ORIGINAL RESEARCH ARTICLE

Lung diffusion capacity in advanced heart failure: relation to central haemodynamics and outcome

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Abstract

Aims   Patients with heart failure (HF) are known to have a reduced pulmonary diffusion capacity for carbon monoxide (D_{LCO}), but little is known about how lung function relates to central haemodynamics. The aim of this study was to investigate the association between haemodynamic variables and pulmonary diffusion capacity adjusted for alveolar volume in congestive HF patients and to analyse how predicted D_{LCO}/V_A affects mortality in relation to the haemodynamic status.

Methods and results   We retrospectively studied right heart catheterization (RHC) and lung function data on 262 HF patients (mean age 51 ± 13 years) with a left ventricular ejection fraction < 45% referred non-urgently for evaluation for heart transplantation (HTX) or left ventricular assist device (LVAD). Univariate and multivariate linear regression models were constructed to examine the associations between predicted values of D_{LCO}/V_A, forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1), and haemodynamic parameters [pulmonary capillary wedge pressure (PCWP), central venous pressure, cardiac index, mean pulmonary artery pressure, and mean arterial pressure] as well as other factors known to affect lung function in HF. FEV_1 was reduced to <80% of predicted value in 55% of the population, and D_{LCO}/V_A was reduced in 63% of the population. D_{LCO}/V_A correlated positively with pulmonary capillary wedge pressure in both univariate and multivariate analyses for all included patients ($P < 0.001$ and $P = 0.045$, respectively) and a restricted population of patients with the shortest time between RHC and lung function testing ($P = 0.005$, $P = 0.015$). D_{LCO}/V_A predicted mortality in multivariate models [hazard ratio 1.5 (1.1–2.1)] but not the combined endpoint of death, LVAD implantation, or HTX. There was no significant correlation between haemodynamics and predicted FVC or FEV_1.

Conclusions   Pulmonary diffusion capacity correlates positively with left ventricular fillings pressures, and reduced values predict increased mortality in patients with HF. This might be driven by increased lung capillary volume in patients with pulmonary congestion.

Introduction

Heart failure (HF) is frequently associated with functional and structural changes in the lungs. Indeed, lung function abnormalities such as impaired respiratory mechanics and gas exchange can be attributed to HF in the absence of respiratory diseases.[1,2] However, pulmonary co-morbidities also frequently co-exist with HF, and chronic obstructive pulmonary disease (COPD) is a common finding in the HF population.[3] The co-existence of COPD and HF is often a therapeutic and diagnostic challenge in HF management,[4] and COPD in

patients with HF is associated with a worse clinical status and an increased risk of cardiovascular death and hospitalizations.[5] HF-related changes in pulmonary function are likely multifactorial and explained by interstitial and/or alveolar oedema, increased heart size leading to lung tissue displacement, pulmonary vascular remodelling, and respiratory muscle weakness.[6–9] It is well known that patients with congestive HF (CHF) have a reduction in pulmonary diffusion capacity for carbon monoxide (D_{LCO}),[1] and CHF is known to increase the resistance to gas transfer across the alveolar–capillary membrane.[10] Some studies have shown that a

reduced diffusion capacity contributes to exercise intolerance[11] and is a predictor of mortality in HF patients.[12] The mechanism behind these findings, however, is unresolved. It is clear that cardiopulmonary interaction is an important element in HF pathophysiology. Little is known about the association between central haemodynamics and pulmonary diffusion capacity in CHF, and the intention of this article was to investigate the role of haemodynamics in the interaction between heart and lungs. Limited data are available, and the importance of haemodynamic status, particularly pulmonary artery and left ventricular filling pressures for diffusion capacity in advanced HF, is not clear. Nor is it known if an association between D_{LCO} and outcome is driven by haemodynamic abnormalities in these patients. The aim of this study was to investigate the association between haemodynamic variables and pulmonary diffusion capacity adjusted for alveolar volume in CHF patients and to analyse how predicted D_{LCO}/V_A affects mortality in relation to the haemodynamic status.

