Somaye Mohammadi[1], Mohammad Mostafa Ansari Ramandi[2], Ali Safaei[1], Mahsa Mirdamadi[1], Sepideh Taghavi[1], Ahmad Amin[1], Nasim Naderi[1]

[1]Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, Iran
[2]Cardiovascular Diseases Research Center, Birjand University of Medical Sciences, Birjand, Iran

Prognostic significance of lung diffusion capacity and spirometric parameters in relation to hemodynamic status in heart transplant candidates

Abstract

Introduction: Investigations have described a correlation between the severity of heart failure and the severity of pulmonary function abnormalities. In this study, we investigated the association of resting spirometric parameters, lung diffusion for carbon monoxide (DLCO), and the transfer coefficient (KCO) with hemodynamic variables and outcomes in a cohort of heart transplant candidates.

Material and methods: Between January 2018 and January 2020, a total of 100 patients with advanced heart failure who were scheduled for right heart catheterization (RHC) as a pre-transplant evaluation measure were enrolled. Spirometry and D_{LCO} were performed in all patients within 24 hours of their RHC. All selected patients were followed for a median (IQR) time of 6 (2–12) months. The end points of interest were heart failure-related mortality and a combined event involving HF-related mortality, heart transplantation (HTX), and need for the placement of a left ventricular assist device (LVAD).

Results: Among 846 patients scheduled for RHC, a total of 100 patients (25% female) with a mean (SD) age of 38.5 (12.8) were enrolled. There was a significant correlation between FEV_1/FVC and CVP ($\rho = -0.22$, p = 0.02), PCWP ($\rho = -0.4$, p < 0.001), mPAP ($\rho = -0.45$, p < 0.001), and PVR ($\rho = -0.32$, p = 0.001). The cardiac output correlated with D_{LCO} ($\rho = 0.3$, p = 0.008). Spirometry parameters, D_{LCO} parameters, and hemodynamic parameters did not correlate with the combined event. Among the several variables, only PVR had an independent association with the combined event.

Conclusion: Both mechanical and gas diffusion parameters of the lung were not associated with outcomes in the homogeneous group of heart transplant candidates.

Key words: heart failure, transplantation, spirometry, lung diffusion for carbon monoxide, hemodynamics

Introduction

Advances in heart failure (HF) treatment have led to an ever-increasing prevalence of end-stage heart failure and it is currently considered a public health priority in most parts of the world. It is estimated that approximately 5–10% of HF patients have advanced (stage D) heart failure [1, 2].

Investigations have thoroughly described a correlation between the severity of heart failure and the severity of pulmonary function abnormalities. Of note, patients with more severe heart failure have more severe abnormalities when compared with those who are at earlier stages of their disease. The abnormal pulmonary capillary hemodynamics in heart failure caused by increases in interstitial and alveolar edema result in impairment of lung mechanics, resistance in membrane conductance, and decreased gas transfer [3–5].

Although both restrictive and obstructive patterns have been seen in patients with heart failure, the mechanical impairment of the lungs in HF is commonly a restrictive lung disease shown by a preserved forced expiratory volume in one second/forced vital capacity (FEV_1/FVC) ratio with a progressively lower FEV_1, FVC, and alveolar volume (VA) as HF severity increases [3, 6]. The severity of mechanical impairment of the lungs correlates with exercise capacity

[5, 7]. Regarding lung diffusion capacity in HF measured by lung diffusion for carbon monoxide (D_{LCO}), some studies have shown that lung diffusion abnormalities not only correlate with HF severity and exercise performance, but also with HF prognosis [3, 8–10].

The association of spirometric parameters and D_{LCO} with hemodynamic status and outcome in patients with advanced (stage D) heart failure is less clear.

Although some studies investigating the prognostic value of spirometry in patients with stage C heart failure showed that spirometric values predict outcomes in these heart failure populations, other studies' spirometric values did not correlate with outcomes in patients with advanced heart failure awaiting heart transplantation [9, 11]. Furthermore, several lines of evidence suggest that D_{LCO} abnormalities persist in HF after optimal fluid removal or heart transplantation [12, 13].

In this study, we investigated the association of resting spirometric parameters, D_{LCO}, and the transfer coefficient (KCO) with hemodynamic variables and outcomes in a cohort of heart transplant (HTX) candidates.

Material and methods

Study population

The study population enrolled included patients scheduled for right heart catheterization (RHC) in our heart failure and transplantation department between January 2018 and January 2020 according to the following inclusion/ /exclusion criteria.

Inclusion criteria:
— Patients with advanced heart failure according to the European Society of Cardiology [2] who were scheduled for pre-transplant evaluation or left ventricular assist device (LVAD) implantation for the first time;
— On optimal guideline-directed medical therapies (GDMT) [2];
— Patients who had interagency registry for mechanically assisted circulatory support (INTERMACS) clinical profiles of 3 (patients who are stable but inotrope dependent) or 4 (patients who have resting symptoms at home on oral therapy) [14].

