Original Article

Lung Function Abnormalities are Highly Frequent in Patients with Heart Failure and Preserved Ejection Fraction

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Background: **Heart failure with preserved ejection fraction (HFPEF) is the most prevalent form of heart failure in outpatients. Yet, the pathophysiology of this syndrome is unclear and pharmacological treatment does not improve prognosis. Because breathlessness during activities of daily living is the most frequent complaint of patients with HFPEF, we hypothesised that lung function may be often abnormal in these patients due to either a direct effect of HFPEF and/or shared risk factors. In this study we explore the frequency, type and severity of lung function abnormalities in HFPEF.**

Methods: **We measured forced spirometry, static lung volumes, pulmonary diffusing capacity (DL_{CO}) and arterial blood gases in 69 outpatients with newly diagnosed symptomatic HFPEF.**

Results: **We found that 94% of the patients showed abnormalities in at least one of the lung function measurements obtained: spirometry was abnormal in 59%, DL_{CO} in 83% and arterial hypoxaemia was present in 62%. Their severity varied between patients, they were more prevalent in patients with NYHA functional class III/IV, and most often they were undiagnosed and untreated.**

Conclusions: **Lung function abnormalities are very frequent in HFPEF patients. A greater awareness among clinicians may contribute to improve their management and health status.**

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Keywords. Airway obstruction; Diastolic; Diffusing capacity; Dyspnoea; Heart failure

Introduction

Heart failure with preserved ejection fraction (HFPEF) is the most prevalent form of heart failure in outpatients, accounting for approximately 40–50% of patients with the clinical syndrome of heart failure (HF) [1–3]. The diagnosis of HFPEF is clinically challenging and requires the presence of: (1) signs and/or symptoms of HF; (2) normal or mildly abnormal left ventricle (LV) ejection fraction (LVEF > 50%) with LV not dilated; and (3) evidence of structural heart disease and/or diastolic dysfunction [4,5] at rest. The pathophysiology of HFPEF is still unclear. Age and arterial hypertension are its main risk factors but other mechanisms inducing myocardial remodelling, such as valvular heart disease, infiltrative myocardial illnesses, obesity and/or cardiac inflammation, can also contribute [6]. Importantly, and opposed to HF with reduced ejection fraction, pharmacological treatment of HFPEF does not improve prognosis [4].

Breathlessness during activities of daily living is the most frequent complaint of patients with HFPEF. This is thought to be the consequence of the increased capillary pressure and subclinical pulmonary oedema that is well described in other forms of HF [7]. However, lung function is not routinely investigated in patients with HFPEF, so the prevalence, type and severity of lung function abnormalities in this population is unknown. Further, patients with HFPEF share several risk factors, such as ageing, smoking and obesity, with other common respiratory diseases. It is likely, therefore, that the latter may occur in these patients independently of HFPEF. If this was the case, breathlessness during activities of daily living in patients with HFPEF may have multiple origins and may be amenable to different therapeutic strategies.

In this study, we hypothesised that lung function abnormalities occur often in patients with HFPEF, that most

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of them are not diagnosed, and that they can contribute to their symptomatology. To test this hypothesis, we sought to characterise lung function comprehensively in outpatients with newly diagnosed HFPEF in order to determine the frequency, type and severity of lung function abnormalities in this population, as well as their level of under-diagnosis.

Patients and Methods

Study Design and Ethics

This is a pilot and observational study. It complies with the Declaration of Helsinki, it was approved by the Ethics Committee of our institution and all participants provided written informed consent.

Patients

All consecutive outpatients with newly diagnosed HFPEF in the specialised HF clinic of our institution between April 2009 and December 2012 were included in the study. The organisation, procedures and population attended in this HF clinic have been previously published [8]. Exclusion criteria were age < 18 years, life expectancy < 1 year and/or inability to perform complete lung function tests. Breathlessness was graded according to the New York Heart Association (NYHA) functional classification [9].