Methods

Patients and study design

This is a retrospective study of HF patients who underwent right heart catheterization (RHC) at the Department of Cardiology at Copenhagen University Hospital, Rigshospitalet, between January 2002 and February 2016. Patients were referred for evaluation for heart transplantation (HTX) or implantation of a left ventricular assist device (LVAD), and optimal medical therapy was instituted before referral. Both hospitalized patients (not in an intensive care unit) and outpatients with advanced CHF were included in this study. If a patient had more than one RHC in the time period, only data from the first catheterization were used. Inclusion criteria were HF with documented left ventricular ejection fraction (LVEF) less than 45% and a record of pulmonary function tests (PFTs) within 3 months of the RHC. Patients previously treated with LVAD or HTX were excluded from the study. Patients were not required to have symptoms of advanced HF at the time of referral, implying that some patients could be characterized as New York Heart Association (NYHA) Class 2 at the time of RHC. These patients were included as they had recently experienced advanced HF symptoms or their HF condition was considered serious enough to justify referral for investigation including undergoing an invasive cardiac catheterization. Patients were identified in the hospitals' cardiac catheterization database, and data were extracted from this database, as well as from patient medical records and the departments' echocardiography database. The research protocol was approved by the Danish Medical Agency (3-3013-1365/1) and the Data Protection Agency

(RH 2015-153). Individual patient consent was not required owing to the retrospective nature of the study.

Haemodynamic evaluation

Right heart catheterization was performed using a Swan–Ganz catheter by four different experienced physicians. All studies were performed in the cardiac catheterization laboratory after appropriate zeroing and calibration of the pressure transducer. The catheter was inserted in the internal jugular or the femoral vein, and the correct placement of the Swan–Ganz catheter was evaluated by fluoroscopy and by visualization of pressure curves on a monitor.

Patients underwent RHC with determination of pulmonary capillary wedge pressure (PCWP), pulmonary artery systolic pressure and pulmonary artery diastolic pressure (PADP), mean pulmonary artery pressure (MPAP), central venous pressure (CVP), cardiac output (CO), cardiac index (CI), and mean arterial pressure (MAP). CI was determined as CO divided by the body surface area (BSA). CO was measured by the thermodilution technique. BSA was determined using the DuBois method. MAP was estimated using the formula MAP = [(2 × diastolic blood pressure) + systolic blood pressure]/3. Pulmonary vascular resistance (PVR) in Wood units was calculated as PVR = (MPAP − PCWP)/CO. The diastolic pressure gradient (DPG) was calculated as PADP − PCWP, and a DPG ≥ 7 was considered to indicate pulmonary vascular remodelling.[13]

Pulmonary function tests

To be included in this study, HF patients were required to have documented PFTs performed within 3 months of the RHC. PFTs included spirometry and diffusion capacity. The spirometry was repeated until (at least) three successful and reproducible results were obtained, and it was reported as the highest values achieved.

Diffusion capacity was measured using single-breath CO technique. Two independent diffusion capacity measurements were performed with a minimum of 4 min intervals. If the results varied <10%, the final result was given as the average value. If the variation was >10%, a third measurement was made and the average of the three measurements was used. All lung function tests were performed in a dedicated laboratory at Rigshospitalet at the Department of Clinical Physiology and Nuclear Medicine. Unless otherwise indicated, lung function variables are expressed as per cent of predicted values[14,15]; e.g. per cent forced expiratory volume in 1 second (%FEV_1) denotes measured FEV_1 divided by expected FEV_1 multiplied by 100.

Statistical analysis

Categorical variables are reported as numbers (n) and percentages (%). Continuous variables are reported as mean ± standard deviation (SD), unless indicated otherwise. We constructed univariate linear regression analyses to examine the associations between FEV_1, forced vital capacity (FVC), D_{LCO}/V_A, and the haemodynamic parameters (PCWP, MPAP, CVP, CI, MAP, PVR, and DPG). Significant variables were included in multivariable models along with other factors known to affect lung function in HF patients (COPD, diabetes mellitus, and smoking). Two-sided P values were used; a P-value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS (Version 25, IBM Corp.).