Exclusion criteria:
— Pulmonary disease which may cause obstructive or restrictive ventilatory defects;
— Smoker who continued smoking less than 4 days before the test;
— Anemia (hemoglobin less than 12 g/L);
— Chronic kidney disease with a glomerular filtration rate of 60% or less and/or end stage renal disease (ESRD) patients;
— Patients who were unable to perform spirometry/D_{LCO};
— Patients with an INTEMACS profile of 1 (patients with cardiogenic shock) or 2 (patients on inotropic support with progressive decline) [14];
— History of recent heart failure decompensation in the preceding month;
— Patients with significant pleural effusion.

The study was approved by the research and ethics committee of our institute (Ethics code: IR.RHC.REC.1399.081) and written informed consent was obtained from all patients.

Patient evaluations

Right heart catheterization (RHC) was performed via the standard method in all patients using a multipurpose A1 catheter in the catheterization laboratory. The pressures were all averaged out after 10 consecutive heart beats at end expiration in supine position. The following variables were measured for each patient: mean right atrial pressure (RAP); systolic and end-diastolic right ventricular (RV) pressure; systolic, diastolic, and mean pulmonary artery pressure (mPAP); pulmonary capillary wedge pressure (PCWP); mean arterial pressure (MAP); and mixed venous oxygen saturation and cardiac output (CO) measured by the Fick method. Cardiac index (CI) was calculated by dividing CO by body surface area (BSA). PVR was calculated by dividing the transpulmonary gradient (TPG) by cardiac output. The transpulmonary gradient was calculated by subtracting the mean PAP from PCWP.

Spirometry and D_{LCO} (PFTs) measurements are among routine pre-transplantation work ups in our center. Spirometry and D_{LCO} measurements were performed for all patients using the Ganshorn Medizin Electronic pulmonary function testing system with D_{LCO} measurement PowerCube® Diffusion+ within 24 hours of their RHC (just before RHC in more than 80% of them).

Spirometry was performed with the patient in a sitting position using the reproducibility and acceptability criteria. Maneuvers were selected according to the American Thoracic Society/European Respiratory Society (ATS/ERS) criteria.[15] In this analysis, we considered absolute and percent-of-predicted forced expiratory volume in one second (FEV_1 and % FEV_1), forced

vital capacity (FVC and %FVC), and the FEV_1/FVC ratio. A restrictive ventilatory pattern was defined as a combination of FEV_1/FVC that was normal or more than the 5th percentile (lower limit of normal [LLN]) and FVC<LLN with decreased calculated total lung capacity. A spirometric obstructive ventilatory pattern was defined as a combination of FEV_1/FVC below the 5th percentile (LLN) and FEV_1<LLN confirmed by an increased RV size with raw and significant reversibility of airway obstruction.

D_{LCO} and D_{LCO} corrected for alveolar volume (D_{LCO}/VA or KCO) was measured in the standard sitting position with the single breath constant expiratory flow technique according to the ATS recommendations which include rapid inspiration, inspired volume at least 90% of the largest vital capacity, breath-hold time between 9 and 11 seconds, and adequate washout and sample volumes [16].

The mean of all acceptable tests was considered. Calculations were standardized for breath-hold time and adjusted for dead space, gas collection conditions, and carbon dioxide concentration.

D_{LCO} was at STPD (standard temperature, pressure, and dry) and VA was at BTPS (standardized Body Temperature, Pressure, and Saturation)

The predicted values of D_{LCO} (%D_{LCO}) and KCO (%KCO) were calculated using the predictive equations for D_{LCO} and KCO derived by Amra et al. for the Iranian population [17].

Patients' follow-up and outcome measures

All selected patients were followed after the index right heart catheterization until the end of July 2020 with a median follow up time of 6 months. The end points of interest were heart failure-related mortality as well as a combined event of HF related-mortality, heart transplantation (HTX), and left ventricular assist device implantation (LVAD).

Statistical analysis

All analyses were conducted using IBM SPSS statistics 22 for Windows (IBM Corp, Armonk, NY, USA). One sample Kolmogorov Smirnov test was used to assess the normal distribution of variables.

Continuous variables with and without normal distribution are presented as means ± standard deviation and medians (interquartile range), respectively. They were compared using the Student's t-test and the Mann–Whitney U-test, as appropriate. Categorical data are presented as

numbers and percentages and were compared by the χ^2 test. The correlations between spirometric parameters, D_{LCO}, KCO, and hemodynamic parameters were assessed via Spearman's rank correlation coefficient. Stepwise binary multiple regression analysis was performed to assess the independent correlation between spirometric parameters, D_{LCO}, KCO, and hemodynamic findings with the outcome measure. All reported probability values were two-tailed and a p value < 0.05 was considered statistically significant.

Results

Among 846 patients scheduled for RHC, a total of 100 patients were enrolled according to our inclusion criteria. The mean (SD) age of patients was 38.5 (12.8) years. One-fourth of the patients were female. More than 90% of patients were already on guideline-directed medical therapies (GDMT). All of them were using loop diuretics, mineralocorticoid receptor antagonists (MRA), and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB). Beta-blockers could not be tolerated in 8 patients. The baseline characteristics of patients and their status at the end of the study are summarized in Table 1.

