic peptide (NT-proBNP), which was included with missing values imputed based on the group median.

RESULTS

PATIENTS. On December 31, 2014, our database contained 1,054 patients with various forms of PH. From this database we identified 115 patients with post-capillary PH who fulfilled the inclusion and exclusion criteria described. Seven of these patients were excluded because the survival status could not be ascertained. Thus, 108 patients with a diagnosis of PH-HFpEF were eligible for the present analysis.

As shown in **Table 1**, the patients were characterized by an average age of 72 years; a well-preserved left ventricular EF; and a high prevalence of hypertension, diabetes mellitus, coronary heart disease, and atrial fibrillation. Except for the DLCO, lung function tests were normal or nearly normal in all patients. By definition, right heart catheterization showed post-capillary PH in all patients. All but 1 patient had a pre-capillary component to their PH, as indicated by a diastolic pressure gradient >7 mm Hg and a PVR >240 $dyn \cdot s \cdot cm^{-5}$.

Figure 1 shows the distribution of DLCO measurements. The average DLCO was moderately impaired (49% of the predicted value). Twenty percent of the patients presented with a normal DLCO (>70% of the predicted value).

Patients in the $DLCO_{<45\%}$ group were more often male and on average 3 years older than patients in the $DLCO_{\geq 45\%}$ group (**Table 1**). They had a slightly lower

TABLE 1 Patient Characteristics at the Time of the First Right Heart Catheterization

	PH-HFpEF (Whole Group)	$DLCO_{<45\%}$	$DLCO_{\geq 45\%}$	p Value $DLCO_{<45\%}$ vs. $DLCO_{\geq 45\%}$
Number of patients	108	52 (48)	56 (52)	–
Age, yrs	72 ± 7	74 ± 7	71 ± 7	0.049
Female	61 (57)	20 (38)	41 (73)	<0.001
Body mass index, kg/m^2	30 ± 5	29 ± 5	31 ± 5	0.033
Comorbid conditions				
Diabetes mellitus	47 (44)	27 (52)	20 (36)	0.066
Systemic hypertension	90 (83)	42 (81)	48 (86)	0.333
Coronary heart disease	57 (53)	34 (65)	23 (41)	0.010
Atrial fibrillation	67 (62)	28 (54)	39 (70)	0.068
Exercise capacity				
NYHA functional class II/III/IV	4/98/6	1/46/5	3/52/1	0.055
6-min walking distance, m, n = 106	269 ± 112	249 ± 116	289 ± 106	0.065
Hemodynamics and NT-proBNP				
Heart rate, beats/min	74 ± 15	71 ± 16	76 ± 15	0.085
Right atrial pressure, mm Hg	12 ± 5	11 ± 6	12 ± 5	0.540
PAPm, mm Hg	45 ± 10	46 ± 10	45 ± 11	0.703
PAPsyst, mm Hg	73 ± 19	76 ± 15	71 ± 22	0.154
PAPdiast, mm Hg	29 ± 7	29 ± 7	28 ± 7	0.776
PAWP, mm Hg	19 ± 3	19 ± 4	19 ± 3	0.951
Diastolic pressure gradient, mm Hg	10 ± 7	10 ± 6	10 ± 7	0.795
CO, l/min, n = 98	4.3 ± 1.1	4.3 ± 1.0	4.2 ± 1.3	0.776
Cardiac index, l/min/m^2, n = 98	2.5 ± 0.6	2.6 ± 0.7	2.5 ± 0.6	0.674
PVR, dyn·s·cm^{-5}, n = 98	537 ± 216	552 ± 200	524 ± 233	0.536
SVR, dyn·s·cm^{-5}, n = 74	1,701 ± 492	1,717 ± 535	1,685 ± 451	0.779
SvO_2, %, n = 74	64 ± 6	64 ± 6	64 ± 6	0.922
Laboratory variables				
NT-proBNP, ng/l, n = 63	2,678 ± 1895	2,988 ± 2,209	2,430 ± 1,591	0.249
NT-proBNP, ng/l, n = 63	2,097 (1,395–3,577)	2,538 (1,466–3,741)	1,911 (1,395–3,405)	0.326
GFR, ml/min, n = 73	52 ± 13	52 ± 15	53 ± 12	0.602
Bilirubin, µmol/l, n = 71	16 ± 11	15 ± 13	17 ± 10	0.346
Hemoglobin, g/dl	14 ± 2	14 ± 2	14 ± 2	0.783
Echocardiographic findings				
LVEF, %	58 ± 4	58 ± 5	58 ± 4	0.959
LA diameter, mm, parasternal long-axis view, n = 102	43 ± 7	44 ± 7	42 ± 6	0.292
LVEDD, mm, parasternal long-axis view, n = 97	46 ± 5	46 ± 5	46 ± 5	0.668
RVEDD, mm, apical 4-chamber view, n = 93	44 ± 8	44 ± 9	43 ± 7	0.692
TAPSE, mm, n = 60	19 ± 10	21 ± 13	17 ± 4	0.098
Diastolic E/e′, n = 54	15 ± 7	14 ± 7	14 ± 6	0.303
Blood gas analysis and pulmonary function				
PaO_2, mm Hg	62 ± 12	58 ± 10	66 ± 12	0.002
SaO_2, %	92 ± 4	91 ± 5	93 ± 3	0.005
$PaCO_2$, mm Hg	37 ± 5	36 ± 5	38 ± 4	0.037
TLC, % pred	89 ± 13	87 ± 13	90 ± 13	0.399
FVC, % pred	86 ± 14	87 ± 16	84 ± 13	0.270
FEV_1, % pred	73 ± 12	73 ± 12	73 ± 12	0.919
RV/TLC, %	47 ± 9	47 ± 7	48 ± 11	0.533
DLCO, % pred	49 ± 22	30 ± 9	66 ± 17	<0.001