Follow-up date was set to 1 February 2016. Events were defined as patients being alive at follow-up date, undergoing LVAD implantation or HTX, or dead. Implantation of an LVAD was used as bridge to transplantation or destination therapy. Kaplan–Meier survival curve was plotted, and Cox proportional hazards models were used to estimate hazard ratios with 95% confidence intervals. Patients were divided into three groups according to tertiles of $\%FEV_1$, %FVC, and $\%D_{LCO}/V_A$. Cox regression analyses were performed to identify predictors of death (censoring patients at time of LVAD or HTX) or predictors of the combined endpoint of death, LVAD implantation, or HTX.

Results

Baseline characteristics

A total of 519 patients with LVEF $< 45\%$ underwent RHC in the study period, but 257 were excluded owing to missing PFTs within the allowed time frame. Hence, a total of 262 subjects formed the study population. Their characteristics are listed in *Table 1*. The mean age was 51 years; most were men (78%) and mildly overweight (body mass index = 26.4 kg/m^2). The vast majority (91%) had a severely reduced LVEF $\leq 25\%$, and 64% were in NYHA Class 3 or 4 at the time of examination. One or more clinical signs of congestion such as elevated jugular pressure and peripheral oedema were present in 49% at the time of examination. While 19% were active smokers, the majority were previous smokers (53%). Only 8% were diagnosed with COPD. Most patients were treated with recommended HF medications, although only 68% tolerated beta-blocker. Only 5% of patients were treated with inotropes at the time of RHC, and none were receiving mechanical circulatory support (as this was an exclusion criterion). Bronchodilators for COPD or asthma were used by 3% of the population.

Percentage FEV_1 was abnormally low ($<80\%$) in 55% of the population, and mean $\%D_{LCO}/V_A$ was reduced (63%).

Haemodynamics are presented in *Table 1*. Patients had signs of increased filling pressures and depressed CO.

Association between haemodynamic variables and lung function parameters

Mean time between PFTs and RHC was 7 days. To test for a potential influence of time elapsed from RHC to pulmonary function testing, sensitivity analyses were performed restricted to the population to those with a maximum of 2 days between the two measurements. Univariate and multivariate linear regression models are shown in *Table 2*. With the use of univariate analysis, a significant, positive association between $\%D_{LCO}/V_A$ and PCWP ($r^2 = 0.051$, $P = 0.005$) was found (*Figure 1*). Further, $\%D_{LCO}/V_A$ and MPAP were associated ($r^2 = 0.029$, $P = 0.036$). There were no significant associations between $\%D_{LCO}/V_A$ and CI, MAP, DPG, PVR, or CVP.

When multivariate analyses were performed including the variables PCWP, MPAP, history of smoking, diabetes mellitus, and COPD, PCWP remained significantly associated with $\%D_{LCO}/V_A$ ($P = 0.015$).

Analyses were repeated including all 262 patients, and there was still a significant correlation between $\%D_{LCO}/V_A$ and PCWP in both univariate ($r^2 = 0.048$, $P \leq 0.001$) and multivariate analyses ($P = 0.045$) with similar coefficients compared with those of the restricted population.

Pulmonary vascular resistance was significantly correlated with %FVC ($r^2 = 0.016$, $P = 0.047$) and $\%FEV_1$ ($r^2 = 0.022$, $P = 0.018$) but not with $\%D_{LCO}/V_A$ for all patients included.

Smoking and chronic obstructive pulmonary disease

Active smokers had a reduced $\%FEV_1$ (72% vs. 82%), %FVC (79% vs. 84%), and $\%D_{LCO}/V_A$ (77% vs. 92%) than had non-smokers. There was also a significant correlation between $\%D_{LCO}/V_A$ and PCWP in this subpopulation ($r^2 = 0.103$, $P = 0.03$). There were no significant changes in our results when patients diagnosed with COPD were excluded from the analysis.

The use of bronchodilators or beta-blockers was not significantly correlated to any of the lung function parameters.

