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ORIGINAL RESEARCH ARTICLE

Pulmonary function assessment post-left ventricular assist device implantation

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Abstract

Aim The lungs—and particularly the alveolar-capillary membrane—may be sensitive to continuous flow (CF) and pulmonary pressure alterations in heart failure (HF). We aimed to investigate long-term effects of CF pumps on respiratory function.

Methods and results We conducted a retrospective study of patients with end-stage HF at our institution. We analysed pulmonary function tests [e.g. forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1)] and diffusing capacity of the lung for carbon monoxide (D_{LCO}) from before and after left ventricular assist device (LVAD) implantation and compared them with invasive haemodynamic studies. Of the 274 patients screened, final study analysis involved 44 patients with end-stage HF who had CF LVAD implantation between 1 February 2007 and 31 December 2015 at our institution. These patients [mean (standard deviation, SD) age, 50 (9) years; male sex, n = 33, 75%] received either the HeartMate II (Thoratec Corp.) pump (77%) or the HeartWare (HeartWare International Inc.) pump. The mean (SD) left ventricular ejection fraction was 21% (13%). At a median of 237 days post-LVAD implantation, we observed significant D_{LCO} decrease (−23%) since pre-implantation ($P < 0.001$). ΔD_{LCO} had an inverse relationship with changes in pulmonary capillary wedge pressure (PCWP) and right atrial pressure (RAP) from pre-LVAD to post-LVAD implantation: ΔD_{LCO} to ΔPCWP (r = 0.50, $P < 0.01$) and ΔD_{LCO} to ΔRAP (r = 0.39, $P < 0.05$). We observed other reductions in FEV_1, FVC, and FEV_1/FVC between pre-LVAD and post-LVAD implantation. In mean (SD) values, FEV_1 changed from 2.3 (0.7) to 2.1 (0.7) (P = 0.005); FVC decreased from 3.2 (0.8) to 2.9 (0.9) (P = 0.01); and FEV_1/FVC went from 0.72 (0.1) to 0.72 (0.1) (P = 0.50). Landmark survival analysis revealed that ΔD_{LCO} from 6 months after LVAD implantation was predictive of death for HF patients [hazard ratio (95% confidence interval), 0.60 (0.28–0.98); P = 0.03].

Conclusions Pulmonary function did not improve after LVAD implantation. The degree of D_{LCO} deterioration is related to haemodynamic status post-LVAD implantation. The ΔD_{LCO} within 6 months post-operative was associated with survival.

Keywords Continuous flow pumps; D_{LCO}; Pulmonary circulation

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Introduction

In the past decade, left ventricular assist devices (LVADs) have become an integrated component of treatment algorithms for patients with end-stage heart failure (HF) in the clinical setting of lifelong destination therapy. Use of LVADs generating continuous flow (CF) has increased exponentially as survival rates have increased up to 80% at year 1 and ~70% at year 2 post-implantation.[1,2] Despite the evidence of beneficial effect of LVAD therapy on gross pulmonary haemodynamics,[3] respiratory failure occurs in 2.73 events per 100 patient-months in the first 12 months post-LVAD implantation, exceeding the rate of renal dysfunction or stroke or the incidence of right ventricle failure.[4] Furthermore, respiratory failure incidence in the LVAD population increased from the 2008–11 period to the 2012–14 period.[4] However, it is not clearly understood how LVADs influence the lungs.

The heart and lungs serve as an integrated organ system. They are linked neurohumourally and hemodynamically (e.g. atrial natriuretic peptide, brain-type natriuretic peptide, and angiotensin II).[5] Structural and functional alterations of the lungs in HF are well described[5,6] and correlate to HF severity and patient survival.[7]

Therefore, it is hypothesized that the alteration in CF LVAD influences pulmonary function (PF) and is related to survival rate. However, knowledge is still lacking about the long-term effect of CF pumps on the lungs.[2,8,9] Accordingly, the present retrospective study was to investigate changes in PF post-LVAD placement in relation to the haemodynamic changes and their association with survival.

Methods

Patients

From the 274 patients screened, final study analysis involved 44 patients with end-stage HF who had CF LVAD implantation between 1 February 2007 and 31 December 2015 at Mayo Clinic in Rochester, Minnesota. Study participants included only the patients originally indicated as a bridge to transplant with pulmonary function tests (PFTs) and invasive haemodynamic studies available pre-LVAD and post-LVAD implantation as part of follow-up evaluation on waiting list. Patients with PFTs provided in non-hemodynamically stable conditions or with comments of not 'adequate' or poor effort were excluded, as were those who underwent cardiac transplant. In addition, patients with implanted pulsatile pumps were excluded; patients were excluded if they had received concomitant right ventricle mechanical support, had received extracorporeal membrane oxygenation perioperatively, or had missed post-LVAD PFT or invasive haemodynamic study follow-up. Patient demographic characteristics were evaluated for functional and haemodynamic qualities. Maximal exercise capacity test before LVAD implantation was available for 34 patients (77%) and showed a mean (standard deviation, SD) peak oxygen consumption at 11.8 (4.1) mL/kg/min. At hospital discharge, mean (SD) LVAD pump power, speed, and flow were 6.25 (0.77) W, 9270 (260) rpm, and 5.3 (0.7) L/min for HeartMate II (Thoratec Corp.) and 6.75 (0.52) W, 2630 (150) rpm, and 5.0 (1.0) L/min for HeartWare (HeartWare International Inc.), respectively.