Continued on the next page

body mass index, a higher incidence of coronary heart disease, and a nonsignificant trend toward a higher incidence of diabetes. Lung function parameters were almost identical in the 2 groups, whereas blood gas analysis showed more severely impaired oxygenation in the $DLCO_{<45\%}$ group. Hemodynamics and laboratory variables including NT-proBNP levels did not differ between the 2 cohorts. Patients in the $DLCO_{<45\%}$ group had a more frequent smoking history and a higher number of pack years (Table 1).

ROC ANALYSIS. According to receiver-operating characteristic analysis, DLCO at 45% of the

TABLE 1 Continued

	PH-HFpEF (Whole Group)	$DLCO_{<45\%}$	$DLCO_{\geq 45\%}$	p Value $DLCO_{<45\%}$ vs. $DLCO_{\geq 45\%}$
Smoking status				
Current/former smokers, n = 104	45 (43)	33 (66)	12 (22)	<0.001
Pack years, n = 104	18 ± 25	31 ± 29	5 ± 11	<0.001
Concomitant medication				
Anticoagulants	79 (73)	34 (65)	45 (80)	0.079
Beta-blockers	83 (77)	42 (81)	41 (73)	0.352
ACE inhibitors/angiotensin receptor blockers	87 (81)	41 (79)	46 (82)	0.665
Diuretics	105 (97)	51 (98)	54 (96)	0.602
Mineralocorticoid receptor antagonists	50 (46)	22 (42)	28 (50)	0.423
Digitalis glycosides	21 (19)	9 (17)	12 (21)	0.589
Amiodarone	3 (3)	1 (2)	2 (4)	0.602

Values are n, n (%), mean ± SD, or median (interquartile range). Values are for the full cohort (N = 108) unless indicated otherwise.

ACE = angiotensin-converting enzyme; CO = cardiac output; DLCO = diffusion capacity for carbon monoxide; E/e′ = mitral flow velocity (E)/myocardial diastolic motion (e′); FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; GFR = glomerular filtration rate; LA = left atrium; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; $PaCO_2$ = partial arterial pressure of carbon dioxide; PaO_2 = partial arterial pressure of oxygen; PAPdiast = diastolic pulmonary arterial pressure; PAPm = mean pulmonary arterial pressure; PAPsyst = systolic pulmonary arterial pressure; PAWP = pulmonary artery wedge pressure; PH-HFpEF = pulmonary hypertension due to heart failure with preserved ejection fraction; % pred = % predicted; PVR = pulmonary vascular resistance; RV = residual volume; RVEDD = right ventricular end-diastolic diameter; SaO_2 = saturation of oxygen; SvO_2 = mixed venous oxygen saturation; SVR = systemic vascular resistance; TAPSE = tricuspid plane annular systolic excursion; TLC = total lung capacity.

predicted value was the best prognostic discriminator with a sensitivity of 68.8%, a specificity of 72.7%, and an area under curve of 0.727 (95% CI: 0.630 to 0.825; $p < 0.001$) (Figure 2).

