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REVIEW

What can we learn from pulmonary function testing in heart failure?

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Pulmonary diseases frequently coexist in heart failure (HF), thus posing diagnostic and therapeutic challenges to cardiologists evaluating patients with overlapping symptoms and implementing recommended HF treatments. There is a growing body of evidence suggesting that pulmonary function testing might provide useful information for the best management of these patients. The availability of portable devices, allowing the measurement of spirometry and lung diffusion capacity for carbon monoxide outside of hospital-based pulmonary lung function laboratories, provides an opportunity for a more widespread use of these measures in the cardiology community, but their interpretation can be challenging. In this work, after a brief review of the methodologies, we discuss the interpretation of pulmonary function testing in patients with HF alone or associated with pulmonary diseases, and its contribution in differentiating cardiac and pulmonary symptoms and preventing acute cardiac decompensation. In addition, we examined recent evidence suggesting how the use of pulmonary function testing may provide independent prognostic information in HF patients with and without pulmonary disorders, and help therapeutic decisions to fill the treatment gap that still exists in HF patients with concomitant pulmonary diseases.

Keywords Heart failure • Pulmonary disease • Spirometry • Pulmonary function testing

Introduction and purpose

Heart failure (HF) is an increasing public health problem worldwide, related to population aging.[1,2] Among risk factors for HF is cigarette smoking, which is also the major risk factor for chronic obstructive pulmonary disease (COPD).[3] Therefore, it is not surprising that these two conditions frequently coexist in the same patient. Moreover, HF and COPD often present with similar symptoms, such as dyspnoea and exercise intolerance, muscle weakness, sleep disturbances, cachexia, and anxiety,[4] which makes the assessment of both conditions challenging in clinical settings.

Irrespective of left ventricular ejection fraction (EF), cardiopulmonary interaction is a critical component of the HF syndrome.[4,5] A number of recent studies have highlighted important aspects in this context, which include: (i) the importance of pulmonary congestion in HF, and sensitive methods for its detection,[6,7] (ii) the impact of concomitant lung disease on HF course, symptoms and treatments,[7–9] (iii) the potential impact of COPD therapies on heart function; and (iv) the potential impact of HF therapies on lung function. Hence, although pulmonary function testing (PFT) may provide useful additional information for the management of patients with chronic HF, this is currently underused.

Recent technical advances and the availability of portable devices allowing the measurements of spirometry and lung diffusing capacity for carbon monoxide (D_{LCO}) outside of hospital-based pulmonary function laboratories could likely help to fill this gap.

This article is intended to (i) provide a brief overview of the methodologies for spirometry and D_{LCO}, (ii) highlight the clinical importance of PFT in HF, and (iii) provide practical guidance to cardiologists on the use and interpretation of lung function measurements for the diagnosis and management of patients with chronic HF alone or associated with pulmonary co-morbidities in daily clinical practice.

The authors independently and systematically screened PubMed for relevant, most recent publications (main search terms were

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'pulmonary function testing' and 'heart failure'). Selection for this review was based on the judgment of relevance for the topic as agreed by the authors.

Methodology and interpretation of pulmonary function testing

The most common PFT is spirometry, which is the measure of the lung volumes that can be mobilized with inspiratory or expiratory manoeuvres. D_{LCO} is a clinically useful test that provides a quantitative measure of gas transfer from the lungs to blood, thus complementing spirometry in the evaluation and management of patients with respiratory and/or cardiac disease.

D_{LCO} is determined by structural and functional properties, the most important of which are the lung gas volume, the path length for diffusion in the gas phase, the surface and thickness of the alveolar-to-capillary membrane, and the volume of blood available for gas exchange in pulmonary capillaries.[10]

The methodology of spirometry and D_{LCO} measurements is summarized in *Table 1*.[10–12]

Reference values

The Global Lung Function Initiative produced multi-ethnic reference equations for spirometry over an age range from 5 to 95 years [13] and is currently working on the development of similar reference equations for D_{LCO}. These equations provide mean predicted values and 90% confidence intervals. The lower limit of normality (LLN) is assumed to correspond to the 5th percentile of the healthy reference population, which is calculated as the difference between the mean value and the residual standard deviation multiplied by −1.645. As for most biological tests used for clinical purposes, this can be taken as a reasonable threshold to define abnormality with an expected 5% probability of falsely positive diagnosis. Moreover, the difference between measured and predicted values divided by the residual standard deviation (z-score) provides an unbiased estimate of the deviation from abnormality in individual patients.[14] The use of LLN and z-score avoids age, sex, and height biases, which would result from the use of fixed cut-offs [e.g., 80% of predicted for forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), and D_{LCO} and 0.70 for the FEV_1/FVC ratio] to define the presence of abnormality.[15]