All PFTs were performed within 24 hours of RHC. The median (IQR) of the time interval between RHC and PFTs was 4 (3–5) hours. The PFTs were performed less than 6 hours before RHC in 82% of our study population. In 18% of patients, they were performed within 18–24 hours (the day before or after RHC).

Table 2 depicts hemodynamic variables and spirometry/D_{LCO} parameters.

Seventy percent (70%) of patients had a FEV_1 less than 80% of predicted value, 67% of patients had a FVC less than 80% of predicted value, and all patients had a FEV_1/FVC ratio over 70%. Figure 1 shows the spirometric patterns of our study population. Most patients show a restrictive ventilatory pattern in their pulmonary function tests (PFTs).

Regarding lung diffusion parameters, D_{LCO} and KCO were less than 80% of the predicted values in 71% and 26% of patients, respectively.

The spirometric and D_{LCO} measurement study results did not differ significantly in patients with and without a history of smoking. However, most cases from the smoker group (90%) involved former smokers; only 4 patients were current smokers who were smoking occasionally.

Table 1. Baseline characteristics of patients (n = 100)

Baseline characteristics		Value
Age in years, mean [SD]		38.5 (12.8)
Gender, number [%]	Female	25 (25)
	Male	75 (75)
BSA, m², mean [SD]		1.8 (0.2)
Heart failure type, number [%]	ICMP	23 (23)
	Non-ICMP	77 (77)
INTERMACS clinical profile, number [%]		
	3	65
	4	35
LVEF, % median [IQR]		10 (10–20)
Smokers, number [%]		31 (31)
Alcohol overuse, number [%]		21 (21)
DM, number [%]		10 (10)
ICD/CRT, number [%]		45 (45)
GDMT, number [%]		92 (92)
NT-Pro BNP, median [IQR], ng/dl		4926 (2613–14102)
Serum creatinine mean [SD], mg/dl		1.23 (0.55)
Hemoglubin, mean [SD], g/L		13.1 (2.1)
Intermittent inotrope therapy, number [%]		43 (43)
Heart transplantation		38 (38)
LVAD		3 (3)
Heart failure mortality		14 (14)

BNP — brain natriuretic peptide; BSA — body surface area; ICMP — ischemic cardiomyopathy; DM — diabetes mellitus; GDMT — guideline-directed medical therapy; ICD — implantable cardioverter defibrillator; INTERMACS — Interagency Registry for Mechanically Assisted Circulatory Support; LVAD — left ventricular assist device; LVEF — left ventricular ejection fraction

Table 2. Hemodynamic variables and PFT parameters (n = 100)

	Value
Hemodynamic parameters	
SBP [mm Hg], mean [SD]	103 (15.5)
DBP [mm Hg], mean [SD]	65 (11.5)
HR [beats/min], median [IQR]	95 (81–100)
CVP [mm Hg], mean [SD]	13.6 (7.4)
MPAP [mm Hg], mean [SD]	32 (11)
PADP [mm Hg], mean [SD]	24.7 (9.2)
PCWP [mm Hg], mean [SD]	25.5 (8.5)
Cardiac index [L/min/m²], mean [SD]	1.7 (0.52)
Cardiac output [L/min], mean [SD]	3.3 (0.97)
SVR [WU], median [IQR]	20.3 (16–24.6)
PVR [WU], median [IQR]	2.1 (1.05–3.5)
PFT parameters	
FEV_1 [L]	2.6 (2.2–3.2)
Percent of predicted FEV_1 [%]	71.5 (61–84.2)
FVC [L]	3.2 (2.5–3.8)
Percent of predicted FVC [%]	71 (62–83)
FEV_1/FVC	81 (79–83)
DLCO [mL/min/mm Hg]	8.3 (6.7–9.5)
Percent of predicted D_{LCO} [%]	73.9 (63.4–83.2)
KCO [mmol/min/kPa/Lit]	1.85 (1.6–2.1)
Percent of predicted KCO [%]	92.5 (80.2–104)

CVP — central venous pressure; DBP — diastolic blood pressure; D_{LCO} — diffusing capacity of the lungs for carbon monoxide; DPG — diastolic pulmonary gradient. FVC — forced vital capacity; FEV_1 — forced expiratory volume in one second; HR — heart rate; KCO — transfer coefficient of the lung for carbon monoxide; MPAP — mean pulmonary artery pressure; PADP — pulmonary artery diastolic pressure; PCWP — pulmonary capillary wedge pressure; PVR — pulmonary vascular resistance; SBP — systolic blood pressure; SVR — systemic vascular resistance; WU — wood units

Association between lung function parameters and hemodynamic variables

The Spearman's rank correlation coefficient showed a significant negative correlation between FEV_1/FVC and CVP (ρ = -0.22, p = 0.02), PCWP (ρ = -0.4, p < 0.001), mPAP (ρ = -0.45, p < 0.001), and PVR (ρ = -0.32, p = 0.001).