Heart Function Measurements

The diagnosis of HFPEF was established according to international cardiology guidelines [9,10] and the algorithm proposed by Paulus et al. [5] that combines clinical history, chest X-ray, electrocardiogram, Doppler-echocardiography measurements of diastolic function and type-B natriuretic peptide (BNP) levels. The echocardiographic study was performed on a Vivid 7 (General Electric-Vingmed, Wisconsin, USA) and included: measurement of LV volumes and LVEF by Simpson methodology, left atrial volume (LAVol) and LV mass indexed by body surface, LV filling pressures in mitral valve (E, A) determined by pulsed-Doppler, lateral mitral annulus by tissue-Doppler (E′, A′) and pulmonary veins flow (S/D). Diastolic function was classified into four patterns: normal, impaired relaxation, pseudo-normal or restrictive. The E/E′ index was calculated and the pulmonary capillary wedge pressure (PCWP) and systolic pulmonary arterial pressure were estimated [11].

Lung Function Measurements

Lung function measurements (Jaeger, MasterScreen; Würzburg, Germany) included forced spirometry (FEV_1, FVC) before and after bronchodilation, static lung volumes (TLC, RV) by body plethysmography, carbon monoxide diffusing capacity corrected for haemoglobin (DL_{CO}) by the single breath test, and arterial blood gases (PaO_2, $PaCO_2$, $AaPO_2$; Ciba Corning 800, USA). All measurements were performed according to international recommendations [12,13] and reference values correspond to a Mediterranean population [14,15].

An obstructive ventilatory defect was diagnosed if the FEV_1/FVC ratio was lower than 0.7, and its severity was graded according to the FEV_1 value expressed as % of reference, following international recommendations (mild ≥80%; moderate 50–79%; severe 30–49%; or very severe <30%) [16]. Restrictive ventilatory defects were diagnosed when TLC was lower than 80% of reference (mild 70–80%; moderate 50–69%; severe 40–49%; or very severe <40%). A mixed ventilatory abnormality was defined by the presence of both obstructive and restrictive spirometric patterns. Impairment of DL_{CO} was graded as mild (60–80% reference), moderate (40–59% reference) or severe (<40% reference). Arterial hypoxaemia (PaO_2 ≤80 mmHg) was graded as mild (PaO_2 70–80 mmHg), moderate (PaO_2 60–69 mmHg) or severe (PaO_2 40–59 mmHg).

According to the 2013 GOLD guidelines [17], the diagnosis of COPD was established in individuals with symptoms (dyspnoea, chronic cough and/or sputum production) plus a history of exposure to risk factors for the disease (mostly tobacco smoking) plus the presence of non-fully reversible airflow limitation (FEV_1/FVC <0.7). Non-fully reversible airflow limitation indicates an FEV_1/FVC <0.7 after bronchodilation. Patients not fulfilling these criteria but still showing airflow limitation likely represent the coexistence of other pulmonary diseases and/or the effect of heart failure upon lung function, as discussed below.

Statistical Analysis

Results are shown as mean ± standard deviation, frequency distribution or proportions, as appropriate. The χ^2-test was used to compare categorical variables. Correlations between variables of interest were explored using the Pearson correlation test. A p-value lower than 0.05 (two sided) was considered significant.

Results

Demographics and Clinical Data

We originally recruited 79 patients with HFPEF, but 10 of them declined to participate, so lung function measurements were obtained in 69 of them. Patients were mostly elderly females (Table 1) with high body mass index (BMI). Two-thirds of them were in functional class of NYHA II, whereas the remaining third were in class III; in essence essentially all cases are II or III excepting one (class I). Most participants had arterial hypertension, about half of them had dyslipidaemia and a fourth diabetes. Importantly, 28% had been (or still were) smokers, albeit cumulative smoking exposure (pack years) was relatively small. Atrial fibrillation occurred in 46% of patients and other concomitant disorders in a reduced proportion of patients (Table 1). Two patients had required hospitalisation during the year before entering the study (2.8%), one because of new onset atrial fibrillation and another because of respiratory failure.

About 71% of the patients did not refer to any previous respiratory diagnosis. In those who did, about 10% had been diagnosed with COPD, 1% with asthma and 9% with bronchiectasis. Nine percent of patients were receiving

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Table 1. *Main demographic, clinical and functional characteristics of patients. Categorical variables are presented as number (and percentage) whereas continuous variables are expressed as mean ± standard deviation.*