Interpretation of pulmonary function test

According to the recommendations of the American Thoracic Society and the European Respiratory Society,[16] the first step in the interpretation of PFTs is to determine if *airflow obstruction* is present. An $FEV_1/FVC < LLN$ is generally used to indicate airway obstruction, though the ratio of FEV_1 to slow vital capacity may provide an even better estimate of airway obstruction.[17] A spirometry repeated 15–30 min after a bronchodilator is required to determine whether obstruction is reversible (suggestive of bronchial asthma) or fixed (suggestive of COPD). The second step is to determine whether *lung restriction* is present. This may be suggested by an $FEV_1/FVC \geq LLN$ with $FVC < LLN$. But, this spirometric pattern is not specific and needs to be confirmed by the evidence of reduced total lung capacity (TLC). In patients with restrictive disorders, the alveolar volume (VA) measured by single-breath inert gas dilution during the D_{LCO} manoeuvre provides a valid approximation of TLC. In patients with obstructive disorders, intrapulmonary gas mixing may be incomplete during breath hold and VA underestimates TLC, which can be more accurately determined whole body plethysmography.[18] The third step is to determine if D_{LCO} is reduced. In asthma, D_{LCO} is usually normal. In COPD, a low D_{LCO} is highly suggestive for the presence of emphysema. A low D_{LCO} is usually found in patients with lung restriction due to pulmonary fibrosis, but it may be also present in chronic HF and in pulmonary vascular disorders without restriction. When spirometry and lung volume measurements fail to show obstructive or restrictive disorders in the presence of a reduced D_{LCO}, computed tomography of the lung may be required for a differential diagnosis.[19] The final step is severity grading of lung function abnormalities. This has been traditionally based on percentage reductions of FEV_1, though the use of z-score has been suggested as more appropriate, as discussed above.[14,20]

Pulmonary function testing in heart failure

Heart failure without pulmonary disease

A number of studies have demonstrated that patients with HF develop pulmonary function abnormalities, ranging from relatively minimal restriction to a mixed restrictive/obstructive pattern.[21,22] In HF with either reduced (HFrEF) or preserved EF (HFpEF), the backward transmission of elevated left-sided filling pressure leads to pulmonary congestion, which may be moderate and precedes the clinical signs of cardiac decompensation. In fact, there is a continuum of elevated filling pressures in the left heart, leading to progressive pulmonary hypertension, ultimately resulting in right heart dysfunction and peripheral congestion, and thus weight gain.[5] In the CHAMPION trial, elevations of pulmonary artery pressure as measured by an implantable monitoring device (CardioMEMS) preceded the occurrence of peripheral oedema and episodes of acutely decompensated HF.[7,8] The fact that adjustments of diuretic treatment were able to substantially reduce HF-associated hospitalizations in these patients[23] indicates that the increases in pulmonary artery pressure were mainly caused by pulmonary congestion. In addition to haemodynamics, changes in lung function may represent a sensitive signal of early cardiac decompensation in HF. As left ventricular filling pressure increases, pulmonary congestion and interstitial oedema develop, causing reductions of lung volume and D_{LCO}, while FEV_1/FVC remains normal. Thus, FVC and particularly D_{LCO} may decline with even moderate congestion, whereas an obstructive-like pattern (low FEV_1/FVC) may emerge in decompensated HF due to bronchial wall oedema (*Figure 1*). Indeed, when Melenovsky *et al.*[24] compared 'dry lung HF' with 'wet lung HF', the latter was associated with increased pulmonary vascular resistance and reduced pulmonary artery compliance, as well as with a restrictive spirometric pattern (reduced FVC with normal FEV_1/FVC) and a reduction in D_{LCO}. Furthermore, 'wet lung HF' was associated with reduced survival in chronic HF.[24] Likewise, it has been recently shown that D_{LCO} and its subcomponents (i.e. pulmonary capillary blood volume and alveolar–capillary membrane conductance) are significantly lower in patients with HFpEF as compared to age-, sex- and exercise-matched control subjects, both at rest

Table 1 Methodology and standardization of pulmonary function testing

Spirometry[a]

- Measure of lung volumes that can be mobilized with single inspiratory or expiratory manoeuvres.
- Key spirometric measurements:

  1 Maximal volume that can be mobilized with either relaxed (VC) or forced (FVC) manoeuvres
  2 FEV_1
  3 FEV_1/FVC ratio (or Tiffeneau index).

