Exertional dyspnoea in interstitial lung diseases: the clinical utility of cardiopulmonary exercise testing

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ABSTRACT

Interstitial lung diseases (ILDs) represent a heterogeneous group of pathologies characterised by alveolar and interstitial damage, pulmonary inflammation (usually associated with fibrosis), decreased lung function and impaired gas exchange, which can be attributed to either a known or an unknown aetiology. Dyspnoea is one of the most common and disabling symptoms in patients with ILD, significantly impacting quality of life. The mechanisms causing dyspnoea are complex and not yet fully understood. However, it is recognised that dyspnoea occurs when there is an imbalance between the central respiratory efferent drive and the response of the respiratory musculature. The respiratory derangement observed in ILD patients at rest is even more evident during exercise. Pathophysiological mechanisms responsible for exertional dyspnoea and reduced exercise tolerance include altered respiratory mechanics, impaired gas exchange, cardiovascular abnormalities and peripheral muscle dysfunction.

This review describes the respiratory physiology of ILD, both at rest and during exercise, and aims to provide comprehensive and updated evidence on the clinical utility of the cardiopulmonary exercise test in the assessment and management of these pathological entities. In addition, the role of exercise training and pulmonary rehabilitation programmes in the ILD population is addressed.

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Introduction

Interstitial lung diseases (ILDs) represent a heterogeneous group of pathologies characterised by alveolar and interstitial space damage, pulmonary inflammation (usually coupled with fibrosis), decreased pulmonary capacity and impaired gas exchange [1]. ILD can be attributed to a known or an unknown aetiology [2] (figure 1). The former includes pneumoconiosis, hypersensitivity pneumonitis, iatrogenic and post-infectious ILD. The idiopathic forms are represented by ILD in the context of systemic diseases, such as those related to connective tissue diseases [3] and the recently described forms of interstitial pneumonia with autoimmune features [4] as well as the idiopathic interstitial pneumonias (IIPs). The classification of IIPs has been revised periodically [5–7], and older classifications included patients that today are classified differently. The most recent update of the international multidisciplinary classification of the IIPs distinguishes major, rare and unclassifiable forms on the basis of patient’s clinical history and high-resolution computed tomography peculiar features [8]. Among the IIPs, the most relevant clinical picture is represented by idiopathic pulmonary fibrosis (IPF), which is defined as a form of “chronic, progressive fibrosing interstitial lung disease, of unknown cause, characterised by a progressive worsening of dyspnoea and lung function and associated with a poor prognosis” [9, 10]. Additional, alternative groupings have been proposed according to a disease behaviour approach [8].

Despite novel classifications based on an improved understanding of pathophysiological mechanisms and significant progress in treatment strategies, the prognosis of ILD remains often poor, particularly in IPF where only 20–30% of patients have a life expectancy >5 years from the first diagnosis [9, 11, 12]. Table 1 lists the major reported determinants of prognosis in IPF. This emphasises for the need for early and accurate assessment.

Independent of pathophysiological characteristics, ILDs usually share a common pattern of clinical and functional abnormalities. Dyspnoea is one of the most common and disabling symptoms in patients with ILD, significantly impacting quality of life [9, 13]. The mechanisms causing dyspnoea are complex and not yet fully understood. However, it is recognised that dyspnoea occurs when there is an imbalance between the central respiratory efferent drive and the response of the respiratory musculature. This imbalance may be consciously perceived as the distressing sensation of unsatisfied inspiration [14]. Dyspnoea is often triggered by physical activity and represents an important reason for premature exercise interruption in lung diseases. Exertional dyspnoea is commonly evaluated using respiratory investigations including pulmonary function tests and arterial blood gas determination, or cardiac assessments, such as ECT and echocardiography. However, information from these tests, which are performed in a resting state, may

![Diagram of ILD classification](https://doi.org/10.1183/16000617.0099-2016)

