

FUNCTIONAL RESPIRATORY ASSESSMENT IN INTERSTITIAL LUNG DISEASE

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ABSTRACT

Interstitial lung diseases are a heterogeneous group of disorders that affect, to a greater or lesser degree, the alveolus, peripheral airway, and septal interstitium. Functional assessment in patients suspected of having an interstitial lung disease has implications for diagnosis and makes it possible to objectively analyze both response to treatment and prognosis. Recently the clinical value of lung-diffusing capacity and the six-minute walking test has been confirmed, and these are now important additions to the traditional assessment of lung function that is based on spirometry. Here we review the state-of-the-art methods for the assessment of patients with interstitial lung disease. (REV INVEST CLIN. 2015;67:5-14)

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INTRODUCTION

Interstitial lung diseases (ILD) are a heterogeneous group of disorders that affect, to a greater or lesser degree, the alveolus, the peripheral airway, and the septal interstitium. Although ILD share certain physiological, clinical, and radiological characteristics, they are distinct entities^{1,2}. The American Thorax Society and the European Respiratory Society propose a classification into two categories: ILD with known etiology, and idiopathic ILD. The latter is further classified as: (i) major idiopathic interstitial pneumonias; (ii) rare

idiopathic interstitial pneumonias; and, (iii) unclassifiable idiopathic interstitial pneumonias^{1,3,4}. Of the idiopathic forms, idiopathic pulmonary fibrosis (IPF) is the most common and has the worst prognosis since it is characterized by patches of dense, sub-pleural fibrosis alternating with areas of healthy lung tissue. Other idiopathic ILD are characterized by varying degrees of inflammation and fibroproliferative activity⁵⁻⁷.

As in other respiratory diseases, the functional evaluation of patients with suspected ILD has implications for diagnosis and the assessment of treatment. In addition,

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prognosis depends on the patient's functional condition at the time of diagnosis and the changes that occur in the months following treatment onset⁸. In recent years, understanding of the functional changes that occur in patients with ILD⁹⁻¹² has expanded, so the objective of the present review is to examine the current state of knowledge in the field and to analyze the contribution of relevant developments to improve the prognosis. We believe that this information will be of great interest to clinicians who treat patients with ILD. We conducted a thorough review of the publications listed in PubMed, using the following keywords for our search: interstitial lung disease, pulmonary fibrosis, pulmonary function test, spirometry, diffusing capacity, 6-minute walking test, lung volumes, and cardiopulmonary exercise test.

GENERAL CONSIDERATIONS ON LUNG FUNCTION EVALUATION

Any adequate evaluation of lung function, must include at least an assessment of pulmonary mechanics, gas exchange, and response to exercise (Table 1). The standard test for evaluating respiratory mechanics is spirometry, while lung-diffusing capacity of carbon monoxide (DLCO) is the best test for assessing gas exchange. The cardiopulmonary exercise test (CPET) is the best means available for analyzing integrated responses to exercise, but due to its complexity and cost, it is not very practical. The six-minute walking test (6MWT) is a simple, low-cost alternative.

ABNORMALITIES IN LUNG MECHANICS

In ILD patients, the functional pattern is predominantly restrictive, manifested by a progressive reduction of pulmonary volume and capacity. Most patients show a decrease in total lung capacity (TLC), vital capacity (VC), and functional residual capacity (FRC). Some exceptions to this restrictive pattern occur in diseases such as lymphangioleiomyomatosis, Langerhans cell histiocytosis and, occasionally, end-stage sarcoidosis. In these diseases, pulmonary volumes may be normal or even increased so these indicators may be useful in differential diagnoses.

Forced spirometry reveals a reduction in forced vital capacity (FVC) with no limitation of the forced expiratory

Table 1. Common functional abnormalities in patients with interstitial lung diseases

Abnormalities in lung mechanics	↓VC ↓Compliance (↓FRC and ↓ITGV) Lung restriction (↓TLC) ↑R5Hz
Abnormalities in gas exchange	↓DLCO ↓PaO ₂ , ↓SaO ₂ ↑A-a O ₂ gradient
Abnormalities during exercise testing	↓VO ₂ ↑VE/VCO ₂ ↑VD/Vt ↓MVV ↑VE/MVV ↓VO ₂ /HR ↓distance in 6MWT

VC: vital capacity; FRC: functional residual capacity; ITGV: intrathoracic gas volume; TLC: total lung capacity; R5Hz: resistance measured at 5 Hertz; DLCO: diffusion capacity; PaO₂: partial pressure for oxygen; SaO₂: arterial saturation of oxygen; A-a O₂ gradient: alveolar-arterial oxygen gradient; VO₂: oxygen uptake; VE: ventilation; VCO₂: carbon dioxide output; VD: dead space; Vt: tidal volume; MVV: maximal voluntary ventilation; HR: heart rate; 6MWT: six minute walking test.