PREDICTORS OF A LOW DLCO. Variables associated with $DLCO_{<45\%}$ were male sex (odds ratio [OR]: 2.71; 95% CI: 1.05 to 6.99; $p = 0.039$) and a history of smoking (OR: 5.01; 95% CI: 1.91 to 13.10; $p < 0.001$).

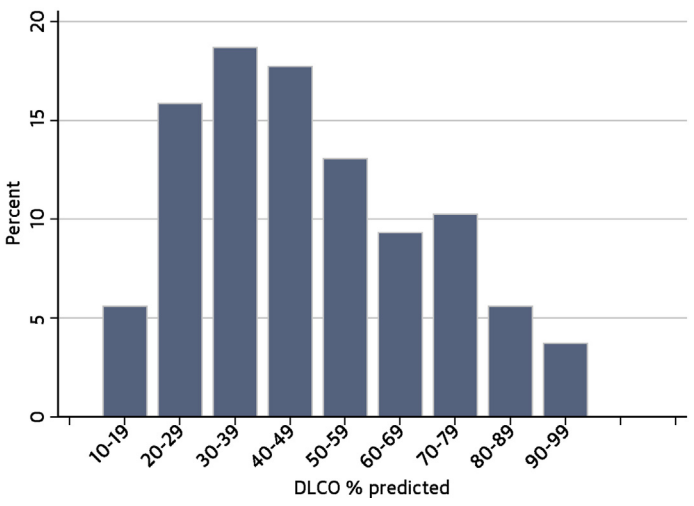
CORRELATIONS BETWEEN DLCO AND OTHER VARIABLES. There were no correlations between the DLCO and other lung function parameters or hemodynamic variables, respectively (data not shown). Significant correlations were found between DLCO and number of pack years ($r = -0.430$; $p < 0.001$), arterial oxygen partial pressure ($r = 0.377$; $p < 0.001$), and arterial oxygen saturation ($r = 0.301$; $p < 0.001$).

COMPUTED TOMOGRAPHY SCANS. In total, we were able to retrieve CT scans or CT reports, respectively, from 64 patients (59%) including 31 patients (60%) with a low DLCO. CT images for on-site review were available from 22 patients (20%), including 8 with a low DLCO. In the majority of CT scans (43 of 64, 67%), no lung parenchymal abnormalities were seen or reported.

In the $DLCO_{\leq 45\%}$ group, 17 (55%) of the 31 CT scans showed no parenchymal abnormalities. In the remaining 14 CT scans, emphysematous changes were reported in 6 patients, fibrotic changes in 4 patients, and combined fibrotic and emphysematous changes in 4 patients. Of these, 6 were rated as mild, 7 as moderate, and 1 as severe. Thirty-three CT scans were available from the $DLCO_{>45\%}$ group; 26 (79%) were described as normal. Parenchymal abnormalities were noted in 7 patients (21%) in the $DLCO_{>45\%}$ group (emphysematous changes, n = 4; fibrotic changes, n = 3), of which 5 were rated as mild, 1 as moderate, and 1 as severe.