Instrument calibration

- Accuracy is verified daily to be within 3% of variation using a 3 L calibration syringe.
- Ultrasound, transit-time based electronic spirometers maintain accuracy for at least 4 years without the need for recalibration[b].

Breathing manoeuvre

- After quiet breathing, subjects make a full inspiration to TLC followed by a forceful expiration of >6 s to residual volume and a forced inspiration to TLC.

Quality control and repeatability

- Manoeuvre is repeated up to eight times to obtain at least three technically acceptable and two repeatable (i.e., with FEV_1 and FVC differences <150 mL) manoeuvres.
- The largest values of FEV_1 and FVC are reported and used to calculate the FEV_1/FVC ratio.

Single-breath D_{LCO}[c]

- D_{LCO} is a measure of gas transfer from alveolar space to blood.

Instrument calibration

- Accuracy of volume measurement is verified daily using a 3 L calibration syringe and gas analyzers are zeroed before each test.
- The long-term variability is checked weekly by testing the same healthy subject and must remain within 12% of the last six measurements.

Breathing manoeuvre

- After quiet breathing, subjects rapidly inhale the test gas containing 0.3% CO, an inert tracer gas (e.g. He), 21% oxygen and nitrogen balance from residual volume to TLC. After 8–12 s of breath hold, subjects make a fast expiration to residual volume during which tracer gas and CO concentrations are measured to obtain VA and gas transfer.

Quality control and repeatability

- The manoeuvre is repeated, at 4 min intervals, to obtain at least two measurements of good quality (i.e. with inspired volume ≥ 90% of largest VC or ≥85% of largest VC and VA repeatable within 200 mL or 5%) matching within 2 units.
- At least two acceptable D_{LCO} measurements within 2 $mL \cdot min^{-1} \cdot mmHg^{-1}$ (0.67 $mmol \cdot min^{-1} \cdot kPa^{-1}$) of each other.
- The average of these measurements is reported.

CO, carbon monoxide; D_{LCO}, diffusing capacity for carbon monoxide; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; TLC, total lung capacity; VA, alveolar volume; VC, vital capacity.
[a]For further details, refer to Miller *et al.*[11]
[b]For further details, refer to Skloot *et al.*[12]
[c]For further details, refer to Graham *et al.*[10]

and during exercise.[25] In addition, in HFpEF patients with overt pulmonary hypertension, low D_{LCO} is also strongly associated with mortality.[26,27] Hence, in HF patients the assessment of pulmonary function, and in particular of D_{LCO}, may be a non-invasive sensitive method for the detection and follow-up of initial pulmonary congestion, which may be supplemental to the measurement of natriuretic peptides (*Figure 1*). Whereas the above studies monitored haemodynamics and pulmonary function at rest, it is important to note the changes in chronic HF patients that occur even with mild exercise. In HF, mild to moderate exercise leads to a substantial increase in left ventricular filling pressure.[28,29] While measures of cardiac function at rest such as cardiac output, stroke volume, and EF poorly correlate with the cardinal symptoms of dyspnoea and reduced exercise capacity in chronic HF patients, a low D_{LCO} at rest was shown to be indicative of high dead space ventilation at maximal exercise during cardiopulmonary exercise testing, which results from ventilation–perfusion mismatching and contributes to inefficient ventilation during exercise.[30]

Concomitant heart failure and chronic obstructive pulmonary disease

Recent studies indicated that 10–40% of HF patients have reported concurrent COPD, which is an independent predictor of rehospitalization and mortality.[9,22]

The diagnosis of COPD is based on respiratory symptoms (cough, expectoration, dyspnoea), exposure to tobacco smoke or other noxious agents, and evidence of airflow obstruction.