Study design

The present single-centre, retrospective, case–control study was approved by the Mayo Clinic Institutional Review Board. We acquired pre-LVAD and post-LVAD data to determine pulmonary pressure and PF. For PF, the maximal amount of air that a person could ventilate -forced vital capacity (FVC), and the maximal amount of air expired from full inspiration in 1 s-forced expiratory volume in 1 s (FEV_1), and the FEV_1 to FVC ratio were acquired in accordance with the American Thoracic Society/European Respiratory Society guideline.[10] For determination of capacity to transfer oxygen from the lungs into the pulmonary capillaries, the diffusing capacity of the lung for carbon monoxide (D_{LCO}) was obtained and was assessed through standardized single-breath technique based on the European Respiratory Society guideline.[11] In addition, right heart catheterization data were obtained from before LVAD implantation, and clinical records were reviewed for follow-up assessment of pulmonary vascular pressures, including right atrial pressure (RAP), pulmonary artery systolic pressure (PASP), pulmonary artery diastolic pressure (PADP), mean pulmonary arterial pressure (mPAP), and pulmonary capillary wedge pressure (PCWP). Cardiac output (CO) and cardiac index were evaluated with thermodilution technique[12]; pulmonary vascular resistance (PVR) with PVR index was calculated by the standard formula PVR = (mPAP − PCWP)/CO.[12] Clinical charts from follow-up visits were correspondingly reviewed for pump characteristics and related blood markers.

Statistical analysis

Variables were summarized as mean (SD) for continuous measurements and frequency (percentage) for categorical measurements. Pre-implantation and post-implantation values were compared with the use of matched-pair *t*-test or Wilcoxon signed rank test. Pearson product moment correlation was conducted to test the relationship between pre-implantation and post-implantation values. For sub-analysis of PF and diffusion capacity, we grouped patients as within 6 months (6MG) and 12 months (12MG) post-LVAD on the basis of time when they had PFTs and D_{LCO} assessments. The groups were analysed separately. This approach allowed for analysis of changes in PFT data in earlier vs. later post-implantation periods. Cox proportional hazards model was used to assess survival experience of the two groups, and log-rank *P*-value and hazard ratio (HR) were reported. $P < 0.05$ was considered statistically significant. Data were analysed through statistical software (JMP Pro 10; SAS Institute Inc.).

Results

Patient demographic characteristics, including medical history, cardiac risk factors, and related blood marker levels, were analysed for functional and haemodynamic qualities (*Table 1*).

Table 1 Characteristics of the 44 study participants

Characteristic	Value[a]
Baseline	
Age, year	59 (9)
Male sex	33 (75)
Weight, kg	87.4 (14.6)
Height, m	1.75 (0.08)
Body mass index, kg/m^2	28.7 (4.7)
Cardiomyopathy	
Non-ischaemic dilated	23 (52)
Ischaemic	17 (39)
Hypertrophic	4 (9)
Diabetes mellitus	15 (34)
Hypertension	21 (47)
COPD	8 (18)
Obstructive sleep apnoea	16 (36)
Chronic kidney disease	30 (68)
Hyperlipidaemia	19 (43)
Atrial fibrillation	25 (56)
Smoking	10 (22)
Functional class NYHA	
III+	4 (10)
IV	40 (90)
Treatment	
β-Blocker	41 (93)
ACE-I/ARB	24 (54)
Amiodarone	26 (59)
Loop diuretic, >80 mg/day	26 (59)
HeartMate II LVAD[b]	34 (77)
HeartWare LVAD[c]	10 (23)
LVEF, %	21 (13)
LVEDD, mm	67.3 (12.2)
Haemoglobin, g/dL	11.5 (1.7)
Leucocytes, ×10^9/L	7.5 (2.6)
Platelets, ×10^9/L	179 (59)
Creatinine, mg/dL	1.4 (0.5)
Serum urea nitrogen, mg/dL	27.1 (16.9)
Potassium, mmol/L	4.1 (0.4)
Total bilirubin, mg/dL	1.5 (1.2)
AST, U/L	62.5 (143.8)
ALT, U/L	62.4 (188.2)
NT-proBNP, pg/mL	5744 (5868)
Functional and haemodynamic	
INTERMACS class	
I	1 (2)
II	12 (27)
III	8 (18)
IV	19 (44)
V	3 (7)
VI	1 (2)
RAP, mm Hg	13.9 (6.3)
PASP, mm Hg	53.8 (14.8)
PADP, mm Hg	25.8 (8.2)
mPAP, mm Hg	38.0 (11.4)
PCWP, mm Hg	22.9 (7.2)
CO, L/min	4.0 (1.4)
CIx, L/min/m^3	2.0 (0.6)
PVR, Woods U	3.9 (2.6)
PVRI, Woods U/m^2	7.9 (5.3)

ACE-I, angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; ARB, angiotensin II receptor antagonist; AST, aspartate aminotransferase; CIx, cardiac index; CO, cardiac output; COPD, chronic obstructive pulmonary disease; INTERMACS, International Registry for Mechanically Assisted Circulatory Support; LVAD, left ventricular assist device; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary artery pressure; NT-proBNP, amino-terminal pro-brain-type natriuretic peptide; NYHA, New York Heart Association; PADP, pulmonary artery diastolic pressure; PASP, pulmonary artery systolic pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; PVRI, pulmonary vascular resistance index; RAP, right atrial pressure.
[a]Values are presented as mean (standard deviation) for continuous measurements and frequency (%) for categorical measurements.
[b]Manufacturer is Thoratec Corp.
[c]Manufacturer is HeartWare International Inc.

Pulmonary function and diffusing capacity of the lung for carbon monoxide post-left ventricular assist device implantation

Pre-LVAD implantation, impaired age-predicted %FVC, %FEV_1, and %D_{LCO} were observed and were further impaired post-LVAD (median, 237 days post-LVAD) (*Figure 1*). *Table 2* illustrates the alteration in PF pre-LVAD and post-LVAD implantation. Significant relationships were found in FVC, FEV_1, and D_{LCO} between pre-LVAD and post-LVAD (r = 0.59, P = 0.001; r = 0.70, $P < 0.001$; and r = 0.74, $P < 0.001$; respectively).