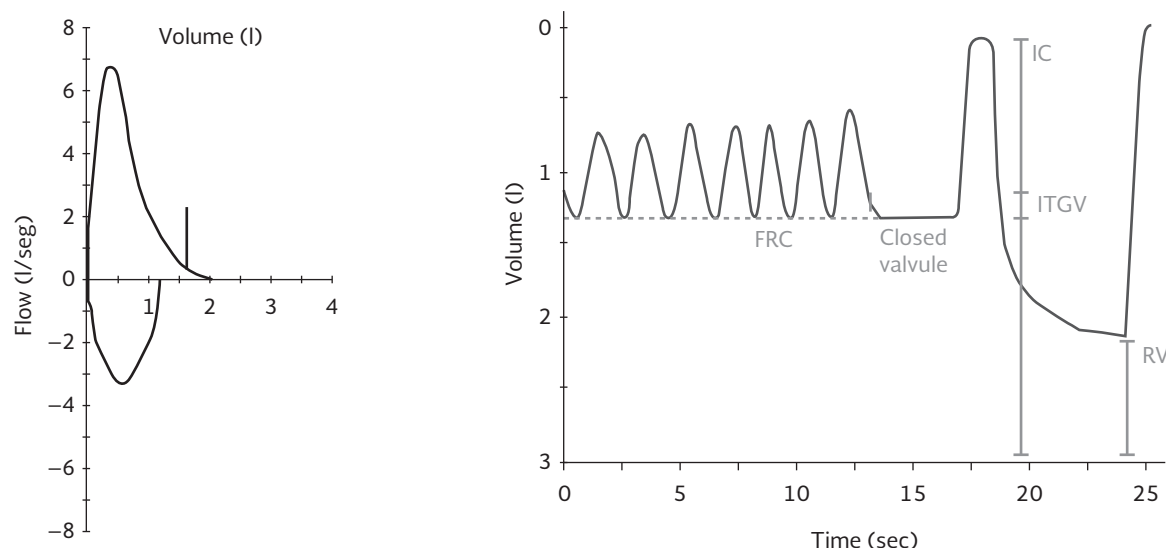
volume in the first second (FEV₁), which produces a normal or elevated FEV₁/FVC (Fig. 1). However, spirometry does not reliably identify lung restriction because it does not measure static lung volumes¹⁰.

For several decades FVC has been used as an outcome when studying patients with IPF. A decline in serial measurements of FVC is a widely accepted indicator of disease progression in IPF and an outcome commonly used in therapeutic trials. A decline of at least 10% in FVC indicates disease progression. Other authors suggest that a reduction of 6% in FVC in a period of 24 weeks may be sufficient to affect the prognosis¹³.

When evaluating respiratory restriction, corporal plethysmography is the standard because it allows measuring static lung volumes¹⁴. This procedure uses direct measurements of FRC, tidal volume (Vt), vital capacity (VC), and inspiratory capacity (IC), to indirectly calculate TLC and residual volume; it is then possible to identify the restrictive ventilatory pattern manifested by TLC, volume of intrathoracic gas, and VC below 80% of that predicted. By using TLC it is possible to assess restriction. Total lung capacity is calculated by adding FRC and IC.

Respiratory restriction may also be determined using imaging methods, the simplest of which is a chest

Figure 1. Flow volume curve obtained from a forced spirometry. The result suggests restriction and is confirmed by measuring pulmonary volumes by corporal plethysmography. Note that the FEV_1/FVC ratio is 89% (normal), with FVC at 75% of the predicted value, and TLC is 62% of predicted. These results confirm restriction. FEV_1 : forced expiratory volume in the first second; FVC: forced vital capacity; RV: residual volume; ITGV: intrathoracic gas volume; TLC: total lung capacity; VC: vital capacity.