Lung function parameters, haemodynamics, and outcome

Mean follow-up time was 3.3 years. At the end of follow-up, 83 patients (32%) had died and 179 were alive (68%). Out of 262 patients, 37 (14%) received an LVAD and 78 (30%) were transplanted. While 68 (38%) were alive with an LVAD or transplant at follow-up, 111 (62%) were alive without.

Table 1 Baseline characteristics

	Total $n = 262$	
	n	
Age (years)	262	51 ± 13
Gender (male)	262	204 (78%)
Body mass index (kg/m^2)	259	26.4 ± 5
NYHA 3 or 4	247	158 (64%)
LVEF ≤ 25%	262	237 (91%)
Ischaemic aetiology	262	85 (33%)
Risk factors		
Smoking[a]	252	181 (71.8%)
Alcohol[b]	262	19 (7.3%)
Medical history		
COPD	260	20 (7.7%)
Diabetes mellitus[c]	262	45 (17.3%)
Clinical signs		
Pleural effusion	71	20 (28.2%)
Pulmonary rales	250	38 (15.2%)
JVP	185	47 (25.4%)
Peripheral oedema	237	67 (28.3%)
Ascites	71	20 (28.2%)
Hepatomegaly	154	34 (22.1%)
S3 gallop	194	234 (17.5%)
NT-pro-BNP (ng/L)	86	3826 ± 4172
Device therapy		
ICD	262	46 (17.6%)
CRT-D	262	39 (14.9%)
CRT-P	262	11 (4.2%)
Pacemaker	262	5 (1.9%)
None	262	161 (61.5%)
Medication		
ACE inhibitors or angiotensin II receptor blockers	262	201 (76.7%)
Beta-blockers	262	179 (68.3%)
Aldosterone receptor antagonists	262	174 (66.4%)
Loop diuretics	262	236 (90.1%)
Inotropic support	262	14 (5.3%)
Resting haemodynamic parameters		
Heart rate (b.p.m.)	190	81 ± 18
Systolic blood pressure (SBP) (mmHg)	196	104 ± 18
Diastolic blood pressure (DBP) (mmHg)	195	65 ± 11
Mean arterial pressure (MAP) (mmHg)	195	78 ± 12
Central venous pressure (CVP) (mmHg)	256	10.9 ± 6.8
Cardiac index (CI) (L/min/m^2)	253	2.4 ± 0.7
Pulmonary capillary wedge pressure (PCWP) (mmHg)	259	20.5 ± 8.4
Mean pulmonary artery pressure (MPAP) (mmHg)	257	28.6 ± 9.9
Pulmonary artery systolic pressure (PASP) (mmHg)	259	42.8 ± 14.5
Pulmonary artery diastolic pressure (PADP) (mmHg)	257	21.5 ± 8.1
Systemic vascular resistance (SVR) (dynes·s/cm^5)	191	1250 ± 457
Pulmonary vascular resistance (PVR) (dynes·s/cm^5)	253	153 ± 115
Diastolic pressure gradient (DPG)	257	1.0 ± 4.1
Pulmonary function tests		
Forced vital capacity (FVC) (L)	262	3.5 ± 1.0
Forced vital capacity (FVC) (% of predicted)	257	81.9 ± 18.9
Forced expiratory volume in 1 s (FEV$_1$) (L)	262	2.7 ± 0.8
Forced expiratory volume in 1 s (FEV$_1$) (% of predicted)	262	77.3 ± 19.8
FEV$_1$/FVC (% of predicted)	262	76.4 ± 9.0
Pulmonary diffusion capacity for carbon monoxide (D$_{LCO}$) (mmol/min/kPa)	259	6.3 ± 1.7
Pulmonary diffusion capacity for carbon monoxide (D$_{LCO}$) (% of predicted)	258	62.6 ± 15.9
Alveolar volume adjusted pulmonary diffusion capacity for carbon monoxide (D$_{LCO}$/V$_A$)	257	1.3 ± 0.3
Alveolar volume adjusted pulmonary diffusion capacity for carbon monoxide (D$_{LCO}$/V$_A$) (% of predicted)	254	84.1 ± 18.1

n defines the number of patients with obtained information in the category. Values are given as numbers and proportions [n (%)] or means with standard deviations (SDs).
ACE, angiotensin-converting enzyme; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; ICD, implantable cardioverter defibrillator; JVP, jugular venous pressure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; NT-pro-BNP, N-terminal pro-BNP.
[a]Current or former.
[b]>14/21 units/week.
[c]Non-insulin-dependent diabetes mellitus or insulin-dependent diabetes mellitus.