Besides airflow obstruction, a major lung function abnormality in COPD is lung hyperinflation.[31,32] This may be due to both static (loss of lung elastic recoil due to emphysema) and dynamic (incomplete emptying during expiration due to airway narrowing)

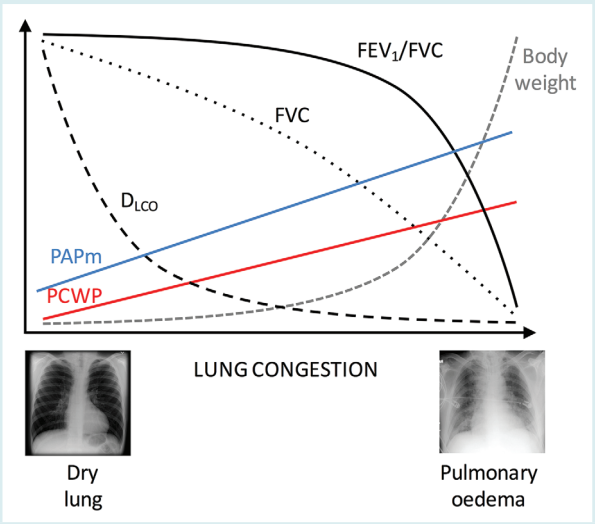

Figure 1 Schematic representation of potential trajectories of lung function, haemodynamics and body weight with lung congestion in heart failure. D_{LCO}, diffusing capacity for carbon monoxide; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; PAPm, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure.

mechanisms. Hyperinflation of the lungs is of great importance for the understanding of heart–lung interaction. In patients with COPD, impaired left ventricular filling associated with a reduced preload was observed by echocardiography, and lung hyperinflation is likely to contribute to this abnormality.[33] In addition, it has been shown that hyperinflation is related to reduction of intrathoracic blood volume,[34] reduced pulmonary vein dimensions[34] and likely contributes to decrease left ventricular volume and stroke volume.[35] Reduction of hyperinflation is likely to improve cardiac function in COPD patients without overt HF.[36,37] In particular, Stone and colleagues reported a significant increase in right and left ventricular stroke volumes in 45 hyperinflated COPD patients randomized to inhaled corticosteroid/long-acting $beta_2$-agonist fluticasone furoate/vilanterol or placebo.[36]

Recently, Cuttica *et al.*[38] reported the loss in lung function in apparently healthy subjects be associated with specific cardiovascular phenotypes in middle-aged individuals. Decline in FEV_1/FVC was associated with underfilling of the left heart and low cardiac output. Decline in FVC with preserved FEV_1/FVC was associated with left ventricular hypertrophy and diastolic dysfunction. Thus, cardiopulmonary interactions apparent with common complex heart and lung diseases evolve concurrently from early adulthood forward.[38]

Differentiating cardiac and pulmonary disorders

Airflow obstruction and hyperinflation are the most important lung function abnormalities associated with COPD. Older patients with dyspnoea may suffer from late-onset asthma. It is important

Table 2 Typical changes differentiating heart failure from obstructive pulmonary diseases

	Dry lung HF	Wet lung HF	COPD	Asthma
FVC	WNL	↓	WNL or ↓	WNL or ↓
FEV_1/FVC	WNL	WNL or ↓	↓	WNL or ↓
D_{LCO}	WNL	↓	↓	WNL
NT-proBNP	WNL	↑	WNL	WNL

COPD, chronic obstructive pulmonary disease; D_{LCO}, diffusing capacity for carbon monoxide; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; WNL, within normal limits.

to identify these patients as treatment with inhaled corticosteroids may result in tremendous improvement of their health status. In poorly controlled asthma and COPD, spirometry shows an obstructive pattern, whereas D_{LCO} is reduced when COPD is associated with significant emphysema. In HF, the spirometric pattern is restrictive with decreased D_{LCO} and VA. Both HF and COPD may show changes in pattern and magnitude of pulmonary function abnormalities, thus serial assessment of lung function is helpful to avoid misinterpretation.[39] Combining spirometry, D_{LCO}, and natriuretic peptide levels may generally allow differentiation between heart and pulmonary disorders in patients with dyspnoea (*Table 2*). However, permanent damage to the alveolar-capillary membrane might be present in patients with chronic 'dry lung HF' and determine a reduction in D_{LCO}, which is independent of pulmonary congestion, and/or COPD.[40,41] In addition, because 'wet lung HF' may present a mixed obstructive/restrictive spirometric pattern, determination of the coexistence or the severity of COPD should wait until HF is optimally treated.[21,42,43] The scenario might be finally further complicated by the presence of associated cardiac conditions, such as atrial fibrillation, pulmonary hypertension and right ventricular strain and failure, which might independently increase natriuretic peptide levels.[44,45]