Subanalysis of pulmonary function based on time since left ventricular assist device implantation

In subsequent analysis, the 6MG (n = 14; median, 103 days post-LVAD) showed significant decreases in mean (SD) D_{LCO} [16.8 (4.5) to 13.2 (6.0) mL/mm Hg/min, P = 0.05], %D_{LCO} [61% (15%) to 48% (17%), P = 0.002], and D_{LCO} to alveolar volume (V_A) [3.6 (0.8) to 3.0 (1.0), P = 0.01] after LVAD. However, no significant changes in %FEV_1 [64% (19%) to 59% (21%), P = 0.27] and %FVC [71% (17%) to 63% (18%), P = 0.07] were observed. In contrast, the 12MG (n = 30; median, 186 days post-LVAD) showed significant declines in mean (SD) D_{LCO} [18.27 (5.2) to 14.24 (4.8) mL/mm Hg/min, $P < 0.001$], %D_{LCO} [67% (20%) to 52% (16%), $P < 0.001$], D_{LCO} to V_A ratio [3.8 (0.9) to 3.2 (0.8), $P < 0.001$], FEV_1 [2.3 (0.7) L vs. 2.0 (0.6) L, P = 0.04], %FEV_1 [66.3% (17.3%) vs. 60.6% (19.6%), P = 0.04], and %FVC [71% (14%) vs. 64% (16%), P = 0.01].

Pulmonary vascular hemodynamic post-left ventricular assist device implantation

In analysis of haemodynamics (n = 28; median, 370 days post-implantation), mean (SD) PCWP was reduced by 10.1 (1.6) mm Hg from pre-LVAD to post-LVAD ($P < 0.01$), which indicates a decrease in left ventricular (LV) filling pressure (*Table 3*). Similarly, reductions were found in mean (SD) mPAP by 15.1 (2.2) mm Hg ($P < 0.01$) and PVR by 1.4 (0.3) Woods U ($P < 0.01$) from pre-LVAD implantation. These results suggest that LV filling pressure and PVR were improved following LVAD implantation. In addition, the data revealed a significant inverse relationship between ΔD_{LCO} and ΔPCWP pre-implantation to post-implantation (r = 0.50, $P < 0.01$). Moreover, ΔD_{LCO} was inversely related to ΔRAP (r = 0.39, $P < 0.05$). However, trends noticed in other variables, including ΔPADP, PASP, PVR, and mPAP, were not related to ΔD_{LCO} ($P > 0.05$) in the available data. *Figure 2* illustrates the relationship between changes in PCWP and D_{LCO}.

Figure 1 Function changes from pre-LVAD to post-LVAD implantation. (A) Age-predicted pulmonary function change. (B) D_{LCO} change. Error bars indicate standard deviation. D_{LCO} indicates diffusing capacity of the lung for carbon monoxide; D_{LCO}/V_A, diffusing capacity of the lung for carbon monoxide to alveolar volume; LVAD, left ventricular assist device; $\%D_{LCO}$, age % predicted diffusing capacity of the lung for carbon monoxide corrected for haemoglobin; $\%FEV_1$, age % predicted forced expiratory volume in 1 s; %FVC, age % predicted forced vital capacity.

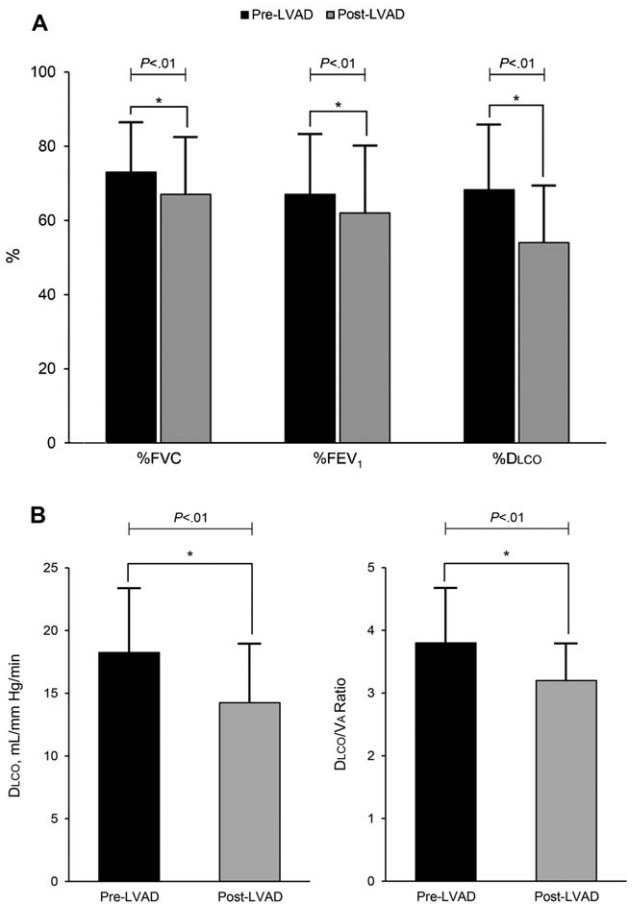


Table 2 Pulmonary function change before to after left ventricular assist device implantation

Variable (N = 44)	LVAD implantation, Mean (SD)		P-value
	Before	After	
D_{LCO}, mL/mm Hg/min	18.3 (5.2)	14.3 (4.8)	<0.01
$\%D_{LCO}$	69 (18)	54 (18)	<0.01
D_{LCO} to V_A ratio	3.8 (0.8)	3.2 (0.8)	<0.01
FEV_1, L	2.3 (0.7)	2.1 (0.7)	<0.01
$\%FEV_1$	68 (17)	62 (19)	0.01
FVC, L	3.2 (0.8)	2.9 (0.9)	0.01
%FVC	73 (14)	68 (16)	<0.01
FEV_1 to FVC ratio	0.72 (0.1)	0.72 (0.1)	0.50

D_{LCO}, diffusing capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; LVAD, left ventricular assist device; SD, standard deviation; V_A, alveolar volume; $\%D_{LCO}$, age % predicted diffusing capacity of the lung for carbon monoxide corrected for haemoglobin; $\%FEV_1$, age % predicted forced expiratory volume in 1 s; %FVC, age % predicted forced vital capacity; V_A, alveolar volume.