Table 2 Association between %D_{LCO}/V_A and haemodynamic variables

Variables	Total (n = 262)			Within 2 days (n = 156)		
	P-value	r²	β	P-value	r²	β
Univariate analysis						
PCWP	<0.001	0.048	0.219	0.005	0.051	0.226
CI	NS			NS		
CVP	NS			NS		
MAP	NS			NS		
MPAP	0.003	0.036	0.190	0.036	0.029	0.170
DPG	NS			NS		
PVR	NS			NS		
Multivariate analysis						
		0.139			0.18	
PCWP	0.045		0.252	0.015		0.388
COPD	0.047		−0.122	0.034		−0.165
Smoking[a]	<0.001		−0.254	<0.001		−0.283
Diabetes mellitus	NS			NS		
MPAP	NS			NS		

%D_{CLO}/V_A, percentage of predicted value of pulmonary diffusion capacity adjusted for alveolar volume; CI, cardiac index; COPD, chronic obstructive pulmonary disease; DPG, diastolic pressure gradient; MAP, mean arterial pressure; MPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance.
[a]Current or former.

Figure 1 Association between %D_{LCO}/V_A and PCWP. PFTs within 2 days of RHC (n = 156). %D_{CLO}/V_A, percentage of predicted value of pulmonary diffusion capacity adjusted for alveolar volume; PFTs, pulmonary function tests; PCWP, pulmonary capillary wedge pressure; RHC, right heart catheterization.
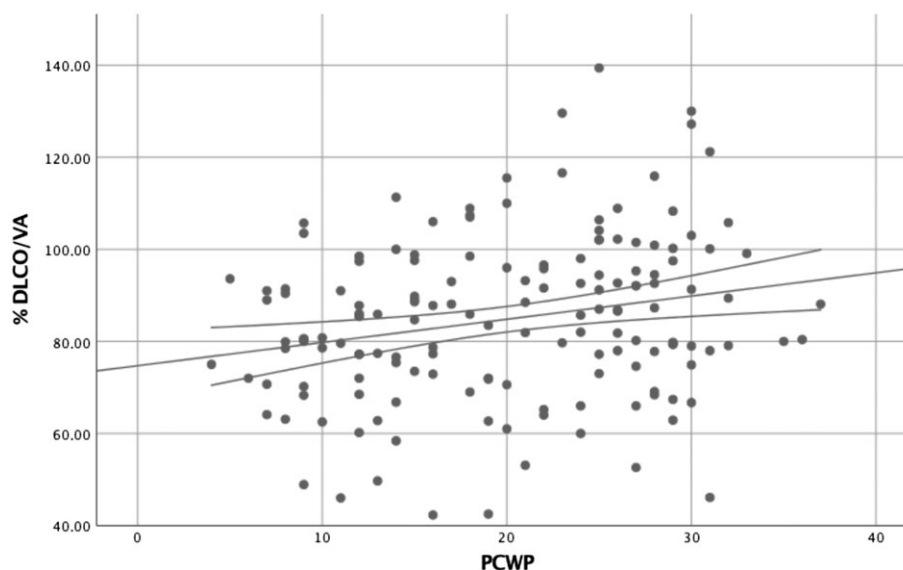
The results of the univariate and multivariate Cox regression models are presented in *Table 3*. In a univariate analysis, patients in the lower tertiles of %FEV_1 and %FVC had a 30% and 40% increased risk of death, LVAD, or transplantation than had those in the highest tertiles (both, $P < 0.05$). In multivariate Cox models adjusted for age and gender, neither %FEV_1 nor %FVC remained significant predictors of the combined endpoint.