	Spirometry				Plethysmography		
	Predicted	REAL	%Pred		Predicted	REAL	%Pred
FVC (l)	2.49	1.86	75	TLC (l)	5.09	3.20	62
FEV_1 (l)	1.79	1.66	92	TGV (l)	3.22	1.89	58
$FEV_1/FVC\%$	72	89		RV (l)	2.14	1.16	54
				VC (l)	2.49	2.08	83

radiograph. In addition, TLC can be quantified using planimetry or by inert gas dilution techniques that may be an alternative when plethysmography is not available.

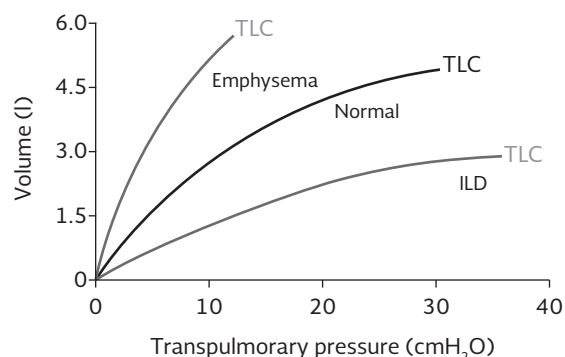
The pressure-volume curve of patients with ILD shows a reduction of lung compliance; the curve is clearly displaced downwards and to the right compared with the curve of a normal subject (Fig. 2). Likewise, there is an increase in elastic retraction pressure. The reduction of compliance increases respiratory effort because the system must generate a larger pressure gradient (ΔP) to displace the same volume of. Lung compliance decreases as a consequence of loss of lung volume, increase in the amount of interstitial connective tissue, and increase in surface tension due to changes in the surfactant or alveolar size. To assess compliance, an esophageal catheter must be introduced to measure the transpulmonary pressure, which produces discomfort. As pulmonary rigidity

increases, so too does the percentage of fibrosis, leading to a worse prognosis.

The pathological mechanisms involved in the reduction of lung volume seen in most ILD patients include the complete or partial obliteration of some alveolar units, invasion of alveolar spaces by cells and inflammatory exudates, thickening of the alveolar walls due to extracellular matrix, and destruction of lung parenchyma (Fig. 3). The increase in elastic retraction pressure reduces the FRC, which, in turn, increases airway resistance.

In the bronchiolocentric forms of ILD, such as hypersensitivity pneumonitis, respiratory bronchiolitis associated with ILD, and sarcoidosis, as well as in patients with concomitant chronic obstructive pulmonary disease, an obstructive or mixed (i.e. restrictive plus obstructive) functional pattern may be observed¹⁵. Table 2 summarizes the characteristics of the obstructive, restrictive, and mixed functional patterns.

Figure 2. Pressure-volume curve from interstitial lung disease patients is characteristically displaced downwards and to the right, compared to normal subjects or to patients with emphysema. This indicates that greater pressure is required to generate the same volume. ILD: interstitial lung disease; TLC: total lung capacity.



Respiratory patterns and gas exchange

In ILD, the abnormalities in gas exchange generally precede changes in respiration mechanics. The characteristic respiratory pattern of ILD patients consists of a decrease in V_t and an increase in respiratory frequency that generates rapid, shallow breathing. This respiratory pattern seems to be mediated by an increase in afferent vagal activity, although extra-vagal influences (i.e. reflexes of the thoracic wall or a behavioral modification dependent on cortical perception of the afferent information from the respiratory system) may also contribute. This rapid, shallow

ventilatory pattern is an adaptive process because it reduces respiratory effort in the presence of reduced lung compliance.

When analyzing gas exchange, the characteristic finding in ILD patients is hypoxemia. In places of high altitude, such as Mexico City, hypoxemia is considered when the partial oxygen pressure (PaO_2) is < 60 mmHg, or the oxygen saturation level (SaO_2) is $< 90\%$ ¹⁶. In the initial stages of ILD, arterial gases at rest tend to be normal. The hypoxemia seen in ILD patients is associated with an increase in the alveolus-arterial oxygen gradient (A-a gradient) that worsens with exercise and is often accompanied by a normal or increased ventilatory state (normo- or hypocapnia); the pH values remain within normal ranges. Carbon dioxide retention is rare, usually manifesting only in terminal stages of the disease. Occasionally, an adequate oxygenation at rest may be seen, but hypoxemia becomes evident once exercise begins since this reduces blood circulation time through the lung capillaries¹⁷. It is important to keep in mind that normal PaO_2 or SaO_2 levels do not rule out the possibility that significant hypoxemia may occur during exercise or sleep.