Table 3 Change in pulmonary vascular haemodynamics before to after left ventricular assist device implantation

Variable (N = 28)	LVAD implantation, Mean (SD)		P-value
	Before	After	
RAP, mm Hg	14.7 (6.0)	11.9 (6.0)	0.03
PASP, mm Hg	55.8 (13.0)	37.7 (12.3)	<0.01
PADP, mm Hg	26.7 (8.1)	16.1 (5.8)	<0.01
mPAP, mm Hg	39.7 (11.4)	24.6 (7.8)	<0.01
PCWP, mm Hg	23.4 (5.9)	13.3 (6.5)	<0.01
CO, L/min	4.3 (1.5)	4.9 (1.1)	0.96
CIx, L/m^3	2.1 (0.7)	2.5 (0.5)	0.99
PVR, Woods U	3.8 (1.7)	2.4 (1.0)	<0.01
PVRI, Woods U/m^2	7.7 (3.3)	4.7 (1.8)	<0.01

CIx, cardiac index; CO, cardiac output; LVAD, left ventricular assist device; mPAP, mean pulmonary artery pressure; PADP, pulmonary artery diastolic pressure; PASP, pulmonary artery systolic pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; PVRI, pulmonary vascular resistance index; RAP, right atrial pressure; SD, standard deviation.

Survival analysis

Survival analysis from a landmark point of 6 months showed that ΔD_{LCO} can be a significant predictor of death for LVAD patients [HR (95% confidence interval, CI), 0.60 (0.28–0.98); P = 0.03]. However, this predictive effect was attenuated when analysed within 12 months [HR (95% CI), 0.88 (0.72–1.06); P = 0.22]. No patient had transplant within 6 months; however, five patients underwent transplant within 12 months. After adjustment for transplant within 12 months, the effect of ΔD_{LCO} on death was not altered [HR (95% CI), 0.88 (0.70–1.07); P = 0.20]. Kaplan–Meier survival curve is carried from the first year on the basis of ΔD_{LCO} stratification (*Figure 3*). Furthermore, D_{LCO} also appeared to be a significant predictor of death at 6 months [HR (95% CI), 0.58 (0.28–0.85); P = 0.03] and 12 months [HR (95% CI), 0.83 (0.70–0.96); P = 0.02] post-LVAD implantation (*Figure 4*).

Discussion

In the present study, we observed significant reductions in D_{LCO} and PF post-LVAD implantation, with decreases in pulmonary arterial resistance, mPAP, and PCWP compared with pre-LVAD implantation. However, degree of D_{LCO} deterioration post-LVAD was relative to the successful intravascular volume management post-LVAD.

A remarkable D_{LCO} decrease in the 6MG without significant changes in $\%FEV_1$ and %FVC may suggest early alteration in D_{LCO} post-LVAD implantation compared with changes in $\%FEV_1$ and %FVC, which may develop later. Furthermore, the degree of reduction in D_{LCO} within 6 months post-LVAD implantation was significantly associated with survival.

Figure 2 Relationship between ΔD_{LCO} and ΔPCWP pre-LVAD to post-LVAD implantation among 28 patients. Solid line indicates linear fit; dashed lines, 95% confidence interval. ΔD_{LCO} indicates change in diffusing capacity of the lung for carbon monoxide; ΔPCWP, change in pulmonary capillary wedge pressure; LVAD, left ventricular assist device; RR, relative risk.

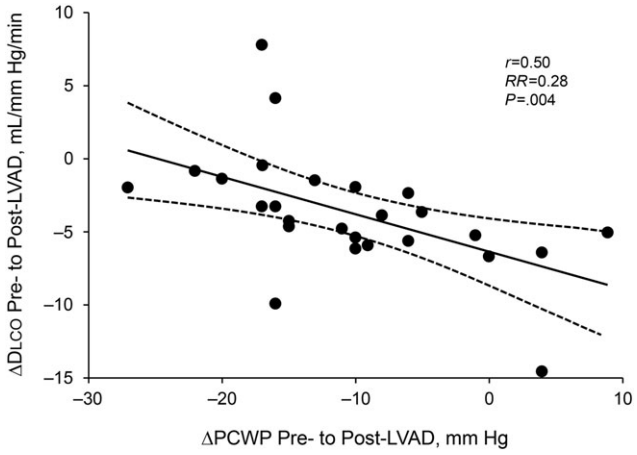
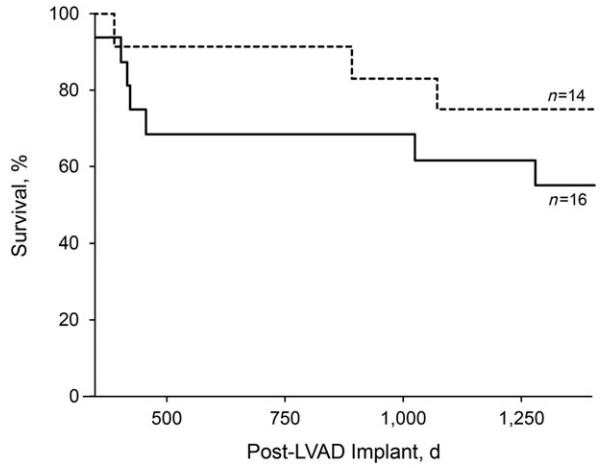