Cardiac output positively correlated with FEV_1 (ρ = 0.2, p = 0.04). There was no association found between any of the hemodynamic variables and %FEV_1, FVC, and %FVC.

Cardiac output positively correlated with D_{LCO} (ρ = 0.3, p = 0.008) in univariate analysis. No correlation was found between %D_{LCO} and the hemodynamic parameters. The multivariable analysis including LVEF, CO, CI, PCWP, MPAP, PVR, history of smoking, diagnosed diabetes mellitus, age, and gender showed an independent association between D_{LCO} and CO (β = 0.7, p = 0.03).

Univariate analysis showed that PCWP (for both variable ρ = -0.2, p = 0.03), mPAP (for both variable ρ = -0.3, p = 0.004), PADP (for both variable ρ = -0.2, p = 0.02), and PVR (for both variable ρ = -0.2, p = 0.02) negatively correlated with both KCO and %KCO.

The multivariable analysis including the variables LVEF, PCWP, MPAP, PVR, history of smoking, diagnosed diabetes mellitus, age, and
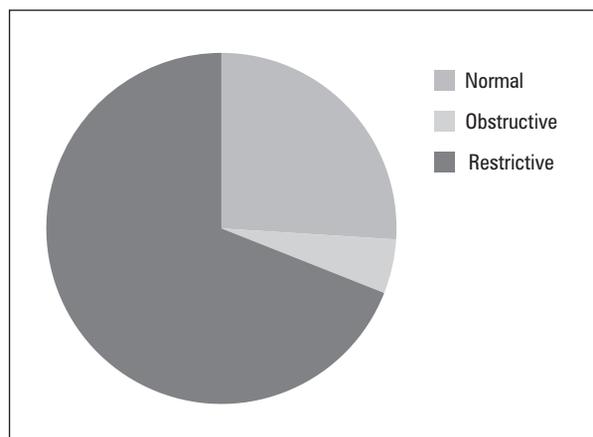
Figure 1. The spirometric patterns of our study population (n = 100)

gender showed no independent association between hemodynamic variables and KCO or %KCO.

Association between PFTs, hemodynamic parameters and outcomes

The median (IQR) follow-up duration was 6 (2–12) months. Outside of 9 patients who had a high PVR (more than 5 wood units), the rest of the patients were listed for HTX. Due to the very limited availability of LVADs in our country, LVAD implantation only became possible for 3 patients as destination therapy during the follow-up period. Heart failure-related mortality was 14%. 38% of patients were eligible to receive a heart transplant. Therefore, the combined event was seen in 54% of the study population.

The median (IQR) amount of time to the end-point (HF-related mortality, HTX, or LVAD implantation) was 89 days (25–120.5). The time to HTX was 31 days (1–108). All of the patients who received HTX had an INTERMACS clinical profile of 3. The median (IQR) amount of time to HF-related mortality was 78 (21–120) days. At the end of the follow-up, 45 patients were still alive.

In univariate analyses, neither the spirometric or D_{LCO} measurement parameters (which included the PFTs patterns) correlated with the combined event. This was also true for the hemodynamic parameters (Figures 2 and 3).

For multivariable analysis, a logistic regression model with a backward elimination method was applied in order to assess the adjusted associations between the combined end-point, PFTs, and hemodynamic parameters. It was found that, among the several variables (which included age, gender, %D_{LCO}, %KCO, %FEV_1, %FVC, FEV_1/FVC ratio, PFT patterns, CVP, PCWP, PVR, mPAP, MAP, and CI), only PVR had an independent association

with the combined event (β = 0.25, p = 0.04, Odd ratio [95% confidence interval] = 1.3 [1–1.6]).

Age (p = 0.02), PCWP (p = 0.02), mPAP (p = 0.02), MAP (p = 0.02), and FEV_1/FVC (p = 0.04) correlated with HF-related mortality in univariate analyses (Figure 4).

Multivariate logistic regression analysis showed that only mPAP had an independent association with HF-related mortality (β = 0.56, p = 0.05, Odd ratio [95% confidence interval] = 1.7 [1–3]).

Discussion

In this study, we showed that FEV_1/FVC, KCO, and %KCO could be correlated with hemodynamic measures in HTX candidates. Among different mechanical and diffusion parameters of lung function, only D_{LCO} was independently associated with cardiac output in our study population.

Regardless of these associations, neither mechanical nor diffusion parameters of pulmonary function were predictive of outcomes in HTX candidates in the current study.

The relationship between lung function values and hemodynamic measures has been relatively well explained in patients with HF, especially in patients with stage C HF. However, data on the importance of pulmonary function values in patients with stage D HF (advanced HF) have been conflicting [5, 8, 12, 13].

In a study by Georgiopoulou *et al.* [11], the spirometric values significantly correlated with filling pressures in a cohort of stage D HF patients, but none of them were correctly predictive of the adverse outcomes. They have also found no association between the functional capacity of HTX candidates and their spirometric values.