The mechanisms involved in the physiopathology of hypoxemia at rest and of the increase of the A-a O_2 gradient are almost exclusively due to an imbalance in the ventilation:perfusion ratio (V/Q) accompanied, with some areas being poorly ventilated but well perfused and others, more importantly, being

Figure 3. Microphotographs that illustrate: **A**) A normal lung with an unaltered terminal bronchiole (arrow head), alveolar space (AS) and the unaltered alveolar septum (arrows); and, **B**) A section of lung from a patient with interstitial lung disease. Arrows indicate localized, thickened sub-pleural septa caused by deposits of collagen fibers and scarce lymphoplasmacytic infiltration. Also visible are zones with end-stage lesions (ESL). Hematoxylin-eosin staining; 4× increase from the original (Courtesy: Miguel Gaixola, M.D.).

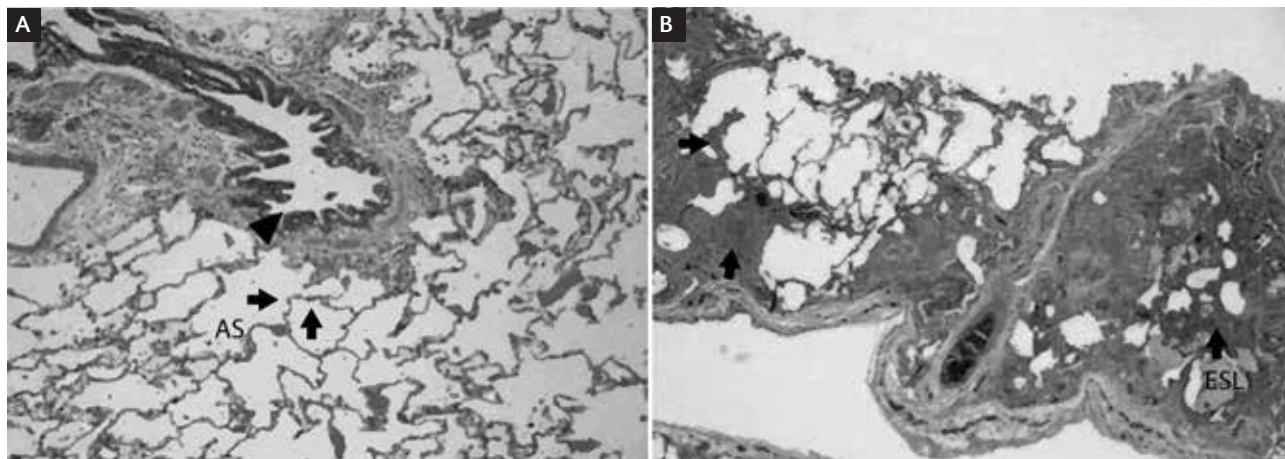


Table 2. Physiologic characteristics observed in obstructive, restrictive, and mixed pattern

Functional pattern	FEV ₁ /FVC quotient	TLC	RV	DLCO
Obstruction due to COPD	↓	Normal or ↑	Normal or ↑	↓
Obstruction due to asthma	↓	Normal or ↑	Normal or ↑	Normal or ↑
Lung restriction	Normal or ↑	↓	↓	↓
Extrapulmonary restriction	Normal or ↑	↓	Normal or ↓	Normal
Mixed	↓	↓	Normal	↓

COPD: chronic obstructive pulmonary disease; DLCO: diffusion lung of carbon monoxide; FEV₁: forced exhaled volume in 1 second; FVC: forced vital capacity; RV: residual volume; TLC: total lung capacity.

well ventilated but poorly perfused, a condition that increases the V/Q ratio. During exercise-induced hypoxemia a second contributing factor, in addition to the V/Q imbalance, is poor oxygen diffusion through the alveolar capillary units that occurs due to, among other causes, a thickening of the membrane, a reduction in the area available for gas exchanges, and a decrease in contact time between alveolar oxygen and the circulating erythrocytes⁸⁻²⁰.