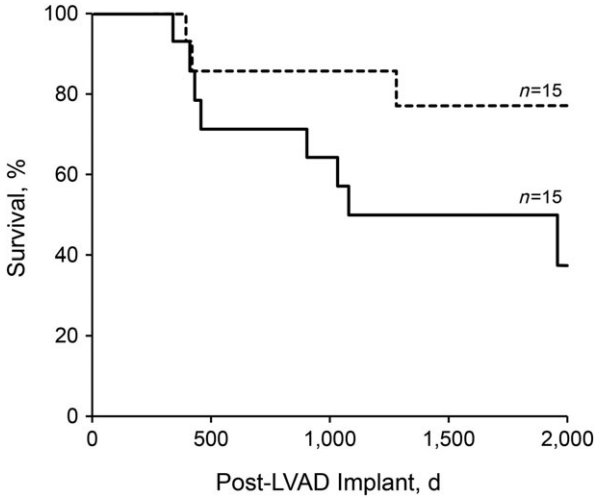
Figure 3 Kaplan–Meier plot based on change in diffusing capacity of the lung for carbon monoxide (ΔD_{LCO}) pre-LVAD to post-LVAD implantation. Dashed line indicates patients with $\Delta D_{LCO} < 4.2$ mL/mm Hg/min; solid line, patients with $\Delta D_{LCO} \geq 4.2$ mL/mm Hg/min. LVAD indicates left ventricular assist device.



Forced vital capacity

With a shared intrathoracic space, an LVAD patient has to accommodate an alien object (pump) with a gross volume from ~50 mL (HeartWare) to ~63 mL (HeartMate II), excluding inflow and outflow conduits, which anatomically has a constant role in certain limitations of maximal inspiration volumes. Cardiothoracic surgery can transiently decrease spirometric measurements.[13–15] In addition, respiratory muscle weakness and consequent reduction in PF have been found in patients

Figure 4 Kaplan–Meier plot based on D_{LCO} at 12 months post-left ventricular assist device implantation. Dashed line indicates patients with $D_{LCO} \geq 13.5$ mL/mm Hg/min; solid line, patients with $D_{LCO} < 13.5$ mL/mm Hg/min (based on median value). D_{LCO} indicates diffusing capacity of the lung for carbon monoxide.



with chronic HF.[16] The acute post-surgical PF changes likely have a minor effect on the observed reduction in FVC due to a longer follow-up. Nevertheless, FVC reduction occurs by ~300 mL in nearly 9 months post-surgery, likely due to a combination of aetiological factors.

Forced expiratory volume in 1 s

Data also showed a reduction in $\%FEV_1$ from pre-LVAD to post-LVAD implantation [mean (SD), 68% (17%) to 62% (19%), $P = 0.01$] with no significant change in FEV_1 to FVC ratio and no significant difference between the 6MG and 12MG. Obstructive PF abnormalities are traditionally associated with congestive HF, mainly as effects of post-capillary pulmonary hypertension.[5,6] Both devices in the present study provide a similar level of circulatory support, allowing improved control of fluid congestion because of increased renal perfusion and a positive effect on LV unloading.[17]

In concordance with previous literature, the haemodynamic follow-up data showed significant reductions in RAP and PCWP (*Table 3*). Despite the haemodynamic and volume optimization post-LVAD implantation documented in approximately two-thirds of the studied population, the data did not show an improvement in $\%FEV_1$ that could have been speculated. Therefore, we hypothesized that the mechanism of airflow obstruction post-LVAD might be different from a conventional HF model. The bronchial circulation surrounding the bronchial tree is the only portion of lung vasculature directly exposed to CF conditions. This exposure could lead to potential engorgement of the bronchial vascular network

during LVAD support, thereby contributing to bronchial obstruction. The currently available data do not provide information to confirm the proposed hypothesis, and thus, this continues to be speculation.

Diffusing capacity of the lung for carbon monoxide

Remarkably, the study data showed a profound decrease in pulmonary D_{LCO} post-LVAD implantation consistent with findings of Mohamedali *et al*.[18] This decline remained significant when corrected for V_A (*Figure 2*) and was clearly evident in subsequent analyses of the 6MG and 12MG.

Because of the retrospective nature of our study, it lacks early post-implantation haemodynamic data, but we can anticipate a decrease of pulmonary pressures in ~3 to 6 months post-LVAD implantation.[19,20] Therefore, we suggest that an early decrease in D_{LCO} is likely related to changes in pulmonary vascular pressures post-LVAD implantation. However, data supported the relationship between optimal haemodynamic unloading and change in diffusing capacity post-LVAD implantation (*Figure 3*). Presented data did not show any other significant relationship between pulmonary vascular pressures and diffusing capacity, probably because of an inability to timely match D_{LCO} data with invasive haemodynamic studies.

The inverse relationship between improved haemodynamics and D_{LCO} is of particular interest. Despite the fact that the study design does not allow for direct understanding, the literature provides several possible concepts, which may support current findings.

The complex relationship between D_{LCO} and the pulmonary vascular pressures and PVR has been described in a chronic HF model.[5] In particular, diffusion capacity is a point of heart and lung concurrence through its two components: *membrane conductance*, a term describing rate of reaction of the gas with haemoglobin, and capillary blood volume (Vc). Decreased membrane conductance, observed in severe chronic HF[21] and inversely correlating with PVR,[22] could represent thickening of the alveolar-capillary barrier from fluid accumulation or fibrosis. According to Gehlbach and Geppert,[5] this phenomenon has been thought to be a protective mechanism against pulmonary oedema in patients with chronic pulmonary venous hypertension.

First, after the heart transplant, fibrotic transformation of the alveolar-capillary membrane may not be fully reversed.[23] In addition, Vc initially decreases, but it eventually increases over time. These fibrotic formations may contribute to a decrease in lung diffusion.[23] A study by Ewert *et al*.[24] reported that lung diffusion did not improve after orthotropic heart transplant and could be the effect of cyclosporine. It is possible that long-term elevation of neurohumoural drive potentiated by CF may contribute to some of the observed changes post-LVAD implantation.[5,25] However, further studies are needed to determine this mechanism.