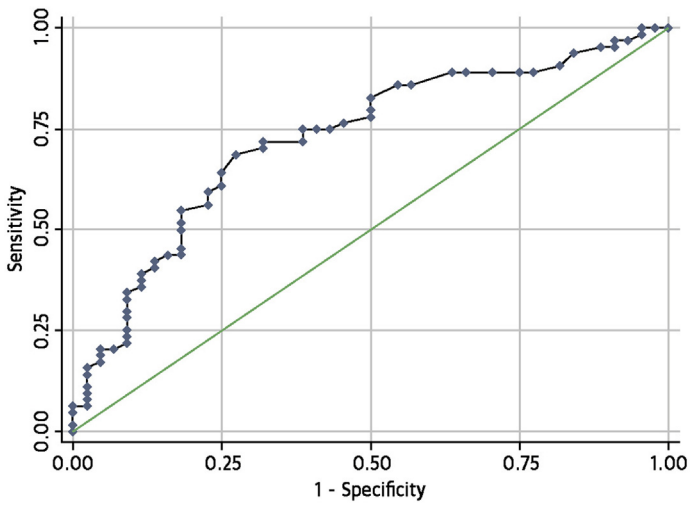
SURVIVAL. The median (interquartile range [IQR]) follow-up time was 40.3 (IQR: 27.4 to 58.9) months

FIGURE 1 DLCO Distribution in the Present Patient Population



Histogram shows the diffusion capacity for carbon monoxide (DLCO) in our cohort.

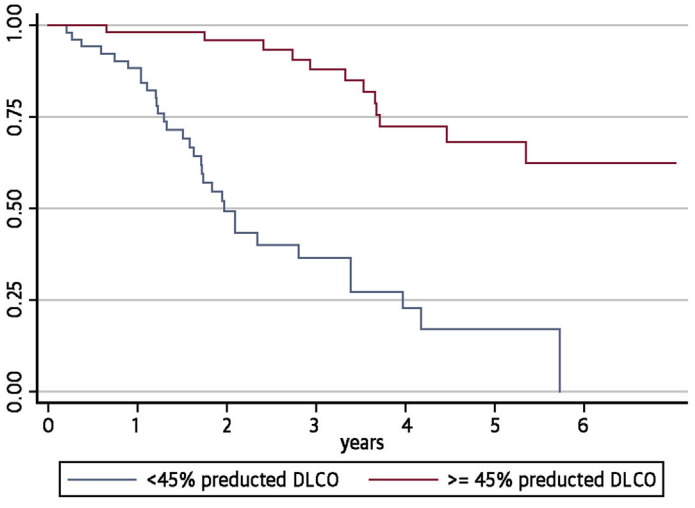
FIGURE 2 ROC Curve Shows the Prognostic Performance of the Lungs' DLCO



Receiver-operating characteristic (ROC) curve showing the prognostic performance of the lung's diffusion capacity for carbon monoxide (DLCO). DLCO at 45% of the predicted value was the best predictor of survival with a sensitivity of 68.8%, a specificity of 72.7%, and an area under curve of 0.727 (95% confidence interval: 0.630 to 0.825; $p < 0.001$).

in the $DLCO_{\geq 45\%}$ group and 20.3 (IQR: 14.7 to 29.2) months in the $DLCO_{<45\%}$ group, the difference resulting from a higher mortality in the low DLCO group. Overall, 44 patients (40.7%) died during the observation period, 32 (62%) in the $DLCO_{<45\%}$ group, and 12 (21%) in the $DLCO_{\geq 45\%}$ group ($p < 0.001$). The survival rates in the whole patient cohort were 93.5%, 74.1%, 64.1%, and 45.5% at 1, 2, 3, and 5 years, respectively. In the $DLCO_{\geq 45\%}$ group, the survival rates at 1, 2, 3, and 5 years were 98.2%, 96%, 87.8%, and 68.2%. In the $DLCO_{<45\%}$ group, the respective survival rates were 88.3%, 49.3%, 36.5%, and 17.1%. The difference between both groups was highly statistically significant ($p < 0.001$ by log-rank analysis) (Figure 3).

FIGURE 3 Kaplan-Meier Analysis Survival Estimates



Kaplan-Meier analysis shows the survival estimates of the whole group, of patients with a DLCO below 45% ($DLCO_{<45\%}$) of the predicted values, and of patients with a DLCO equal to or above 45% ($DLCO_{\geq 45\%}$) of the predicted value. DLCO = diffusion capacity for carbon monoxide. Numbers at risk after 1, 2, 3, 4, and 5 years were 44, 16, 8, 5, and 1, respectively , in the DLCO<45 % group, and 55, 52, 31, 22, and 12, respectively in the DLCO ≥45% group.