In a study by Lizak *et al.* [3], it has also been reported that spirometry is not useful for the diagnosis and grading of pulmonary diseases in HTX candidates. Another study has shown that, as symptoms of HF worsen, the influence of spirometric values on functional capacity diminishes.

In a recent study, Deis *et al.* have shown that spirometric values (%FEV_1 and %FVC) did not correlate with hemodynamics in advanced HF patients who were candidates for heart transplantation. Also, their association with adverse outcomes was not apparent after adjusting for confounding factors [8]. Furthermore, they found that central hemodynamics were modestly associated with %KCO and that PCWP independently correlated with %KCO in these patients.
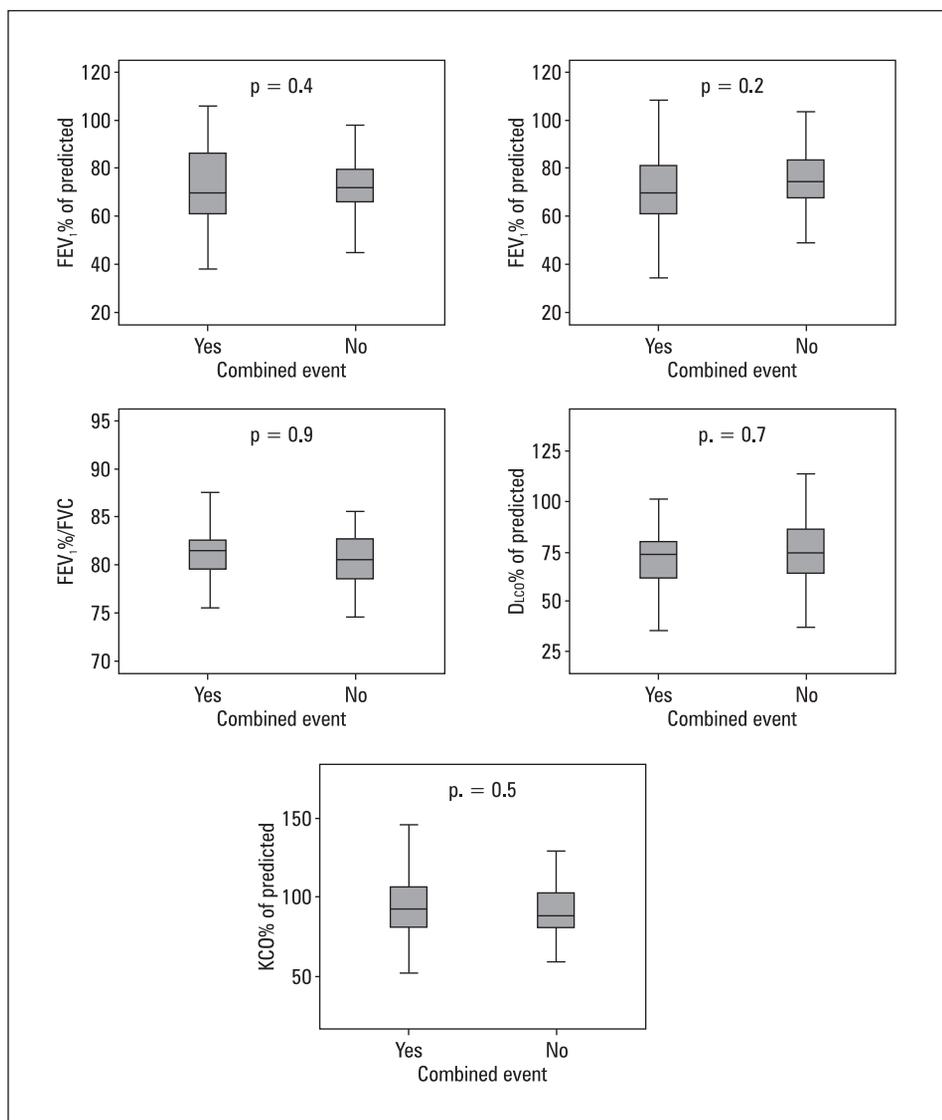
Figure 2. Comparison of PFT parameters in relation to the combined event. D_{LCO} — diffusing capacity of the lungs for carbon monoxide; FEV_1 — forced expiratory volume in one second; FVC — forced vital capacity; KCO — transfer coefficient of the lung for carbon monoxide

They also found a significant association between KCO and adverse outcomes in a cohort of HTX candidates.

There are some differences between our study and the study by Deis *et al.* [8] Although D_{LCO} was similarly reduced in our population, we also found an association between %KCO and PCWP, mPAP, and PVR. However, no association could be found between the %KCO and patient outcome.

There are several potential explanations for our findings. Our study population was a uniform group of HTX candidates who were carefully selected from a group of patients with advanced HF. Most of them were free of severe end organ dysfunction, particularly chronic lung disease, which may considerably attenuate the prognostic value of PFT results.