Multivariate Cox analysis identified %D_{LCO}/V_A as a predictor of mortality with a 50% increased risk when comparing lower tertiles with highest tertiles ($P < 0.05$), but it was not a significant predictor of the combined endpoint. Kaplan–Meier survival curves are presented in *Figure 2*. There was no statistical significant interaction between PCWP and %D_{LCO}/V_A.

Discussion

The main findings of the present study are that pulmonary diffusion capacity adjusted for alveolar volume correlated

Table 3 Hazard ratios in Cox regression models

	Model 1 (combined endpoint)	Model 2 (combined endpoint)	Model 3 (combined endpoint)	Model 4 (all-cause mortality)
%FEV$_1$	1.30* (1.10–1.52)	0.94 (0.67–1.32)	0.93 (0.65–1.33)	1.15 (0.69–1.91)
%FVC	1.40* (1.11–1.64)	1.24 (0.87–1.73)	1.27 (0.89–1.80)	1.35 (0.82–2.22)
%D$_{LCO}$/V$_A$	0.99 (0.81–1.21)	1.22 (0.97–1.53)	1.22 (0.97–1.52)	1.53* (1.11-2.11)
PCWP		1.03 (0.99–1.07)	1.03 (1.00–1.08)	1.03 (0.98–1.07)
CI		0.64* (0.48–0.86)	0.60** (0.45–0.81)	0.59* (0.38–0.90)
MPAP		1.01 (0.98–1.05)	1.01 (0.98–1.04)	1.03 (0.99–1.07)
CVP		1.00 (0.97–1.03)	0.99 (0.97–1.03)	0.97 (0.92–1.03)
Age			1.08* (1.02–1.04)	1.05** (1.05–1.08)
Gender (male)			1.09 (0.68–1.73)	4.50** (1.72–11.77)

Model 1–3: Data are given as hazard ratio (HR) of combined endpoint of death, heart transplantation, or LVAD implantation with 95% confidence interval. Model 4: Data are given as HR of all-cause mortality with 95% confidence interval.
Model 1: Univariate models for lung function parameters in tertiles. Model 2: Multivariate model for lung function parameters in tertiles and haemodynamics. Model 3: Multivariate model for lung function parameters in tertiles and haemodynamics adjusted for age and gender. Model 4: Multivariate model for lung function parameters in tertiles and haemodynamics adjusted for age and gender. Hazard ratios are given per 10 units of increase.
%D$_{LCO}$/V$_A$, percentage of predicted value of pulmonary diffusion capacity adjusted for alveolar volume; %FEV$_1$, percentage of predicted value of forced expiratory volume in 1 s; %FVC, percentage of predicted value of forced vital capacity; CI, cardiac index; CVP, central venous pressure; MPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure.
*$P < 0.05$.
**$P < 0.001$.