Second, in healthy condition, the alveolar type II cell transport of sodium ion provides the major force for excessive water removal from the alveolar space (Starling forces).[26] This mechanism of sodium/water conductance system is important for optimal gas transfer and is altered in HF with increased PCWP.[27] Interestingly, the optimization of the pulmonary pressures may not improve the transport mechanisms in chronic HF.[28] In addition, low pulse pressure of CF LVAD negatively affects nitric oxide production, inflammatory biomarker levels (e.g. tumour necrosis factor-α and C-reactive protein),[25] and endothelial function.[8,29,30] Chronic inflammation may possibly contribute to alteration of sodium/alveolar fluid balance post-LVAD implantation. Alterations of endothelial and alveolar cells are thought to be primarily responsible for lung diffusion decrease in patients with HF. Nevertheless, experimental observations are also consistent with an involvement of alveolar water mechanism.[26]

Third, Permutt and Caldini[31] showed that it is the static recoil pressure relative to the left atrial pressure (and not a total vascular resistance) that provides the driving pressure back to the heart.[32,33] The magnitude of the static pressure is determined by the blood volume and the elastic properties of the blood vessels. An increase in Vc is associated with an increase in the upstream end of the driving pressure returning blood to the heart.[34] The blood volume distribution is also affected by the influence of one ventricle on the other through ventricular interdependence.[35]

For a specified increase in Vc, the increase in static recoil is proportional to the reciprocal of the compliance of the pulmonary circulation.[34,36] Therefore, variable functional uncoupling of right ventricular and LV performance, described by Uriel *et al*.,[37] post-LVAD implantation might also contribute to a potential ventilation–perfusion mismatch and consequently affect the diffusing capacity through a decrease in the capillary recruitment. This occurrence may be related to a relative rigidity of the current pumps, which do not respond to different physiological demands and body positions because of a fixed revolutions per minute setting. Our data showed a significant inverse relationship between ΔD_{LCO} and change in pump flow from discharge to 6 months post-LVAD implantation ($r = -0.35$, $P = 0.04$) for patients with HeartMate II pumps. Because no other relationship reached significance, further prospective evaluation is necessary for profound understanding of D_{LCO} changes post-LVAD implantation.

Lastly, although the CF pumps provide better durability over the pumps providing pulsatile flow,[3] pulsatile flow has been shown to be beneficial for pulmonary capillary recruitment and the rate of oxygen uptake.[38,39] New-generation pumps implementing artificial pulsatility will be of interest for future research of lung diffusion in the LVAD population.[40]

Prospective studies using appropriate techniques (rebreath D_{LCO} assessment) are needed to evaluate the dynamic of changes in membrane conductance and Vc post-implantation. Nevertheless, we have hypothesized that the Vc component has a dominant role within the first 6 months to 1 year post-LVAD implantation. Remodelling of the alveolar-capillary membrane with long-standing changes in membrane conductance may occur in the long term (~12 months) after implantation.

The association between D_{LCO} and survival in the HF population has been previously described, with more recent data also from HF patients with preserved ejection fraction.[41,42] In correspondence with a recently published study by Bedzra *et al.*,[43] our data do not support association between D_{LCO} pre-LVAD implantation and patient survival. Nevertheless, the degree of change between pre-LVAD implantation to 6 months post-implantation does carry predictive value, as well as the D_{LCO} value itself at 6 and 12 month landmark points. The mortality risk associated with D_{LCO} may reflect more complex pathophysiological pathways, in which studying the LVAD model may be of great help for further understanding.

Limitations

The present retrospective study addressed some limitations. Small sample size limits multivariate HR analyses. The study involved eight patients (18%) with chronic obstructive pulmonary, and 10 patients (22%) were smokers. Potential bias could have been introduced in selection of only those patients with available post-LVAD PFT data, who in the present study were patients considered for consequent heart transplant, likely at a younger age and with a greater clinical perspective. However, the post-LVAD PFT data were indicated electively as a part of follow-up evaluation for those on the heart transplant waiting list. To the contrary, this high selection in retrospective design may be of some benefit allowing to more closely elucidate hypothesized mechanisms. Certain time variation between PFTs and absence of serial follow-up data restrict the ability to comment on the development of PFT changes over time post-LVAD implantation. Single-breath D_{LCO} technique does not allow calculation of membrane conductance and Vc components, and the clinical data lack reproducibility. The retrospective nature of the study does not allow for physiological explanation of observed PF changes.

Conclusions

Our findings suggest that PF may not improve following LVAD implantation. However, lung diffusing capacity appears to be a significant predictor of survival in patients with LVADs. Information is lacking for determining alterations in PF and pressure in HF following LVAD implantation. Therefore, these important findings are hypothesis generating for further prospective physiological studies.

The alveolar-capillary interface and bronchial circulation are particularly susceptible to the alterations in blood flow and pressure characteristics of the LVAD population. The described functional changes may be associated with complex pulmonary vascular and cardiac changes, including right ventricular function after LVAD implantation and potential alterations of the alveolar-capillary membrane. We believe these data are important for generation of hypotheses for prospective studies, because studies have not been performed on alterations in breathing mechanics, the gas exchange after LVAD placement, and the association with right ventricular and LV function after LVAD implantation. As a result, a profound understanding of relationships between pulmonary vascular circulation and lung function changes in the LVAD setting could contribute to protection of function in the lung exposed to CF and potentially add to optimization of this therapy in the future. Clinical interpretations of PFTs in the LVAD population must be interpreted with caution until more studies provide solid evidence for clinical outcomes.

Conflict of interest

None declared.