COX REGRESSION ANALYSIS. We performed 2 Cox regression analyses. In the first model (Table 2), DLCO was entered in 10% intervals. Factors associated with an increased risk of death in the simple model were higher NT-proBNP, smoking status, pack years, and a lower DLCO. Male sex and a lower DLCO were significant predictors on survival in the multivariate model. In this model, the C-index for DLCO was 0.635 without DLCO and 0.761 when DLCO was included.

In the second Cox regression model (Table 3), DLCO was categorized into the 2 pre-defined DLCO groups- $DLCO_{<45\%}$ and $DLCO_{\geq 45\%}$. In the univariate model, $DLCO_{<45\%}$, NT-proBNP, smoking history, and pack years were associated with an increased mortality risk, but only $DLCO_{<45\%}$ remained a significant predictor of death in the multivariate model. In this model, the C-index was 0.5 without DLCO and 0.729 when DLCO was included.

In both models, age, sex, New York Heart Association functional class, 6-min walk distance, smoking history, hemodynamic parameters, and pulmonary function test variables other than DLCO did not predict outcome in this patient population, either in the univariate or in the multivariate analysis. Bilirubin, glomerular filtration rate, and mixed venous oxygen saturation were not included in the Cox regression models because more than 30% of the data were missing.

DISCUSSION

The present study showed a wide DLCO distribution among patients with PH-HFpEF. A DLCO below 45% of the predicted value was found in almost one-half of the patients, predominantly in male smokers. Of note, the low DLCO was seen in patients with otherwise normal pulmonary function, the majority of whom also had normal chest CT findings. There was no association between the DLCO and the severity of PH, but a low DLCO was strongly and independently associated with the risk of death. The 3-year mortality in patients with a $DLCO_{<45\%}$ was almost 3× higher

than in the $DLCO_{\geq 45\%}$ group, despite almost identical baseline hemodynamics.

These results have several potential implications. First, they underscore the notion that patients with post-capillary PH presenting with a pre-capillary component need a sophisticated diagnostic assessment to identify other potential causes of or contributors to PH (23). Second, DLCO measurements should be integrated in future epidemiological studies and clinical trials on PH-HFpEF as responses to treatment and outcomes may differ in patients with low and normal DLCO values. Third, and perhaps most important, our observations, together with previous studies in other patient populations, may shed some light on the pathogenesis of pulmonary vascular disease in patients with HFpEF, and perhaps beyond.

The DLCO is determined by the alveolar capillary volume and a membrane diffusion component (13). A low DLCO in patients with pre-capillary PH has been linked to a reduced alveolar capillary volume (24). In patients with PH-HFpEF, chronic interstitial edema impairing membrane diffusion could be a potential cause of a low DLCO as it has been reported in patients with HF with reduced EF (25–27). Melenovsky et al. (28) recently showed that lung fluid overload as determined by pulmonary radiography was associated with a lower DLCO, a higher PVR, and right ventricular dilation (28). However, it is unlikely that interstitial edema contributed substantially to the low DLCO in our patients as we included only patients who presented in a stable, compensated state. In addition, no signs of pulmonary venous congestion were reported on the chest CT scans, and hemodynamics including left ventricular filling pressures were identical in both DLCO groups.

The DLCO tends to be normal or mildly to moderately reduced in the majority of patients with IPAH and chronic thromboembolic PH (13–15,29). In both conditions, the vascular lesions are found predominantly in the pre-capillary vessels, and there is usually little capillary or post-capillary involvement (30), which may explain why DLCO is generally not substantially affected by these conditions. Pulmonary vascular diseases known to be associated with a low DLCO are pulmonary veno-occlusive disease, pulmonary capillary hemangiomatosis, and PAH due to systemic sclerosis (31–34). The latter condition is frequently associated with veno-occlusive changes (33,35). Hence, in the absence of parenchymal lung disease, a low DLCO is seen mainly in pulmonary vascular diseases characterized by significant capillary and post-capillary involvement.