One of the strengths of our study was that catheterization and PFTs were performed almost concurrently. The cardiac and pulmonary systems are intimately linked physiologically and anatomically [18]. As a result, changes in the hemodynamic status of a patient with HF can have profound effects on the pulmonary system which can cause abnormalities in PFT parameters. Changes in hemodynamic status are more frequent in patients with advanced heart failure. Therefore, the presence of a three-month interval between performing PFTs and RHC in the study by Deis et al. can make their results less conclusive [8].

Furthermore, these pulmonary function abnormalities might just indicate that there is a heart-lung relationship in this specific population of HF patients without providing any underlying
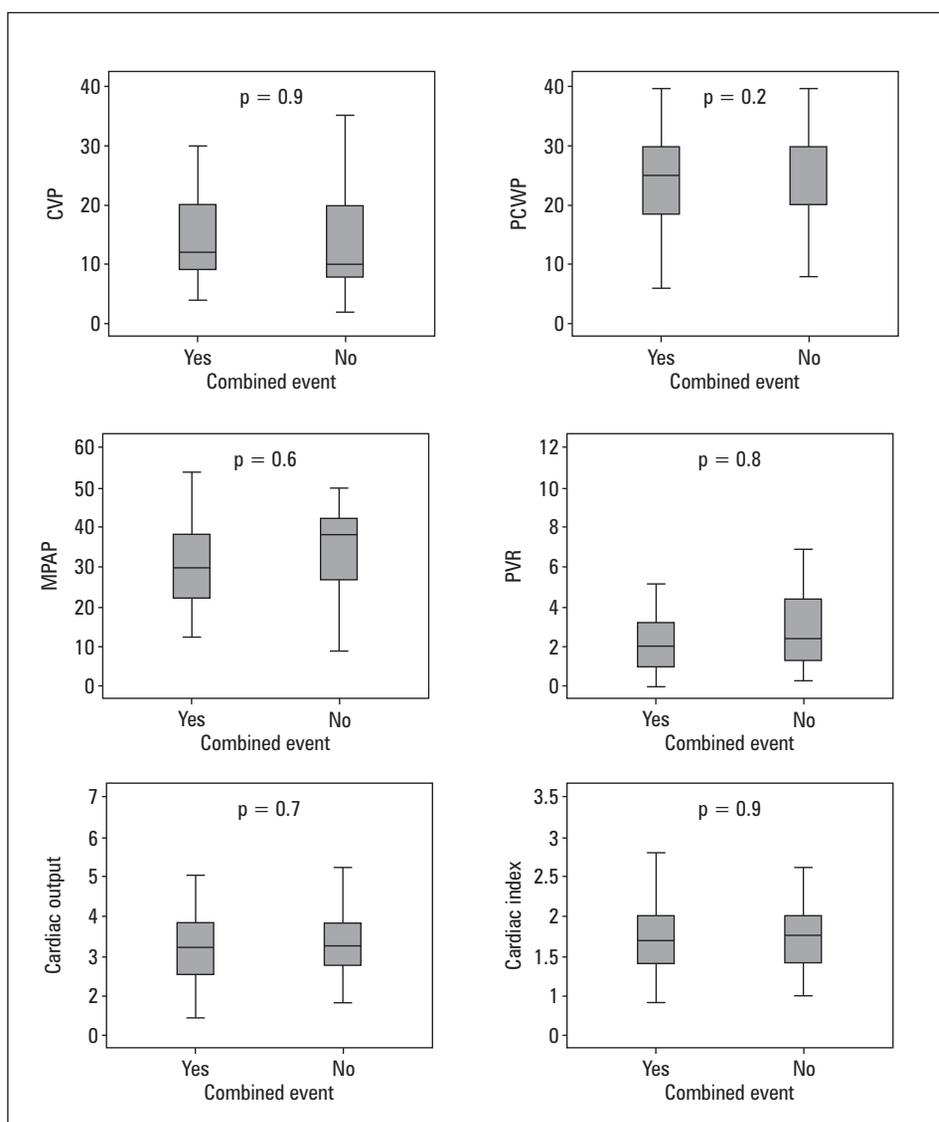
Figure 3. Comparison of hemodynamic parameters in relation to the combined event. CI — cardiac index; CO — cardiac output; CVP — central venous pressure; MPAP — mean pulmonary artery pressure; PCWP — pulmonary capillary wedge pressure; PVR — pulmonary vascular resistance

prognostic importance. Some studies have shown that D_{LCO} abnormalities persist after ultrafiltration or heart transplantation [5, 13]. Chronic damage to the alveolar membrane as a result of long-standing hemodynamic disturbances in HF can lead to decreased D_{LCO} even after optimal HF treatment.

The method of selection of the study population and the definition of the outcomes may be another reason for the different study results. The LVAD is available for a limited number of patients in our country and because of this, HTX is required for the majority of our patients. Many patients with an INTERMACS score of 3 will have a chance to be given a transplant if there are no patients with an INTERMACS clinical profile score of 1 or 2. In summary, more than half of our patients had met the outcome at the end of our

short duration follow-up time. As a result, HTX or LVAD implantation may not be considered as an index event or emergent procedure in our population. In fact, this high number of events in our cohort in conjunction with a high prevalence of PFT abnormalities may be the reason for the observed lack of association of PFT values with outcomes (rather than the absence of biologic association).