Abnormalities in gas exchanges may also be detected by measuring DLCO; indeed, this seems to be the first functional abnormality that is observed in the course of ILD^{21,22}. The DLCO evaluates the transference of carbon monoxide (CO) from the alveolar space to the inside of the lung capillary divided by the difference of CO pressures in the two compartments. Factors that determine gas diffusion through a semipermeable membrane include structural elements such as pulmonary volume, distance to the exchange phase, membrane thickness, exchange surface, effects of the airway closure, and pulmonary capillary blood volume, as well as functional aspects such as absolute V/Q levels, uniformity of the V/Q ratio, alveolar gas composition, diffusion characteristics of the membrane, hemoglobin bonding properties, and gas pressure in the alveolar capillaries. All of these determinants are included in Fick's law:

$$V_{\text{gas}} = A \times D \times (P_1 - P_2)/T$$

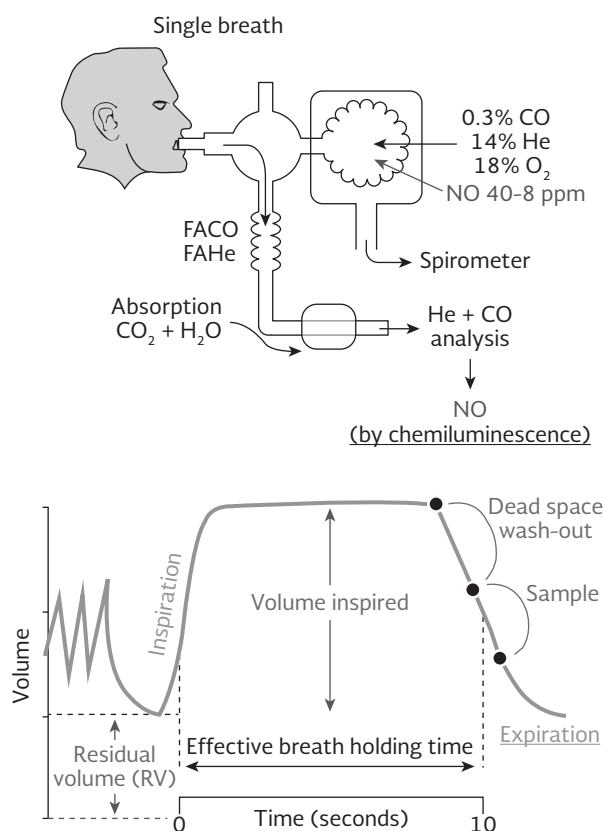
This means that the volume of gas (V_{gas}) which diffuses through a semipermeable membrane is determined by the exchange area (A), the diffusion coefficient of the gas involved (D), and the pressure difference on the two sides of the alveolar-capillary

membrane (P₁ - P₂), while it is inversely proportional to the thickness of the membrane or diffusion distance (T)²³⁻²⁵. This measurement loses accuracy when assessing patients with extremely reduced pulmonary volumes (VC < 1.0 l) (Fig. 4).

Most ILD patients experience a reduction of DLCO, although this is not specific of a particular type of ILD. Reduced DLCO is due, in part, to the destruction of functionally heterogeneous alveolar capillary units. The lung regions with reduced compliance due to fibrosis may be poorly ventilated but continue to be well perfused, a condition that produces low V/Q ratios. The severity of the reduction in DLCO does not correlate well with the state of the disease because the extensive areas of fibrosis do not always translate into severely reduced DLCO. Similarly, some patients with ILD may have a substantial reduction of lung volumes or severe hypoxemia, even though the DLCO is normal or only slightly reduced. This is specially true in cases of sarcoidosis²⁶. The occurrence of moderate-to-severe reductions in DLCO in the presence of normal lung volumes should suggest ILD associated with emphysema, pulmonary vascular disease, Langerhans cell histiocytosis, or lymphangioleiomyomatosis. The DLCO is a useful measure in follow-up to determine prognosis.

Some studies have shown that in the initial stages of sarcoidosis and asbestosis, an increase in the DLCO may be seen²⁶. This increase is made possible by the membrane diffusion component, which is associated with the initial inflammatory phase. The increase in DLCO has been described as a characteristic finding in diffuse pulmonary hemorrhages due to the presence of erythrocytes in the alveolar spaces. In the early inflammatory stages of some ILD, an increase in CO

Figure 4. Diagram of diffusing capacity of carbon monoxide and diffusing capacity of nitric oxide based on the unique respiration method in which a volume of expiratory reserve maneuver is performed on the basis of stable tidal volume respiration. After that, an inspiratory vital capacity maneuver had subjects inhale a mixture of gases (CO 0.3%, He 14%, O₂ 15% and NO 40 ppm) up to their total lung capacity. After an apnea period of 10 seconds, a slow expiratory vital capacity maneuver was performed to take measurements of both CO and NO. The analysis of CO was done by mass spectrometry while NO was analyzed by chemiluminescence. CO: carbon monoxide; FACO: alveolar carbon monoxide fraction; FAHe: alveolar helium fraction; He: helium; NO: nitric oxide.