TABLE 2 Risk of Death in Patients With PH-HFpEF in Relation to Baseline Risk Marker Measurements With DLCO Imputed as 10% Intervals of the Predicted Value

	Single Predictor Model		Multivariable Model	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Male	3.1 (0.8–11.9)	0.107	2.5 (1.1–5.5)	**0.023**
Age, yrs, per 5-yr increase	1.1 (0.8–2.3)	0.803		
BMI, per 5-kg/m^2 increase	0.9 (0.5–1.7)	0.740		
6MWD, per 10-m decrease*	1.0 (0.9–1.1)	0.521		
Heart rate, per 5-beats/min increase	1.0 (0.9–1.2)	0.910		
RA, per 5-mm Hg increase	1.0 (0.4–2.4)	0.986		
PAPm, per 5-mm Hg increase	1.0 (0.4–2.5)	0.913		
PAWP, per 5-mm Hg increase	1.0 (0.3–3.9)	0.997		
DPG, per 5-mm Hg increase	1.2 (0.5–2.8)	0.677		
CO, per 0.5-l/min decrease	0.9 (0.4–1.9)	0.722		
Cardiac index, 0.3-l/min/m^2 decrease	2.0 (0.8–5.3)	0.168		
PVR, per 100-dyn·s·cm^{-5} increase	0.7 (0.3–1.7)	0.436		
Smoking status, former or ever smoker	1.5 (1.2–2.0)	**0.014**		
Pack years, per 10-pack years increase	1.4 (1.1–1.7)	**0.032**		
TLC, per 5% decrease	1.8 (0.6–1.1)	0.188		
FVC, per 5% decrease	1.1 (0.8–1.6)	0.554		
FEV_1, per 5% decrease	1.2 (0.9–1.6)	0.296		
RV/TLC, per 5% increase	0.8 (0.5–1.1)	0.164		
DLCO, per 10% decrease	2.3 (1.3–4.3)	**0.007**	1.6 (1.2–2.0)	**<0.001**
PaO_2, per 10-mm Hg decrease	1.3 (0.5–3.1)	0.625		
$PaCO_2$, per 5-mm Hg increase	1.3 (0.6–2.8)	0.490		
SaO_2, per 5-mm Hg decrease	0.7 (0.1–3.1)	0.592		
Hemoglobin, per 1-g/dl decrease	1.4 (0.9–2.2)	0.130		
NT-proBNP, per 100-ng/l increase	1.0 (1.0–1.1)	**0.037**		

Estimated HR, 95% CI, and p values were calculated by Cox regression analyses. **Bold** values are statistically significant.

6MWD = 6-min walk distance; BMI = body mass index; CI = confidence interval; DPG = diastolic pressure gradient; HR = hazard ratio; RA = right atrial pressure; other abbreviations as in Table 1.

Over the past years, additional patient populations have been reported that were characterized by severe PH, a low DLCO, and an exceptionally high mortality. Trip et al. (15) described a cohort of 166 patients with IPAH, of whom 48 (29%) had a $DLCO_{<45\%}$. Compared with the $DLCO_{\geq 45\%}$ group, these patients were older (67 vs. 46 years) and had a more frequent smoking history (58% vs. 30%). As in our study, there were no major differences in pulmonary function and hemodynamics between both groups, but the survival was much lower in the $DLCO_{<45\%}$ group (3-year survival 38% vs. 80%). Similar observations were made in patients with lung disease and PH (16,17).

It is conceivable that the combination of severe PH and a low DLCO indicates the presence of a unique small-vessel pulmonary vasculopathy that affects post-capillary venules and pulmonary capillaries (15,29,36–38). Smoking appears to be a major risk factor, which is of particular interest as smoking in various animal models was associated with a small vessel pulmonary vasculopathy that preceded the development of emphysema (39,40). However, our

TABLE 3 Risk of Death in Patients With PH-HFpEF in Relation to Baseline Risk Marker Measurements With DLCO Dichotomized Into the $DLCO_{<45\%}$ Group and the $DLCO_{\geq 45\%}$ Group