Demographics and clinical data	
Age, years	76 ± 8
Females (%)	75.4%
BMI (Kg/m^2)	29 ± 5
NYHA (I–II/III–IV) (%)	60.9%/39.1%
I (*n*)	1
II (*n*)	41
III (*n*)	27
IV (*n*)	0
Barthel index	97 ± 10
Charlson index	2 ± 2
Cardiovascular risk factors	
Hypertension	60 (87.0%)
Dyslipidaemia	35 (50.7%)
Diabetes	19 (27.5%)
Smoking status, *n* (%)	
Current smokers	3 (4.3%)
Former smokers	16 (23.2%)
Never smokers	50 (72.5%)
Cumulative smoking exposure (pack years)	12 ± 25
Previous pulmonary diagnosis	
None	49 (71.0%)
COPD	7 (10.1%)
Asthma	1 (1.4%)
Bronchiectasis	6 (8.7%)
Unknown but treated (*)	6 (8.7%)
Previous use of inhaled therapy	
None	57 (82.6%)
LABA	10 (14.4%)
LAMA	9 (13.0%)
ICS	5 (7.2%)
Other CV diseases	
Atrial fibrillation	32 (46.4%)
Ischaemic heart disease	7 (10.1%)
Comorbidities	
Depression	31 (44.9%)
Chronic anaemia	17 (24.6%)
Brain vascular disease	6 (8.7%)
Chronic kidney failure	3 (4.3%)

(*) Patients receiving bronchodilator treatment without any specific respiratory diagnosis; LABA: long-acting β2 adrenergic bronchodilators; LAMA: long-acting anti-muscarinic bronchodilators; ICS: inhaled corticosteroids.

Table 2. *Heart function and lung function measurements expressed as mean ± standard deviation. Volumes and masses are indexed by body surface. Normal range values are shown between brackets.*

Heart function	
BNP (pg/mL) [<35]	159.0 ± 122.8
Left ventricle end-diastolic volume (mL/m^2) [<97]	59.4 ± 15.7
Left ventricle end-systolic volume (mL/m^2) [<43]	25.4 ± 8.8
Left ventricle ejection fraction (%) [≥50%]	60 ± 6
Left atrial volume (mL/m^2) [≤34]	59.2 ± 23.7
Left ventricle mass (g/m^2) [≤95 in women, ≤115 in men]	129.7 ± 28.1
E/E′ [<8]	11.2 ± 5.2
Pulmonary capillary wedge pressure (mmHg) [<12]	15.8 ± 6.5
Systolic pulmonary arterial pressure (mmHg) [<35]	40 ± 11
Lung function	
FEV_1, % reference [>80%]	81.4 ± 20.3
FVC, % reference [>80%]	76.3 ± 15.7
FEV_1/FVC, % [>70%]	71.3 ± 12.0
TLC, % reference [>80%]	90.3 ± 13.8
RV, % reference [>80%]	121.7 ± 35.3
RV/TLC, % [>40%]	54.1 ± 9.2
DL_{CO}, % reference [>80%]	64.8 ± 15.3
K_{CO}, % reference [>80%]	81.1 ± 16.5
PaO_2, mmHg [>80] %]	77.4 ± 11.9
$AaPO_2$, mmHg [<15]	24.7 ± 10.3

E/E′: ratio of the mitral inflow E wave to the tissue Doppler E′ wave; FEV_1: forced expiratory volume in the first second of a forced spirometry manoeuver after bronchodilation; FVC: forced vital capacity after bronchodilation; TLC: total lung capacity; RV: residual volume; DL_{CO}: single-breath carbon monoxide diffusing capacity; K_{CO}: transfer factor (DL_{CO}/alveolar volume); PaO_2: arterial partial pressure of oxygen (mmHg); $AaPO_2$: alveolar-arterial oxygen gradient.

bronchodilator treatment without any specific respiratory diagnosis. No patient was being treated with domiciliary oxygen therapy or non-invasive ventilation.

Heart Function

By definition, LVEF was higher than 50% in all patients (60 ± 6%). LV volumes were preserved but all patients had evidence of abnormal LV relaxation, filling, diastolic distensibility and diastolic stiffness (Table 2) according to the international recommendations for HFPEF diagnosis [5]. Doppler of pulmonary veins was abnormal (S < D) in 20 patients (29%), normal in 41 (59%) and not measurable in eight (12%). Diastolic function patterns were altered in all patients: 34 of them (49%) showed impaired relaxation, 30 (44%) a pseudo-normal pattern and five (7%) a restrictive