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References

1. Jorde UP, Kushwaha SS, Tatooles AJ, Naka Y, Bhat G, Long JW, Horstmanshof DA, Kormos RL, Teuteberg JJ, Slaughter MS, Birks EJ, Farrar DJ, Park SJ, HeartMate II Clinical Investigators. Results of the destination therapy post-Food and Drug Administration approval study with a continuous flow left ventricular assist device: a prospective study using the INTERMACS registry (Interagency Registry for Mechanically Assisted Circulatory Support). *J Am Coll Cardiol* 2014; **63**: 1751–1757.
2. Slaughter MS, Rogers JG, Milano CA, Russell SD, Conte JV, Feldman D, Sun

B, Tatooles AJ, Delgado RM 3rd, Long JW, Wozniak TC, Ghumman W, Farrar DJ, Frazier OH, HeartMate II Investigators. Advanced heart failure treated with continuous-flow left ventricular assist device. *N Engl J Med* 2009; **361**: 2241–2251.
3. Sajgalik P, Grupper A, Edwards BS, Kushwaha SS, Stulak JM, Joyce DL, Joyce LD, Daly RC, Kara T, Schirger JA. Current status of left ventricular assist device therapy. *Mayo Clin Proc* 2016; **91**: 927–940.
4. Kirklin JK, Naftel DC, Pagani FD, Kormos RL, Stevenson LW, Blume ED, Myers SL, Miller MA, Baldwin JT, Young JB. Seventh INTERMACS annual report: 15,000 patients and counting. *J Heart Lung Transplant* 2015; **34**: 1495–1504.
5. Gehlbach BK, Geppert E. The pulmonary manifestations of left heart failure. *Chest* 2004; **125**: 669–682.
6. Ceridon ML, Morris NR, Hulsebus ML, Olson TP, Lalande S, Johnson BD. Influence of bronchial blood flow and conductance on pulmonary function in stable systolic heart failure. *Respir Physiol Neurobiol* 2011; **177**: 256–264.
7. Olson TP, Denzer DL, Sinnett WL, Wilson T, Johnson BD. Prognostic value of resting pulmonary function in heart failure. *Clin Med Insights Circ Respir Pulm Med* 2013; **7**: 35–43.
8. Baba A, Dobsak P, Mochizuki S, Saito I, Isoyama T, Takiura K, Shibata M, Abe Y, Chinzei T, Vasku J, Imachi K. Evaluation of pulsatile and nonpulsatile flow in microvessels of the bulbar conjunctiva in the goat with an undulation pump artificial heart. *Artif Organs* 2003; **27**: 875–881.
9. Radovancevic B, Vrtovec B, de Kort E, Radovancevic R, Gregoric ID, Frazier OH. End-organ function in patients on long-term circulatory support with continuous- or pulsatile-flow assist devices. *J Heart Lung Transplant* 2007; **26**: 815–818.
10. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows: Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal: official statement of the European Respiratory Society. *Eur Respir J Suppl* 1993; **16**: 5–40.
11. Macintyre N, Crapo RO, Viegi G, Johnson DC, van der Grinten CP, Brusasco V, Burgos F, Casaburi R, Coates A, Enright P, Gustafsson P, Hankinson J, Jensen R, McKay R, Miller MR, Navajas D, Pedersen OF, Pellegrino R, Wanger J. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J* 2005; **26**: 720–735.
12. Baim DS. *Grossman's Cardiac Catheterization, Angiography, and Intervention*. Philadelphia (PA): Lippincott Williams & Wilkins; 2006.
13. Chetta A, Bobbio A, Aiello M, Del Donno M, Castagnaro A, Comel A, Malorgio R, Carbognani P, Rusca M, Olivieri D. Changes in lung function and respiratory muscle strength after sternotomy vs. laparotomy in patients without ventilator limitation. *Eur Surg Res* 2006; **38**: 489–493.
14. Ragnarsdottir M, Kristjánsdottir A, Ingvarsdottir I, Hannesson P, Torfason B, Cahalin L. Short-term changes in pulmonary function and respiratory movements after cardiac surgery via median sternotomy. *Scand Cardiovasc J* 2004; **38**: 46–52.
15. Buchman AS, Boyle PA, Wilson RS, Gu L, Bienias JL, Bennett DA. Pulmonary function, muscle strength and mortality in old age. *Mech Ageing Dev* 2008; **129**: 625–631.
16. Dall'Ago P, Chiappa GR, Guths H, Stein R, Ribeiro JP. Inspiratory muscle training in patients with heart failure and inspiratory muscle weakness: a randomized trial. *J Am Coll Cardiol* 2006; **47**: 757–763.
17. Drakos SG, Wever-Pinzon O, Selzman CH, Gilbert EM, Alharethi R, Reid BB, Saidi A, Diakos NA, Stoker S, Davis ES, Movsesian M, Li DY, Stehlik J, Kfoury AG, UCAR (Utah Cardiac Recovery Program) Investigators. Magnitude and time course of changes induced by continuous-flow left ventricular assist device unloading in chronic heart failure: insights into cardiac recovery. *J Am Coll Cardiol* 2013; **61**: 1985–1994.
18. Mohamedali B, Bhat G, Yost G, Tatooles A. Changes in spirometry after left ventricular assist device implantation. *Artif Organs* 2015; **39**: 1046–1050.
19. Morgan JA, Paone G, Nemeh HW, Murthy R, Williams CT, Lanfear DE, Tita C, Brewer RJ. Impact of continuous-flow left ventricular assist device support on right ventricular function. *J Heart Lung Transplant* 2013; **32**: 398–403.
20. Salzberg SP, Lachat ML, von Harbou K, Zund G, Turina MI. Normalization of high pulmonary vascular resistance with LVAD support in heart transplantation candidates. *Eur J Cardiothorac Surg* 2005; **27**: 222–225.
21. Siegel JL, Miller A, Brown LK, DeLuca A, Teirstein AS. Pulmonary diffusing capacity in left ventricular dysfunction. *Chest* 1990; **98**: 550–553.
22. Assayag P, Benamer H, Aubry P, de Picciotto C, Brochet E, Besse S, Camus F. Alteration of the alveolar-capillary membrane diffusing capacity in chronic left heart disease. *Am J Cardiol* 1998; **82**: 459–464.
23. Bussieres LM, Pflugfelder PW, Ahmad D, Taylor AW, Kostuk WJ. Evolution of resting lung function in the first year after cardiac transplantation. *Eur Respir J* 1995; **8**: 959–962.
24. Ewert R, Wensel R, Bettmann M, Spiegelsberger S, Grauhan O, Hummel M, Hetzer R. Ventilatory and diffusion abnormalities in long-term survivors after orthotopic heart transplantation. *Chest* 1999; **115**: 1305–1311.
25. Hall JL, Fermin DR, Birks EJ, Barton PJ, Slaughter M, Eckman P, Baba HA, Wohlschlaeger J, Miller LW. Clinical, molecular, and genomic changes in response to a left ventricular assist device. *J Am Coll Cardiol* 2011; **57**: 641–652.
26. Guazzi M. Alveolar gas diffusion abnormalities in heart failure. *J Card Fail* 2008; **14**: 695–702.
27. West JB. Invited review: pulmonary capillary stress failure. *J Appl Physiol* 2000; **89**: 2483–2489.
28. Guazzi M, Agostoni P, Bussotti M, Guazzi MD. Impeded alveolar-capillary gas transfer with saline infusion in heart failure. *Hypertension* 1999; **34**: 1202–1207.
29. Thacher T, Gambillara V, da Silva RF, Silacci P, Stergiopulos N. Reduced cyclic stretch, endothelial dysfunction, and oxidative stress: an ex vivo model. *Cardiovasc Pathol* 2010; **19**: e91–e98.
30. Maltais S, Jaik NP, Feurer ID, Wigger MA, Disalvo TG, Schlendorf KH, Ahmad RM, Lenihan DJ, Stulak JM, Keebler ME. Mechanical circulatory support and heart transplantation: donor and recipient factors influencing graft survival. *Ann Thorac Surg* 2013; **96**: 1252–1258.
31. Permutt S, Caldini P. Regulation of cardiac output by the circuit: venous return. In Baan J, Noordergraaf A, Raines J, eds. *Cardiovascular System Dynamics*. Cambridge, Massachusetts: MIT Press; 1978. p465–478.
32. Karam M, Wise RA, Natarajan TK, Permutt S, Wagner HN. Mechanism of decreased left ventricular stroke volume during inspiration in man. *Circulation* 1984; **69**: 866–873.
33. Sylvester JT, Goldberg HS, Permutt S. The role of the vasculature in the regulation of cardiac output. *Clin Chest Med* 1983; **4**: 111–126.
34. Permutt S, Wise RA, Brower RG. How changes in pleural and alveolar pressure cause changes in afterload and preload. In Scharf SM, Cassidy SS, eds. *Heart–Lung Interactions in Health and Disease*. New York: Dekker; 1989. p243–250.
35. Santamore WP, Bove AA, Heckman JL. Right and left ventricular pressure-volume response to positive end-expiratory pressure. *Am J Physiol* 1984; **246**: H114–H119.
36. Guyton AC. Determination of cardiac output by equating venous return curves with cardiac response curves. *Physiol Rev* 1955; **35**: 123–129.
37. Uriel N, Sayer G, Addetia K, Fedson S, Kim GH, Rodgers D, Kruse E, Collins K, Adatya S, Sarswat N, Jorde UP, Juricek C, Ota T, Jeevanandam V, Burkhoff D, Lang RM. Hemodynamic ramp tests in patients with left ventricular assist devices. *JACC Heart Fail* 2016; **4**: 208–217.