diffusion may be found, possibly associated with an increase in alveolar-capillary permeability. A recently described index of alveolar gas transference called “diffusing capacity of nitric oxide” (DLNO) is being evaluated. Nitric oxide is captured 4.3-times faster than CO using the single-breath method. This observation, although somewhat fortuitous, has stimulated the research into alveolar transference (diffusion) since DLNO is considered to express the true diffusion capacity of the membrane due to its very high affinity for hemoglobin and its independence from pulmonary capillary blood volume (Fig. 4)²⁷.

ALTERATIONS IN PULMONARY CIRCULATION

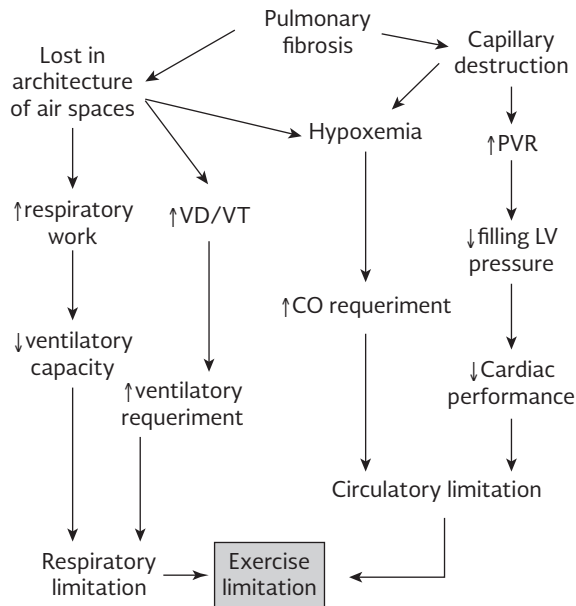
Vascular abnormalities are characteristics shared by all ILD. The development of pulmonary hypertension (PH) is a determinant for prognosis, especially in patients with IPF or pulmonary disease associated with scleroderma. The traditional concept that PH in IPF patients is caused by hypoxic pulmonary vasoconstriction and loss of pulmonary capillaries has not been fully demonstrated in recent clinical studies. The biological processes that underlie progressive fibrogenesis may also contribute to vascular remodeling and PH^{28,29}. Recent studies suggest that there is a relationship between fibrosis of the lung parenchyma and the mechanisms that cause structural and functional abnormalities of the pulmonary blood vessels³⁰. The fact that there is an anatomical proximity of the blood vessels, the interstitial space, and the alveolar epithelium may help to understand the pathogenic mechanisms that lead to the development of PH in ILD patients. The presence of PH in IPF, sarcoidosis, or systemic sclerosis is considered an indicator of poor prognosis in terms of respiratory function, quality of life, and survival.

According to the guidelines for diagnosis and treatment of PH, IPF is classified in Group 3 (i.e. PH due to pulmonary disease or hypoxia) to distinguish this illness from other clinical conditions that cause PH. Pulmonary hypertension is defined as ≥ 25 mmHg in the mean pressure of the pulmonary artery (mPAP) measured at rest by right heart catheterization. Although the definition of PH during exercise is less standardized, IPF patients may show normal hemodynamics while at rest and develop significant PH only while exercising. Some coexisting disorders, such as obstructive sleep apnea, coronary artery disease with left ventricular dysfunction, and pulmonary embolism, may contribute to the development of PH in IPF patients.

EXERCISE CAPACITY

Exercise deeply affects the respiratory function of ILD patients. Figure 5 shows the factors that contribute to limitations during exercise, a situation that generally produces rapid, shallow breathing with a significant worsening of dyspnea and a significant reduction of PaO₂. The ILD patients also show a significant reduction in their exercise capacity. The most commonly used

Figure 5. Factors that limit exercise capacity in ILD patients. CO: cardiac output; PVR: pulmonary vascular resistances; VD: dead space; LV: left ventricle; VT: tidal volume.