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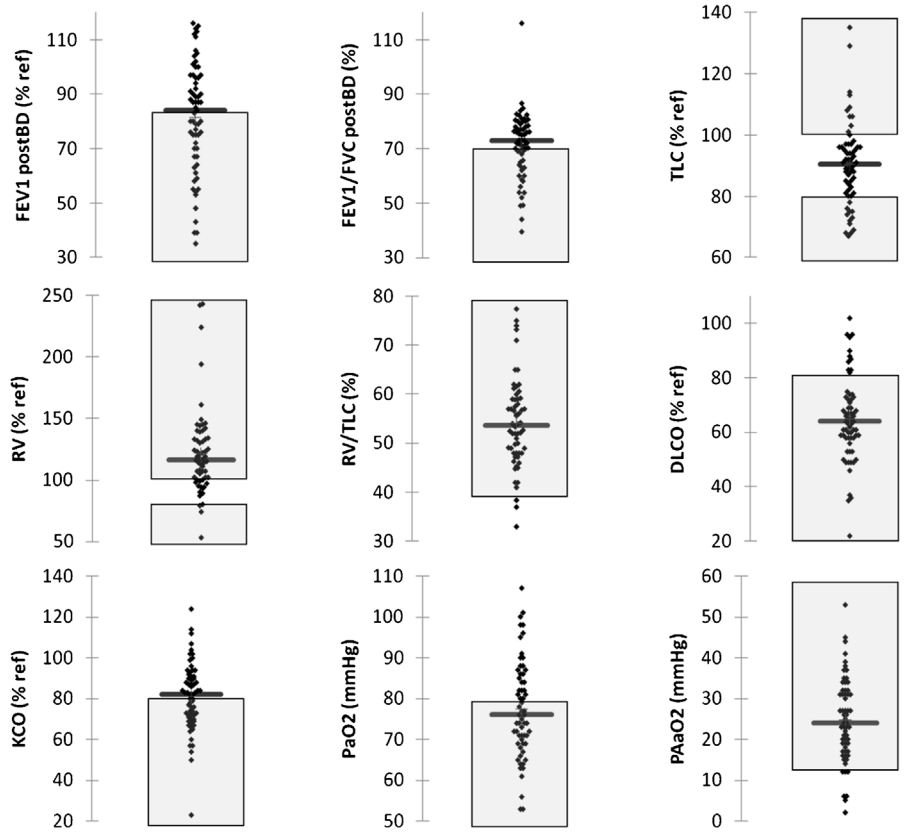

Figure 1. *Individual and mean (bar) values of the main lung function variables determined in the study. Grey areas indicate abnormal values. For abbreviations, see footnote to Table 1.*

pattern. Right ventricle dysfunction was present in three patients (4%).

Lung Function

Fig. 1 shows the individual and mean (bars) values of the main lung function variables studied. Grey areas indicate abnormal values. Most patients (94%) had at least one abnormal lung function test. Table 2 presents the mean (±SD) values of the main lung function variables studied here.

VENTILATORY MECHANICS. Spirometry was technically non-interpretable in three out of the 69 patients tested (4%). In the remaining 66 patients, spirometry was abnormal (i.e., either obstructive, restrictive or mixed) in 39 (59%). An obstructive ventilatory pattern was present in 20 patients (30%), whereas 10 patients (15%) had a restrictive ventilatory defect and seven patients (11%) had a mixed pattern. Fig. 2 shows that these ventilatory defects were mild in 23% of the patients, moderate in 27% and severe in 9%. Spirometric abnormalities occurred in 53% of patients in NYHA functional class I/II and in 68% of those in class III–IV ($p = 0.05$). Most smokers (68%) had airflow limitation ($FEV_1/FVC < 0.7$) but, importantly, the latter occurred also in 32% of never smokers ($p = 0.006$). Also of interest, 93% of patients with a restrictive ventilatory abnormality (TLC <80% ref.) were overweight (BMI >25 kg/m^2). Most patients (82%) had gas trapping (RV/TLC >40%). Of the 39 patients with abnormal spirometry, only eight had been diagnosed before (20%), so 4/5ths of them were unrecognised and untreated. Fourteen patients (21%) fulfilled the diagnostic criteria for COPD. Only seven of them (50%) had been identified before.