Figure 2 Kaplan–Maier curve. Blue = highest tertile of %D$_{LCO}$/V$_A$. Red = intermediate tertile of %D$_{LCO}$/V$_A$. Green = lowest tertile of %D$_{LCO}$/V$_A$. %D$_{CLO}$/V$_A$, percentage of predicted value of pulmonary diffusion capacity adjusted for alveolar volume.
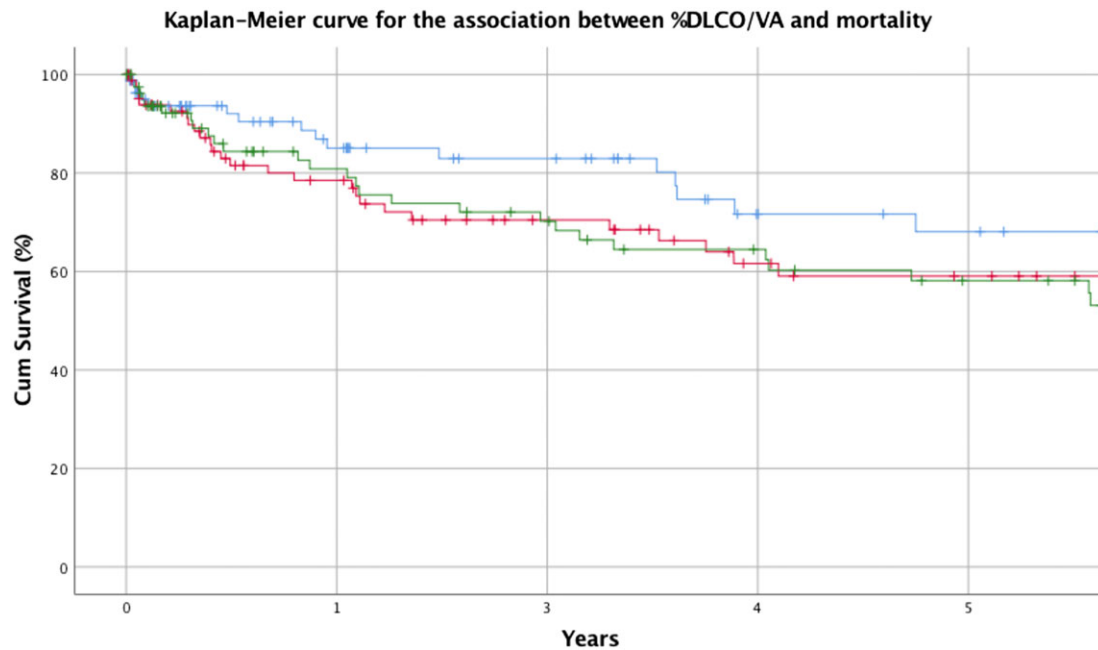
positively, albeit modestly, with left ventricular filling pressures while dynamic lung parameters (%FEV$_1$ and %FVC) did not correlate with haemodynamics in advanced HF. Further, %FEV$_1$ and %FVC predicted adverse outcome, although this association was not apparent after adjustment for confounding factors, whereas diffusion capacity predicted mortality when adjusting for confounders.

Pulmonary diffusion capacity for carbon monoxide (D$_{LCO}$) is reduced in HF,[1,2,7,10,16,17] which was also confirmed in the current study when compared with the applied reference material.

Only limited data have been published on the association between central haemodynamics and pulmonary diffusion capacity in CHF. In this study, PCWP was the only

haemodynamic variable associated with $\%D_{LCO}/V_A$ in univariate and multivariate analyses, and, interestingly, there was a positive association between predicted diffusion capacity adjusted for alveolar volume and PCWP. Alteration in D_{LCO} depends on changes in its two components, the alveolar–capillary membrane resistance (D_M) and the amount of blood volume available for gas exchange (V_C).

The two components modify D_{LCO} in opposite ways, where D_M decreases and V_C increases D_{LCO}.[17,18] PCWP is an indirect estimate of left atrial pressure and the left ventricular end-diastolic pressure (LVEDP). Increases in LVEDP are transmitted back to the pulmonary capillaries. As pulmonary congestion usually increases capillary blood volume,[1,18] it could theoretically explain the positive association between PCWP and D_{LCO}/V_A. Further studies are of course necessary to verify this hypothesis.

It is well established that lung volume is reduced in HF patients; and the importance of alveolar volume (V_A), i.e. the volume of air in the lung available for gas exchange, in interpreting diffusion capacity is, therefore, not without significance. In addition, V_A, furthermore, bears a prognostic value because reduced V_A is also found to be a significant, independent predictor of mortality in patients with systolic HF.[19]

Wright et al.[7] studied 132 patients with severe chronic CHF referred for HTX and found no association between PCWP and D_{LCO}. Compared with patients in the present study, their population did, in general, have a higher PCWP (26 vs. 20.5 mmHg in the present study) and a slightly higher D_{LCO} (64.5 vs. 62.6%). Also, they did not specify time between RHC and PFTs.