Study limitations

Although the careful selection of our study population may be a strength of our study, the most important limitation of our study and other similar studies may be acquiring optimal PFTs in patients with advanced HF. The presence of signi-
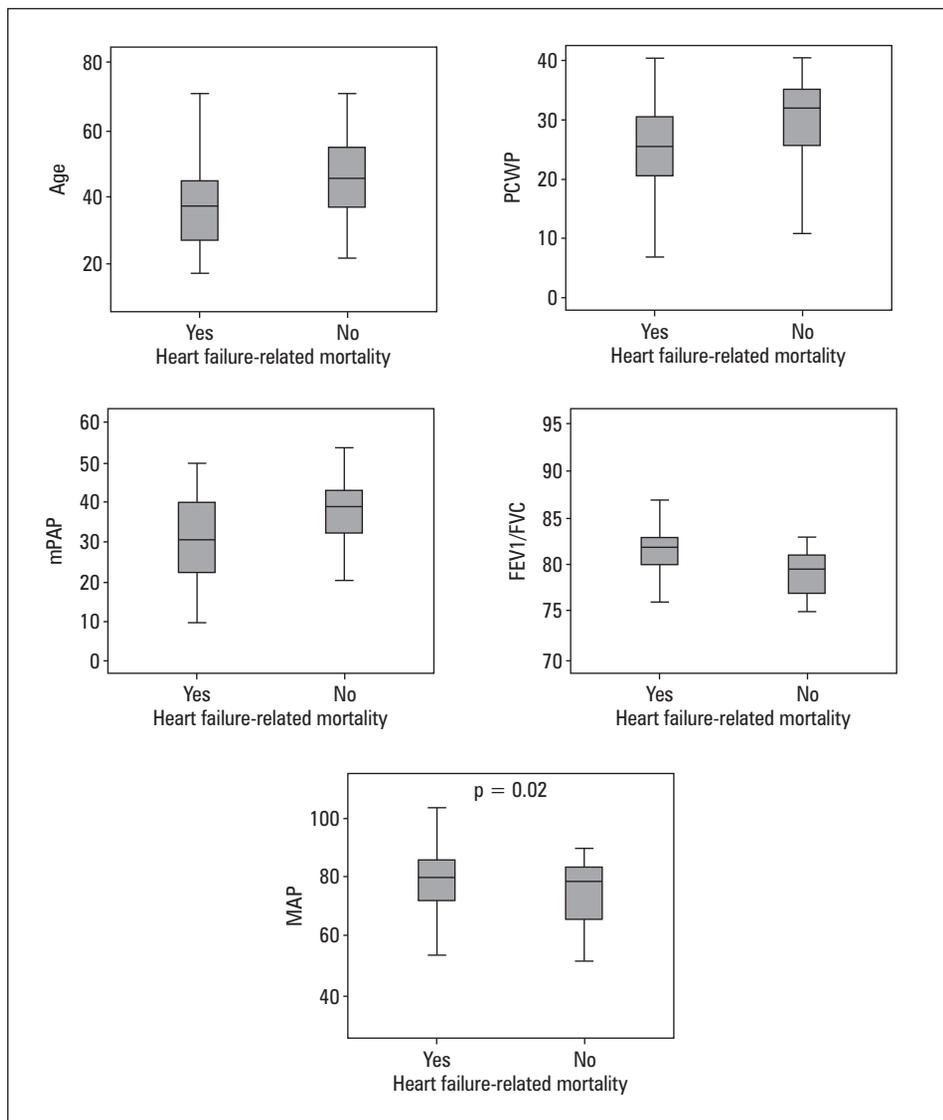
Figure 4. Comparison of PFTs and hemodynamic parameters in relation to heart failure-related mortality. FEV_1 — forced expiratory volume in one second; FVC — forced vital capacity; MAP — mean arterial pressure; MPAP — mean pulmonary artery pressure; PCWP — pulmonary capillary wedge pressure

ficant pulmonary congestion and hypertension, sarcopenia, and respiratory muscle weakness can make the result of our study suboptimal.

In summary, although the prognostic significance of PFTs in patients with chronic lung disease is well known, both mechanical and gas diffusion parameters of the lung were not associated with outcomes in the homogeneous group of heart transplant candidates. Advanced and severe HF leads to significant changes in lung function parameters. Therefore, the usefulness of PFTs to diagnose and grade pulmonary function abnormalities in this population and the importance of pulmonary function abnormalities in heart failure survival needs further evaluation.

The duration of HF, the number of decompensation episodes, and novel heart failure therapies (such as medical and surgical neurohormonal modulations) all may play a role in the development and progression of pulmonary abnormalities. This underscores the fact that more investigations are needed to find definite responses to the remaining questions.

Acknowledgment

Conflict of interest

None declared.