38. Presson RG, Baumgartner WA, Peterson AJ, Glenny RW, Wagner WW. Pulmonary capillaries are recruited during pulsatile flow. *J Appl Physiol* 2002; **92**: 1183–1190.
39. Hauge A, Nicolaysen G. Pulmonary O_2 transfer during pulsatile and non-pulsatile perfusion. *Acta Physiol Scand* 1980; **109**: 325–332.
40. Mehra MR, Goldstein DJ, Uriel N, Cleveland JC, Yuzefpolskaya M, Salerno C, Walsh MN, Milano CA, Patel CB, Ewald GA, Itoh A, Dean D, Krishnamoorthy A, Cotts WG, Tatooles AJ, Jorde UP, Bruckner BA, Estep JD, Jeevanandam V, Sayer G, Horstmanshof D, Long JW, Gulati S, Skipper ER, O'Connell JB, Heatley G, Sood P, Naka Y, for the MOMENTUM 3 Investigators. Two-year outcomes with a magnetically levitated cardiac pump in heart failure. *N Engl J Med* 2018; **378**: 1386–1395.
41. Hoeper MM, Meyer K, Rademacher J, Fuge J, Welte T, Olsson KM. Diffusion capacity and mortality in patients with pulmonary hypertension due to heart failure with preserved ejection fraction. *JACC Heart Fail* 2016; **4**: 441–449.
42. Olson TP, Johnson BD, Borlaug BA. Impaired pulmonary diffusion in heart failure with preserved ejection fraction. *JACC Heart Fail* 2016; **4**: 490–498.
43. Bedzra EKS, Dardas TF, Cheng RK, Pal JD, Mahr C, Smith JW, Shively K, Masri SC, Levy WC, Mokadam NA. Pulmonary function tests do not predict mortality in patients undergoing continuous-flow left ventricular assist device implantation. *J Thorac Cardiovasc Surg* 2017; **154**: 1959–1970.e1.