In a study of HF patients, Puri et al.[17] reported that a lower D_{LCO} was associated with more severe HF and found that the main component of the impaired diffusion capacity is related to the membrane component (D_M). Fluid accumulation is a classic clinical feature in HF, and patients with lung congestion have been shown to display a greater reduction in D_{LCO}.[19] A reversible reduction in membrane diffusion capacity can be observed by infusion of saline into CHF patients,[20,21] suggesting that, to some extent, there is a variable component in diffusion capacity seen in CHF, which could be targeted for therapeutic intervention. However, several of studies of patients after HTX have shown that while HTX has a positive effect on total lung capacity, FEV_1 and FVC, it does not improve D_{LCO} or D_{LCO}/V_A at long-term follow-up.[22,23] This suggests that chronic irreversible changes that leads to permanently reduced diffusion capacity despite improved haemodynamics may occur as a consequence of remodelling.

Reduction in diffusion capacity is important in CHF as inability of the alveolar–capillary membrane to maintain an effective gas diffusion contributes to exercise intolerance in CHF.[11] However, the importance of D_{LCO} may extend beyond that as studies of both HF patients with reduced ejection fraction[12] and preserved ejection fraction[24] have reported a significantly worse outcome and higher mortality rate in HF patients with lower diffusion capacity. Olson et al.[12] studied 134 HF patients without co-morbidities that could influence pulmonary function and examined the utility of resting pulmonary function measures in predicting event-free survival in patients with HF. FEV_1 and FVC demonstrated the strongest relationship with event-free survival, but D_{LCO} and V_A were also found to be important prognostic markers. In our study, $\%D_{LCO}/V_A$ was a significant prognostic predictor of mortality but did not predict the combined endpoint of death, LVAD, or transplantation, while $\%FEV_1$ and $\%FVC$ were predictors for the combined endpoint in univariate Cox analysis but did not remain significant in multivariate models. One reason for this discrepancy could be differences in patient selection and the endpoints for the study, as fewer patients were transplanted and LVAD implantation was not included in the Olsen study. There is growing evidence suggesting that pulmonary function testing could provide useful additional information in most patients with CHF with or without respiratory co-morbidities in relation to daily management and as a predictor of mortality.[16,25]

There were no significant changes in our results when patients diagnosed with COPD were excluded from all of our analysis; hence, we decided not to exclude them from the study.

Clinical implication

The heart and lungs are anatomically connected, but our knowledge as to how haemodynamics are related to lung function is sparse. We investigated this relationship and found a positive correlation between diffusion capacity and PCWP, which could be explained by an increase in blood volume available for gas exchange, a consequence of pulmonary congestion. This information is of importance when interpreting PFTs in patients worked up for HTX of LVAD. As we have shown that diffusion capacity is related to mortality, the data should spike further research aimed at clarifying the pathophysiology in lung diffusion capacity in HF and leading to a better understanding of the mechanisms of the lung–heart interactions.

Study limitations

Owing to the limitations of a cross-sectional study, we cannot conclude on any cause–effect relationship between PCWP and diffusion capacity, and furthermore, because the data collection was limited to one time point, it may not be representative of the entire trajectory of HF patients. In our study population, only 7% of the patients were diagnosed with COPD, which is significantly less than in the general

population. This is probably because clinicians are more reluctant to refer patients with (severe) COPD to evaluation for HTX and/or LVAD, and thus, there is most likely selection bias at the referral level.

We investigated a selected HF population with a mean age of 51, which is considerably younger than average HF patients, which may limit the generalizability to the general HF population.

In addition, our study did not allow us to distinguish between the vascular and membrane components of D_{LCO}.

Conclusions

This study explored the association between haemodynamic variables and lung function parameters in patients with CHF. This study is the first to demonstrate a positive association between D_{LCO}/V_A and PCWP, possibly explained by an increase in blood volume available for gas exchange, a consequence of pulmonary congestion. D_{LCO}/V_A predicted mortality but not the combined endpoint of death, LVAD implantation, and HTX. Further studies allowing for distinction between the vascular and membrane components of D_{LCO} are necessary to explore this association between diffusion capacity and PCWP.

Conflict of interest

None declared.

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