References:

1. Mancini D, Lietz K. Selection of cardiac transplantation candidates in 2010. Circulation. 2010; 122 (2): 173–183, doi: 10.1161/CIRCULATIONAHA.109.858076, indexed in Pubmed: 20625142.

2. Ponikowski P, Voors A, Anker S, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. European Heart Journal. 2016; 37 (27): 2129–2200, doi: 10.1093/eurheartj/ehw128.

3. Lizak MK, Zakliczyński M, Jarosz A, et al. The influence of chronic heart failure on pulmonary function tests in patients undergoing orthotopic heart transplantation. Transplant Proc. 2009; 41 (8): 3194–3197, doi: 10.1016/j.transproceed.2009.07.072, indexed in Pubmed: 19857708.

4. Hoeper MM, Meyer K, Rademacher J, et al. Diffusion capacity and mortality in patients with pulmonary hypertension due to heart failure with preserved ejection fraction. JACC Heart Fail. 2016; 4 (6): 441–449, doi: 10.1016/j.jchf.2015.12.016, indexed in Pubmed: 26874383.

5. Agostoni P, Bussotti M, Cattadori G, et al. Gas diffusion and alveolar-capillary unit in chronic heart failure. Eur Heart J. 2006; 27 (21): 2538–2543, doi: 10.1093/eurheartj/ehl302, indexed in Pubmed: 17028107.

6. Magnussen H, Canepa M, Zambito PE, et al. What can we learn from pulmonary function testing in heart failure? Eur J Heart Fail. 2017; 19 (10): 1222–1229, doi: 10.1002/ejhf.946, indexed in Pubmed: 28805996.

7. Ingle L, Shelton RJ, Cleland JGF, et al. Poor relationship between exercise capacity and spirometric measurements in patients with more symptomatic heart failure. J Card Fail. 2005; 11 (8): 619–623, doi: 10.1016/j.cardfail.2005.06.430, indexed in Pubmed: 16230266.

8. Deis T, Balling L, Rossing K, et al. Lung diffusion capacity in advanced heart failure: relation to central haemodynamics and outcome. ESC Heart Fail. 2019; 6 (2): 379–387, doi: 10.1002/ehf2.12401, indexed in Pubmed: 30784223.

9. Guazzi M, Pontone G, Brambilla R, et al. Alveolar-capillary membrane gas conductance: a novel prognostic indicator in chronic heart failure. Eur Heart J. 2002; 23 (6): 467–476, doi: 10.1053/euhj.2001.2803, indexed in Pubmed: 11863349.

10. Hoeper MM, Meyer K, Rademacher J, et al. Diffusion capacity and mortality in patients with pulmonary hypertension due to heart failure with preserved ejection fraction. JACC Heart Fail. 2016; 4 (6): 441–449, doi: 10.1016/j.jchf.2015.12.016, indexed in Pubmed: 26874383.

11. Georgiopoulou VV, Deka A, Li S, et al. Pulmonary function testing and outcomes in subjects with heart failure listed for heart transplantation. Respir Care. 2015; 60 (5): 731–739, doi: 10.4187/respcare.03709, indexed in Pubmed: 25737570.

12. Mettauer B, Lampert E, Charloux A, et al. Lung membrane diffusing capacity, heart failure, and heart transplantation. The American Journal of Cardiology. 1999; 83 (1): 62–67, doi: 10.1016/s0002-9149 (98)00784-x.

13. Ravenscraft SA, Gross CR, Kubo SH, et al. Pulmonary function after successful heart transplantation. One year follow-up. Chest. 1993; 103 (1): 54–58, doi: 10.1378/chest.103.1.54, indexed in Pubmed: 8417937.

14. Stevenson LW, Pagani FD, Young JB, et al. INTERMACS profiles of advanced heart failure: the current picture. J Heart Lung Transplant. 2009; 28 (6): 535–541, doi: 10.1016/j.healun.2009.02.015, indexed in Pubmed: 19481012.

15. Culver BH, Graham BL, Coates AL, et al. Recommendations for a standardized pulmonary function report. An official american thoracic society technical statement. Am J Respir Crit Care Med. 2017; 196 (11): 1463–1472, doi: 10.1164/rccm.201710-1981ST, indexed in Pubmed: 29192835.

16. Graham BL, Brusasco V, Burgos F, et al. Executive Summary: 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung. Eur Respir J. 2017; 49 (1), doi: 10.1183/13993003.E0016-2016, indexed in Pubmed: 28049167.

17. Amra B, Asadi M, Salehi H, et al. Normative reference values for lung transfer factor in Isfahan, Iran. Respirology. 2006; 11 (4): 477–481, doi: 10.1111/j.1440-1843.2006.00876.x, indexed in Pubmed: 16771920.

18. Skoczyński S, Mizia-Stec K, Semik-Orzech A, et al. Lung-heart clinical crosstalk in the course of COPD exacerbation. Pneumonol Alergol Pol. 2015; 83 (1): 30–38, doi: 10.5603/PiAP.2015.0004, indexed in Pubmed: 25577531.