Cardiopulmonary exercise tests in patients with heart failure and respiratory disorders

The majority of patients with cardiovascular diseases and respiratory disorders complain of dyspnoea on exercise. Therefore, when dyspnoea is not explained by pulmonary or cardiac investigations, it is reasonable to submit symptomatic patients to cardiopulmonary exercise testing (CPET). The importance of CPET has recently been summarized for cardiopulmonary[46] as well as respiratory disorders.[47] Here, we mainly emphasize that easily available PFT may be of added value in the functional characterization of patients with chronic HF with or without respiratory co-morbidities. When applying PFT, the knowledge of lung function data may even predict some results of CPET. For instance, a recent study demonstrated that in patients with mild COPD, parameters of CPET have a strong association with D_{LCO}.[48] Nevertheless, CPET parameters

may provide important additional information in individual patients, and detailed recommendations for this test have been summarized elsewhere.[46,47]

Pulmonary function tests and cardiovascular outcomes

Population studies have consistently shown that impaired lung function is an independent predictor of both of all-cause[49] and cardiovascular[49,50] mortality and is associated with reduced systolic and diastolic cardiac function.[51] The FVC, but not FEV_1/FVC, appeared to be the true predictor of survival in a general population of adults.[52] Even in patients admitted to hospital because of HF, impaired lung function is an independent predictor of mortality.[53] Olson *et al.*[54] have shown that spirometry and D_{LCO} significantly predicted mortality in patients with stable HF of more than 1-year duration. This result was specific to HF, as patients with pre-existing COPD, asthma, diabetes, or other diseases that may influence pulmonary function and survival were excluded.

Attention to the use of D_{LCO} in HF has been increasing in recent years, as a prognostic indicator more specifically linked to pulmonary hypertension associated with HF. In HFpEF with pulmonary hypertension, without evidence of concomitant pulmonary diseases, impaired D_{LCO} predicted prognosis: patients with a $D_{LCO} < 45\%$ of predicted had a 37% survival rate at 3 years compared with an 88% survival rate in patients with $D_{LCO} > 45\%$ of predicted.[27] Similarly, in HFrEF, low D_{LCO} was an indicator for high dead-space ventilation during exercise and resulting dyspnoea.[30]

One study showed that VA measured by dilution during D_{LCO} test, which is a reliable measurement of lung volume in restrictive disorders, was an independent predictor of mortality in patients with HFrEF.[55]

Pulmonary function tests to guide therapeutic decisions in heart failure

Treatment of heart failure without pre-existing respiratory abnormalities

Although HF treatment is not influenced by the presence of a restrictive spirometric pattern, this should be considered as an independent risk factor for morbidity and mortality.[49,50] Furthermore, some HF therapies might evoke adverse pulmonary effects, regardless of the presence of COPD. In particular, angiotensin-converting enzyme inhibitors may cause dry cough without lung function test abnormalities in up to 20% of treated patients; this symptom is usually reversible with cessation of treatment,[56] and replacement with an angiotensin receptor blocker is recommended. Beta-blocker acute administration may be associated with new-onset bronchospasm and episodic dyspnoea, and reveal previously undetected asthma, for which specific pulmonary testing would be appropriate.[57] Other HF therapies, including mineralocorticoid receptor antagonists and angiotensin receptor-neprilysin inhibitor, are not known to cause any lung function test abnormality. Special consideration, however, should be paid to patients with HF on amiodarone treatment. Approximately 2% of patients prescribed with this drug experience pulmonary toxicity as a side effect.[58] This toxicity appears to be dose- and time-dependent but can be idiosyncratic and does not necessarily cause additional lung damage in patients with pre-existing lung disease.[59] Because many patients undergoing amiodarone treatment may have already reduced FVC and D_{LCO} due to HF, it is advisable to have them measured at baseline and during treatment to detect changes that are potentially attributable to amiodarone toxicity.[60]

Treatment of heart failure in the presence of airflow obstruction

Airflow obstruction in HF may be due to co-morbid COPD or airway wall oedema due to congestion. Decompensated HF may manifest with episodes of dyspnoea, particularly at night (so-called 'cardiac asthma'). Unlike bronchial asthma, this condition does not respond to inhaled corticosteroids, though a slight response to bronchodilators may be present.