	Single Predictor Model		Multivariable Model	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Male	2.4 (0.6–9.1)	0.221		
Age, per 5-yr increase	0.9 (0.6–2.1)	0.823		
BMI, per 5-kg/m^2 increase	0.8 (0.5–1.4)	0.416		
6MWD, per 10-m decrease	1.0 (1.0–1.1)	0.298		
Heart rate, per 5-beats/min increase	0.9 (0.8–1.1)	0.373		
RA, per 5-mm Hg increase	0.7 (0.3–1.7)	0.437		
PAPm, per 5-mm Hg increase	1.3 (0.5–3.5)	0.537		
PAWP, per 5-mm Hg increase	1.3 (0.3–6.1)	0.734		
DPG, per 5-mm Hg increase	1.7 (0.7–3.9)	0.253		
CO, per 0.5-l/min decrease	0.7 (0.3–1.4)	0.327		
Cardiac index, 0.3-l/min/m^2 decrease	2.4 (0.9–6.0)	0.071		
PVR, per 100-dyn·s·cm^{-5} increase	0.8 (0.3–2.0)	0.705		
Smoking status, former or ever smoker	1.6 (1.4–2.0)	**0.010**		
Pack years, per 10-pack years increase	1.4 (1.1–1.6)	**0.017**		
TLC, per 5% decrease	0.8 (0.6–1.1)	0.836		
FVC, per 5% decrease	1.2 (0.8–1.7)	0.396		
FEV_1, per 5% decrease	1.1 (0.8–1.6)	0.444		
RV/TLC, per 5% increase	0.9 (0.5–1.4)	0.525		
DLCO, <45% predicted	10.3 (2.1–51.2)	**0.005**	6.6 (2.6–16.9)	**<0.001**
PaO_2, per 10-mm Hg decrease	1.7 (0.7–4.2)	0.284		
$PaCO_2$, per 5-mm Hg increase	1.0 (0.5–2.1)	0.977		
SaO_2, per 5-mm Hg decrease	0.5 (0.1–2.8)	0.464		
Hemoglobin, per 1-g/dl decrease	1.3 (0.8–1.9)	0.264		
NT-proBNP, per 100-ng/l increase	1.0 (1.0–1.1)	**0.041**		

Estimated HR, 95% CI, and p values were calculated by Cox regression analyses. **Bold** values are statistically significant.

Abbreviations as in Tables 1 and 3.

study population as well as the patient cohort described by Trip et al. (15) included a relevant number of patients with a low DLCO but no smoking history, especially among women.

STUDY STRENGTHS AND LIMITATIONS. Our study's strengths include the fact that our patients were well characterized in terms of comorbidities, smoking status, pulmonary function, and hemodynamics. Demographics, comorbidities, and survival rates of our patients were comparable with other populations of PH-HFpEF patients (2,19,41). The main limitations were the single-center setting, the retrospective design, missing values for some of the variables under study, missing information on chest CT findings, and the lack of histological data. Our study was therefore not sufficiently powered to detect other potentially important predictors of survival. No adjustments were made for multiple comparisons. In addition, our analyses did not allow us to distinguish between the vascular and the membrane component of the DLCO. Finally, our study included almost only patients with HFpEF who had a significant pre-capillary component to their PH. It is unclear whether a low DLCO is also a risk predictor in patients with HFpEF and isolated post-capillary PH or no PH all.

CONCLUSIONS

A low DLCO was found in almost one-half of our patients with PH-HFpEF and was associated with a high mortality risk. The majority of patients with a low DLCO had a history of smoking, whereas lung function tests and chest CT findings were normal or near normal. Together with previous reports from other patient populations, these findings may indicate the presence of a smoking-related small-vessel pulmonary vasculopathy affecting pulmonary capillaries and post-capillary venules. Future studies including modern imaging techniques and histological examinations are needed to further elucidate the mechanisms responsible for a low DLCO in patients with PH-HFpEF.

REPRINT REQUESTS AND CORRESPONDENCE TO: Dr. Marius M. Hoeper, Department of Respiratory Medicine, Hannover Medical School, Carl-Neuberg-Strasse 1, Hannover, Lower Saxony 30625, Germany. E-mail: hoeper.marius@mh-hannover.de.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with PH-HFpEF, a low DLCO is associated with a high mortality risk.

TRANSLATIONAL OUTLOOK: These data open new research perspectives to determine the mechanisms associated with a pulmonary vasculopathy in patients with PH-HFpEF.

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