**FIGURE 1** Idiopathic and non-idiopathic interstitial lung disease (ILD). IIP: idiopathic interstitial pneumonia; CTD: connective tissue disease; IPAF: interstitial pneumonia with autoimmune features; LIP: lymphocytic interstitial pneumonia; PPFE: pleuroparenchymal fibroelastosis; COP: cryptogenic organising pneumonia; AIP: acute interstitial pneumonitis; IPF: idiopathic pulmonary fibrosis; NSIP: nonspecific interstitial pneumonia; RB: respiratory bronchiolitis; DIP: desquamative interstitial pneumonia.
correlate poorly with symptoms occurring during physical activity [15]. Performing measurements during exercise therefore provides more relevant physiological information and may give a more accurate estimate of the individual’s functional capacity. Furthermore, disease is often not confined to a single organ or system, such as the lung, and testing the body’s global physiological response to exercise provides additional useful data.

This review describes the respiratory physiology in ILD, both at rest and during exercise, and aims to provide comprehensive and updated evidence on the clinical utility of the cardiopulmonary exercise test (CPET) as a diagnostic, monitoring and prognostic tool. In addition, the roles of exercise training and pulmonary rehabilitation programmes in the ILD population are addressed.

Electronic searches were undertaken in MEDLINE, Web of Science, the Cochrane Library and Scopus databases. The registers were searched using the following combination of keywords: “exercise” AND (“dyspnoea” OR “dyspnea”) AND (“interstitial lung disease” OR “ILD” OR “idiopathic pulmonary fibrosis” OR “IPF”) from the date of inception to July 2016. The search strategy yielded 1462 articles. Following the removal of duplicates, the authors independently selected papers of potential interest on the basis of titles and abstracts for a full-text assessment and reached an agreement in cases of lack of consensus. Furthermore, reference lists of included studies, recent reviews and textbooks were hand-searched for relevant citations. Manuscripts considered relevant to the aim of this review are discussed here.

### Resting respiratory physiology in ILD

Pulmonary function tests have been used widely in ILD for establishing diagnosis, severity and prognosis, as well as for monitoring disease progression and response to therapy [16–19]. The typical observed respiratory pattern is a restrictive deficit, with decreased lung compliance and increased recoil pressures [16, 20]. Underlying mechanisms are multifactorial, including loss of lung volume, reduced alveolar elasticity and size and increased surface tension [19]. Static lung volumes, such as vital capacity, functional residual capacity and total lung capacity (TLC) are reduced, as is the forced vital capacity (FVC). The residual volume (RV) is usually preserved, with an increased RV/TLC ratio [17]. Patients with combined pulmonary fibrosis and emphysema may have preserved lung function, but with a high prevalence of pulmonary hypertension [21]. Subjects with pulmonary sarcoidosis also may present with preserved lung function [16].

Gas exchange impairment is a further typical feature of ILDs [9]. This is mainly due to ventilation/perfusion mismatch and diffusion limitation [16–18]. The diffusion capacity of the lung for carbon monoxide (DLCO) is typically reduced in ILD, particularly in IPF compared to other forms such as sarcoidosis [16, 17], representing a negative prognostic factor [9]. In addition, DLCO and transfer coefficient are predictive of desaturation during exercise, reflecting the degree of diffusion limitation as well as the severity of pulmonary vascular insufficiency [22]. Finally, resting blood gas abnormalities include hypoxaemia and increased alveolar–arterial oxygen tension gradient (P(A-a)O2) [16, 17, 19].