exercise tests are the 6MWT and CPET. The most important measurement in the 6MWT is the number of meters that the patient walks, but modifications in oxygen saturation provide additional information to evaluate in more detail the progression of the disease or response to treatment³¹. The 6MWT may also provide information that is more accurate than other pulmonary function tests, especially in IPF patients^{32,33}. Some retrospective cohort studies suggest that a reduction of 30 meters in the distance walked has implications for prognosis³². Another study reports that after 24 weeks of follow-up, a decrease of 50 meters, or walking fewer than 207 meters, bring a fourfold greater risk of dying within a year, compared with patients who walk more than this distance³³. An index proposed by Lettieria, et al. includes both the distance walked and the degree of desaturation during the 6MWT. The nadir of SpO₂ multiplied by the distance walked in meters (the distance-saturation product) has been shown to have high sensitivity and specificity to determine survival at 12 months in IPF patients³⁴. Studies using the 6MWT have also described a factor called “heart rate recovery”, defined as the reduction in the heart rate during the first minute after finishing the 6MWT; that is, the heart rate is measured at the end of the 6MWT and then compared with the heart rate after one minute. When a subject’s heart rate

does not decrease by at least 14 beats per minute, chronotropic incompetence is suspected due to a disturbance in parasympathetic activity that is associated with poor prognosis³⁵.

In the CPET, the most common finding in patients with ILD is a reduction in maximum oxygen uptake (VO₂max) because the respiratory system is unable to respond to the increased demand for oxygen at tissue level, such that exercise ends early with a low anaerobic threshold. This threshold is defined as the moment in which anaerobic energy producing mechanisms are activated. Other findings include a progressive increase in dead space during exercise (i.e. an increase in the VD/Vt ratio) and a higher ventilation/VCO₂ quotient. The latter reflects the system’s inefficiency in eliminating CO₂ at a given level of ventilation; that is, the lesser the inefficiency of the system the greater the ventilation required to eliminate a given quantity of CO₂, conditions that lead to increases in the ventilation/VCO₂ quotient. This quotient increases even more with a co-existing PH because the restriction in the pulmonary vascular bed reduces the availability of CO₂.

The ventilation/maximum voluntary ventilation ratio is high in patients with chronic respiratory disorders, including those with ILD. In healthy subjects, maximum ventilation during exercise does not exceed 80% of the amount the subject is capable of breathing (maximum voluntary ventilation); that is, there is a respiratory reserve of approximately 20%. But patients with chronic respiratory disorders have a reduced ventilatory capacity (maximum voluntary ventilation), that is, when ventilation increases during exercise they quickly reach their maximum respiratory capacity, which means that the ventilation/maximum voluntary ventilation ratio approaches 1, thereby depleting the respiratory reserve.

Left ventricular dysfunction is another factor that may reduce an individual’s capacity to exercise. Factors related with it include reduced cardiac output (heart rate × systolic volume). In CPET, this phenomenon may be indirectly assessed by measuring oxygen pulse (VO₂/HR), which is equivalent to systolic volume and therefore will be low in patients with ventricular dysfunction.

From the clinical perspective, the disproportionate limitation to exercise related with abnormalities in

pulmonary volume and oxygen desaturation during exercise could be an indicator of the development of PH in IPF patients^{29,36}. Since hypoxemia is not always evident at rest, and it is not always possible to detect severe exercise-induced hypoxemia, it may be important to consider conducting a CPET that involves serial measurement of arterial gases, or measuring oxygen saturation by pulse oxymetry. Arterial oxygen desaturation, or the inability to adequately reduce the volume of dead space by exercising (e.g. a high VD/Vt ratio), together with an excessive increase in respiratory frequency with a lower-than-expected recruitment of tidal volume, provide useful information regarding physiological abnormalities and the extent of disease development. Longitudinal follow-up of patients with IPF has identified a VO_2max threshold of 8.3 ml/kg/min, below which the risk of death increases significantly (hazard ratio of 3.4)³⁷.

PULMONARY FUNCTION TESTS IN PULMONARY HYPERTENSION

One method for screening ILD patients for PH relies on a formula that predicts mPAP from standard pulmonary function tests. In this equation, pulse oxymetry at room air (SpO_2) together with the percentage of FVC and DLCO are found to be predictor parameters for calculating pulmonary artery pressure. Although this formula has a low positive-predictive value, only 51%, it does provide a high negative-predictive value of 96%, thus identifying IPF patients with a low risk for PH. In one study this formula showed to be a useful tool in IPF patients, with a performance similar to that of transesophageal echocardiography^{38,39}. However, the study, which was conducted in subjects living at sea level, used the pulmonary function test reference equations for subjects different from the population living at high altitudes. Moreover, it included only young patients who were in the waiting list for lung transplantation and, therefore, represented the most severe cases. In the less severe cases no right cardiac catheterization was performed even though such procedure would have confirmed or ruled out the findings calculated by using the prediction formula.