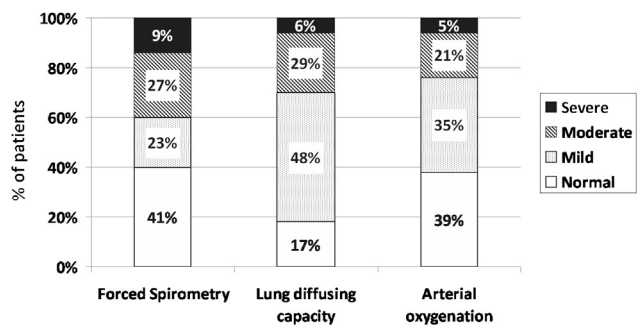

Figure 2. *Distribution of the severity of abnormalities found in forced spirometry, lung diffusing capacity (DL_{CO}) and arterial oxygenation (PaO_2). The severity of spirometric abnormalities was graded according to the FEV_1 value (obstructive; mild ≥80%; moderate 50–79%; severe 30–49%; or very severe < 30%) for obstructive ventilatory defects and/or TLC values (mild 70–80%; moderate 50–69%; severe 40–49%; or very severe <40%)) for restrictive ones. Impairment of DL_{CO} was graded as mild (60–80% reference), moderate (40–59% reference) or severe (<40% reference). Arterial hypoxaemia (PaO_2 ≤80 mmHg) was graded as mild (PaO_2 70–80 mmHg), moderate (PaO_2 60–69 mmHg) or severe (PaO_2 40–59 mmHg). For further explanations, see text.*

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PULMONARY GAS EXCHANGE. **Lung diffusion capacity (DL_{CO}) was impaired in 83% of the 65 patients with an interpretable DL_{CO} test. The degree of severity is shown in Fig. 2.** The prevalence of DL_{CO} abnormalities was 24% in patients in NYHA functional class I-II and 61% of those in class III-IV ($p = 0.003$). K_{CO} was normal in 22 of the patients with impaired DL_{CO} studied here (41%), indicating that in these patients the most likely cause of reduced DL_{CO} was impaired alveolar ventilation. By contrast, in the remaining 59%, K_{CO} correction was either partial ($n = 25$, 46%) or absent ($n = 7$, 13%), supporting the presence of a truly impaired pulmonary diffusing capacity. An isolated reduction in gas transfer (DL_{CO} <80% with normal spirometry) was present in 19 patients (70% of patients with normal spirometry). These patients were mostly females (95%), with less tobacco exposure (10%) and a significant higher E/E′ index (14.25 ± 7.28 versus 10.01 ± 3.66, $p = 0.024$), suggesting that this abnormality could be associated with HFPEF.

Arterial hypoxaemia (PaO_2 <80 mmHg) was present in 62% ($n = 38$) of the 61 patients in whom arterial blood gases could be measured. As shown in Fig. 2, it was mild in 19 patients (38%), moderate in nine (18%) and severe in three (6%). None of these latter three patients had been diagnosed or treated before. Importantly, 87% of patients had an abnormal $AaPO_2$ ($\geq$15 mmHg) (Table 2).

Pulmonary gas exchange abnormalities, including low DL_{CO}, low K_{CO} and low PaO_2, occurred in about one half of the patients with normal spirometry (70%, 42% and 55%, respectively).

Heart–Lung Function Correlations

In general, heart function variables were highly correlated internally. Hence, worse diastolic dysfunction patterns were associated with higher E/E′ index ($r = 0.268$, $p = 0.026$), PCWP (r = 0.268, $p = 0.026$), pulmonary artery pressure ($r = 0.420$, $p = 0.003$) and left atrial volume ($r = 0.308$, $p = 0.01$) values.

Likewise, respiratory function variables were also significantly correlated between them, so DL_{CO} was positively correlated with FEV_1/FVC ($r = 0.363$, $p = 0.003$) and post-bronchodilator FEV_1 (% ref.) ($r = 0.502$, $p < 0.001$), whereas it was negatively related with RV/TLC ($r = -0.431$, $p = 0.001$).

By contrast, heart function variables were generally not related to lung function ones. In particular, PCWP, E/E′ or left atrial volumes were not related to either FEV_1 or DLCO. An interesting exception was the observed relationship between BNP and the $AaPO_2$ gradient ($r = 0.275$, $p = 0.031$).

Discussion

The main observation of this study is that lung function is very often (94%) abnormal in HFPEF patients and, what is clinically more relevant, that most often (80%) they are unrecognised and untreated. These functional abnormalities can be due to either HFPEF itself and/or to the presence of concomitant comorbid respiratory diseases. In the first case, our observations contribute to delineate better the clinical profile of HFPEF syndrome and suggest that lung function can be potentially used as a clinical marker of insufficiently treated HFPEF. In the second, they point towards a number of treatable lung function abnormalities that, if diagnosed appropriately, have the potential to improve the health status of these patients.