### Exercise respiratory physiology in ILD

The respiratory derangement observed in ILD patients at rest is even more evident during exercise [17, 18]. Exertional dyspnoea and consequent reduced exercise tolerance have been reported to be multifactorial [23, 24]. Here, the main pathophysiological mechanisms are described in detail.
Altered respiratory mechanics

Subjects with ILD show a rapid and shallow breathing pattern during mild to moderate exercise [25], which differs to the response observed in healthy subjects, where the augmented ventilatory demand causes an increase in tidal volume (V̇T). Therefore, the markedly elevated minute ventilation (V̇E) in ILD patients during exercise is mainly due to the effect of an increased respiratory frequency (fR) in the setting of reduced lung compliance and low V̇T [26, 27]. The small V̇T and rapid respiratory rate observed in ILD patients are thought to occur secondary to increased inspiratory elastic loading on respiratory muscles and stimulation of peripheral mechanoreceptors [28]. When exercise intensity rises, the inspiratory capacity is progressively diminished due to the increased V̇T, and some ILD patients reach or even exceed their estimated maximal voluntary ventilation (MVV) [29]. In contrast, in normal subjects, the V̇E at peak exercise is usually <80% of the predicted MVV, preserving a degree of breathing reserve [30]. This peculiar breathing pattern contributes to the abnormally high ratio between physiological dead space volume (V̇D) and V̇T in ILD subjects [31]. In fact, while in healthy individuals the V̇D/V̇T ratio decreases as ventilatory requirements increase during exercise, in ILD subjects it is not uncommon for the V̇D/V̇T ratio to remain the same, or even increase under similar conditions, reducing the ability of the lungs to clear the increasing carbon dioxide production during exercise without a further increase in V̇E [32]. Despite this abnormal ventilatory pattern, respiratory mechanics don't seem to be the unique contributors to exercise limitation in ILD patients. Two studies performed in ILD patients with different diagnoses reported that a number of participants had a largely preserved ventilatory reserve at the end of exercise, despite reduced exercise performance [33, 34]. Furthermore, the administration of oxygen during CPET or 6-min walk test improved both performance (i.e. increased peak oxygen uptake (VO2peak), maximal workload, test duration and walk distance) and oxygen uptake (V̇E) (i.e. reduced dyspnoea scores), suggesting the occurrence of other factors in limiting maximal exercise performance in this population [24, 29, 35, 36].

Impaired gas exchange

Remarkable desaturation is frequently seen during both maximal and submaximal exercise, particularly in IPF patients [36]. Impaired gas exchange occurs as a result of destruction of the pulmonary capillary bed and thickening of the alveolar capillary membrane [37]. Ventilation/perfusion (V/Q) mismatch represents the main contributor to arterial hypoxaemia during exercise. In addition, diffusion limitation contributes to a significant degree, as demonstrated by multiple inert gas elimination technique studies [38]. Diffusion limitation may contribute up to 40% to PaO2 during exercise, and patients with a more severe diffusion limitation at rest have been reported to be those with a greater diffusion limitation during exercise. A relationship between the degree of impairment in diffusing capacity and exercise-induced hypoxaemia has been documented in patients with ILDs of various aetiologies. However, there may be differences in the pattern and severity of gas exchange disorders during exercise, which are attributable to specific underlying pathophysiological mechanisms. Patients with IPF seem to show a larger increase in PaO2 during exercise than those with sarcoidosis or asbestosis [39, 40]. In fact, there might be more derangement in oxygen transport on exertion in patients whose disease is characterised by a greater degree of interstitial fibrosis. This hypothesis is supported by the relationships observed between exercise-induced desaturation and the profusion and extent of parenchymal abnormality on imaging [41]. Reduced mixed venous oxygen content is also seen in exercising ILD patients, possibly due to reduced cardiac output, arterial oxygen content and proportionally increased extraction of oxygen by working muscles [37]. The combination of these three factors often leads to significant arterial haemoglobin desaturation, which represents a marker of poor prognosis [42]. Despite the impairment of gas exchange and the mechanical constraints, hypercapnia is not typical in patients with ILD. The increase in fR, and accordingly in V̇E, ensures that eucapnia is maintained. Indeed, the ventilatory response to increasing carbon dioxide output (V̇CO2) during exercise (represented by the V̇E/V̇CO2 relationship) is markedly elevated in exercising ILD subjects, compared with healthy controls [43]. The V̇E/V̇CO2 is therefore considered an index of the degree of V/Q inequality, since it is approximately proportionate to the V̇D/V̇T, as long as the arterial carbon dioxide tension is stable [44].