A still debated problem is the use of beta-blockers in patients with obstructive respiratory disorders. These drugs are often prescribed in cardiovascular diseases, including HF, coronary artery disease, and arterial hypertension. Although recent reports showed an increase in survival[61] and a decrease of exacerbations in COPD patients on beta-blocker therapy,[62] there is still reluctance to prescribe these compounds in COPD patients, perhaps because some of them may also have asthma.[57,63] If PFT shows fixed obstruction, i.e. with incomplete or absent response to bronchodilator, this condition is highly suggestive of COPD (and not asthma), and beta-blockers must not be withheld in patients taking them for cardiovascular indications, because beta-blocker avoidance or withdrawal has been associated with increased mortality.[64] In fact, studies are in progress to establish whether beta-blockers confer benefits on mortality and exacerbations in all patients with COPD, regardless of the presence of cardiovascular disease.[64] FVC and FEV_1/FVC, which are now readily measurable, may prove to be useful in monitoring COPD patients with chronic HF treated with beta-blockers.

In patients with fixed airflow obstruction but unusually high response to bronchodilators, a differential diagnosis between COPD and asthma is not straightforward and additional investigations may be necessary.[65] In elderly HF patients, COPD and asthma may be present with complex interactions. In fact, airway hyperresponsiveness is considered as a characteristic feature of bronchial asthma and is currently assessed by bronchial challenge with inhaled methacholine. In cases of clinical suspicion of the presence of asthma with or without COPD in HF patients requiring beta-blocker therapy, we recommend to perform a methacholine challenge. However, this test is very sensitive but not specific and may also be positive in patients with COPD[66] or abnormal left ventricular function.[67] Nevertheless, a negative test increases the likelihood of no beta-blocker related respiratory side

effects, and with few exceptions, beta-blockers may be started safely.

Treatment of chronic obstructive pulmonary disease in patients with heart failure

The cornerstone pharmacological treatment of COPD is represented by bronchodilators, i.e. long-acting muscarinic antagonists (LAMA) and long-acting beta$_2$-agonists (LABA) given alone or in combination, with the addition of inhaled corticosteroids in the most severe cases.[68] Because of their pharmacological characteristics, both LAMA and LABA may have potential cardiac side effects. Although the majority of clinical trials with these drugs were reassuring in terms of cardiac safety, they are not representative of real life because patients with cardiovascular co-morbidities (arrhythmias, unstable ischaemic heart disease, HF and myocardial infarction) were excluded.[69] Only recently, a large clinical trial in 16 485 COPD patients with heightened cardiovascular risk showed that 3-year treatment with LABA (vilanterol) alone or in combination with inhaled corticosteroid (fluticasone furoate) did not increase the rate of cardiac adverse events.[70,71] A similar safety profile in patients with cardiovascular risk had been reported also for LAMA monotherapy with tiotropium.[72]

Conclusions

As the lungs are not an innocent bystander but rather represent an integral component of cardiopulmonary interaction in HF,[73] PFT using both spirometry and D_{LCO} measurement should be considered complementary to clinical assessment, echocardiography, cardiac biomarkers such as natriuretic peptides and chest imaging. Furthermore, lung function parameters provide prognostic information in patients with HF and may help to guide treatment decisions. Therefore, the use of spirometry and D_{LCO} should be recommended as part of the initial diagnostic procedure as well as follow-up in patients with HF.

Conflict of interest: H.M. is a member of the Advisory Board of ndd Medical Technologies, Andover, MA, USA, which also sponsored a two-day meeting held in Munich, Germany among some of the authors (H.M., M.C., P.E.Z., V.B., S.R.) to discuss topics reviewed in this manuscript. There is no other conflict of interests related to this work.

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