Previous Studies

HF and COPD are prevalent diseases in the general population which, as a result, coexist often [18,19]. It is well established that HF with reduced ejection fraction, can cause pulmonary oedema, airflow limitation and/or low pulmonary diffusing capacity [20–22]. To our knowledge, however, our study is the first to investigate lung function abnormalities, with direct spirometric measurements (an absolute requisite to establish the diagnosis of COPD [17]), in outpatients with HFPEF.

Interpretation of Findings

The main observation of this pilot study is that the frequency of lung function abnormalities is very high (94%) in patients with HFPEF. This is particularly relevant if it is considered that these were ambulatory patients at early stages of their disease. Lung function abnormalities in these patients could be due to HFPEF itself and/or to the coexistence of other respiratory diseases. On the one hand, HF can cause pulmonary oedema [23], hence interfering with lung function [24]. Three observations of our study support this possibility: (1) airflow limitation was present in a substantial proportion (32%) of never smokers; (2) a reduced DL_{CO} was observed in 70% of patients with normal spirometry, and these individuals had the typical phenotypic characteristics of HFPEF patients (mostly females, minimal or no tobacco exposure and higher E/E′ index); and, (3) 87% of patients had evidence of abnormal pulmonary gas exchange ($AaPO_2$ $\geq$15 mmHg) and, interestingly, this was significantly related to BNP values ($r = 0.275$, $p = 0.031$).

On the other hand, smoking, ageing and obesity, which are well-stablished risk factors for both HFPEF and several common respiratory diseases (like COPD), could also be at the origin of some of the lung function abnormalities observed in these patients. In this context, it is of note that: (1) most smokers (68%) had airflow limitation (FEV_1/FVC <0.7); and, (2) 93% of patients with a restrictive ventilatory abnormality (TLC <80% ref.) were overweight (BMI >25 kg/m^2).

Finally, it is possible that both mechanisms (heart function influencing lung function and vice versa) interact since lung hyperinflation is associated with smaller LV end-diastolic and stroke volumes, without changes in LVEF [25], and recent research has shown that the presence of airflow limitation (FEV_1/FVC <0.7) is associated with increased HF risk, underscoring the potential importance of non-cardiac risk factors in predisposing to overt HF manifestations [26]. The observational nature of our study does not allow us to assess the relative importance of these two potential mechanisms. Yet, given their potential clinical relevance, the very high frequency of lung

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function abnormalities in HFPEF patients deserves further research.

Clinical Implications

Our results highlight the need for measuring lung function routinely in patients with HFPEF because they can influence their therapeutic regime. On the one hand, if lung function abnormalities reflect heart dysfunction in these patients, they can be used as clinical markers to guide therapy of HFPEF. On the other, if they are due to the presence of concomitant respiratory diseases that can be easily overlooked and not diagnosed in the context of symptoms that are misattributed to HFPEF, the measurement of lung function can identify other therapeutic targets. In both cases, given that lung function abnormalities are more prevalent in patients with NYHA class III and IV, it is likely that their proper cardiac and respiratory therapeutic management could contribute to reduce breathlessness and improve the quality of life of these patients. In this context, it may be worth noting that the prevalence of HFPEF is increasing and that, contrary to HF with reduced LVEF, its prognosis has not improved [4]. Given that causes of death in patients with HFPEF are predominantly of non-cardiovascular origin [27], it is plausible that a proper diagnosis and treatment of the most frequently encountered comorbidities in these patients, including lung function abnormalities, offer the potential to improve it.

Potential Limitations

Because this was a pilot and observational study, the number of patients investigated was relatively small and we did not include a control group. Therefore, results need to be confirmed in a larger, controlled and interventional study with longitudinal follow-up.

Conclusions

Lung function abnormalities are very frequent (94%) in outpatients with HFPEF, and most often they are undiagnosed and untreated. Forced spirometry, lung diffusing capacity and arterial oxygenation were altered in 59%, 83% and 62% respectively of patients. A greater awareness of this possibility and a multidisciplinary approach of HFPEF patients may contribute to identify novel therapeutic targets with the potential to improve the symptomatology, health status and, ideally, prognosis of patients suffering this frequent disease.

Conflict of Interest Statement

None declared.

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