Pulmonary hypertension is common in the combined syndrome of pulmonary fibrosis with emphysema, which can be considered a distinct entity with its own characteristic functional profile; i.e. lung volume is

preserved, DLCO is severely reduced, and exercise-induced hypoxemia is present. The severe decrease in DLCO probably represents the cumulative or synergistic effects of emphysema, fibrosis, and pulmonary vascular disease and is one of the hallmarks of this syndrome. Pulmonary hypertension is a critical determinant of poor prognosis^{40,41}.

METHODS FOR FUNCTIONAL FOLLOW-UP

The clinical course of patients with IPF varies. It may have long periods of stability or periods of acute deterioration with a gradual but constant decline in pulmonary function^{42,43}. This unpredictable nature underlines the importance of identifying factors that may help to make more precise prognoses for patients at the time of diagnosis⁴⁴.

Table 3 shows the functional factors present at diagnosis and the changes in physiological parameters in the first six months after diagnosis that result in a poor prognosis. One relevant point is that parameters such as DLCO and high-resolution computed tomography findings have implications both at the moment of diagnosis and during follow-up. Clinical efficacy is best evidenced by a beneficial effect on clinically significant outcomes, including perception of symptoms, functions (i.e. the ability to perform daily life activities), or survival. In ILD, and especially in IPF, the main outcomes are mortality due to all causes and non-elective hospitalizations due to all causes. For IPF, there are no validated measures of symptoms or broader constructs such as health status or functional status. A surrogate outcome is defined as an indirect measure that may well replace clinically significant outcomes. Once they are validated, surrogate outcomes may prove to be an appropriate means of prognosis; however, validation requires evidence that the effect of an intervention or a clinically significant outcome is reliably predicted by the effect of an intervention in the surrogate outcome. At present, for patients with IPF, there are no validated surrogate outcomes. In subjects with ILD a reduction of FVC of at least 10%, or of DLCO of at least 15%, over a period of 6-12 months is associated with reduced survival rates. While a change in FVC is a good surrogate for subsequent mortality, it is imperfect because some patients die without a 10% reduction,

while others may live for long periods of time even after a decline of 10% in FVC. This has led to observations in some recent studies of changes in the percentage of predicted FVC as an independent predictor of mortality in IPF, together with the concept of the minimum clinically significant difference. This is the smallest difference in a measure that may be seen as important in terms of benefit or risk, and that would lead clinicians to consider a change in treatment. Hence, it is an important concept in clinical medicine that will help to interpret the significance of changes observed in one measurement, and could affect the perceived efficacy of an intervention. Minimum clinically significant difference may also have implications for the design of clinical trials in terms of selecting primary and secondary outcomes, as well as in estimating the sample size. In these studies, a minimum clinically significant difference for a predicted FVC between 2 and 6% has been identified.

CONCLUSIONS

The evaluation of respiratory function is of great importance in patients with suspected ILD in relation to differential diagnoses, assessing responses to interventions, and establishing prognoses. Among the pulmonary function tests, DLCO is the only one that has implications for prognosis from the moment of diagnosis (baseline measurements). The magnitude of the compromised functionality, especially in terms of hypoxemia and reduced compliance, correlates with the extent of the morphological lesions. It is important to emphasize that alterations in gas exchange tend to precede changes in breathing mechanics; it could increase the sensitivity for diagnosing ILD. As these diseases progress, the fibrosis extends and, as a result, tissue destruction continues and hypoxemia worsens, especially during exercise. In the final stages, hypercapnia will develop, which will signal a poor prognosis. For all these reasons, and to determine prognosis, the identification of trends in the different parameters of pulmonary function is a better approach than making baseline measurements.

It is important to stress that the changes observed in ventilatory mechanics and gas exchange are common to most ILD and therefore do not support specific diagnoses. Also, with the possible exception of the k constant of the pressure-volume curve (which shows

only marginal significance) and the increase in A-a gradient, pulmonary function tests do not discriminate between inflammation and fibrosis. An improvement in the alveolar-arterial oxygen difference during exercise seems to correlate with minimal fibrosis. Finally, the 6MWT is the most useful, practical exercise test in ILD patients because it is easy to perform, requires no sophisticated equipment, and has significant prognostic value.

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