Cardiovascular abnormalities

Cardiovascular abnormalities also play a relevant role in limiting exercise capacity in ILD patients [34]. Circulatory impairment results from pulmonary capillary destruction and hypoxic pulmonary vasoconstriction, a reversible mechanism aimed at optimising V/Q matching [37]. ILD subjects breathing 100% oxygen at rest have increased dispersion in the distribution of blood flow, indicating release of hypoxic pulmonary vasoconstriction. The increase in dispersion is proportionate to the severity of pulmonary hypertension during submaximal exercise and to the degree of exercise-induced desaturation. This reversibility seems to diminish over time, as endothelial remodelling develops [24]. In addition, damage of the lung microvasculature by inflammation and fibrosis further increase exercise pulmonary vascular resistance, contributing to the evolution of pulmonary hypertension in ILD [45]. Since inadequate
Peripheral muscle dysfunction

Peripheral muscle dysfunction is emerging as an important contributor factor to exercise limitation in ILDs [49]. In a study by NISHIYAMA et al. [50], the quadriceps muscle force of 41 IPF patients studied retrospectively was reduced on average to 65% predicted and represented an independent predictor of $V_{\text{O2}}\text{peak}$ at the end of exercise. A more recent prospective study showed reduced quadriceps strength and endurance in IPF and nonspecific interstitial pneumonia patients, compared to age-matched controls [51]. A similar relationship between quadriceps peak torque and both peak workload and functional exercise capacity has been documented in patients with sarcoidosis [52]. The mean value of quadriceps peak torque was 67% pred and was inversely related to the mean daily dose of corticosteroids received in the 6 months before testing. Additionally, respiratory muscle strength may have an impact on exercise performance. In sarcoid patients with no signs of skeletal muscle involvement, twitch mouth pressure during inspiration was a stronger predictor of the 6-min walking distance (6MWD) than respiratory function tests or oxygen saturation [53]. Although proximal skeletal muscle weakness is a well-known manifestation of sarcoidosis, less is known about its potential impact and mechanisms in other ILDs. Moreover, it is likely that physical deconditioning plays a similar role as it does in other chronic lung diseases, with avoidance of activities that cause dyspnoea leading to a vicious cycle of worsening exercise capacity and increasing symptoms. There may also be systemic effects of diseases, such as IPF, that are yet to be fully clarified. Corticosteroid treatment may contribute to myopathy of peripheral and respiratory muscles, although findings are inconsistent [52, 53]. Given the potential for deleterious effects of treatments on skeletal muscle, more information is needed in this field.

The role of cardiopulmonary exercise test in ILDs

Exercise testing has been used increasingly in clinical practice to evaluate the level of intolerance to exercise and the underlying causes following the suggestion that organs and systems fail more easily and quickly while under stress [54]. The CPET is considered the gold standard for the evaluation of exercise intolerance, since it provides a comprehensive assessment of the response to exercise and reflects the influences of the cardiac, respiratory and musculoskeletal systems [55]. CPET provides breath-by-breath data on respiratory gas exchange, including $V_{\text{O2}}$, $V_{\text{CO2}}$, $V_{\text{T}}$ and $V_{\text{E}}$, as well as other variables such as ECT, blood pressure and oxygen saturation. The integration of physiological information allows for an analysis of the system as a whole, while separate investigations help to determine which compartment mainly limits exercise capacity and causes exertional dyspnoea [56].

CPET is usually performed in the laboratory, using an electrically braked cycle ergometer or a treadmill, although newer portable metabolic devices may allow exercise testing in nonstandard settings [57]. Cycle ergometry is often considered the preferred method of testing, as it is less likely to be associated with falls, produces fewer movement artifacts, facilitates arterial blood drawings and allows a smooth increase in workload. Furthermore, it is less affected by weight and gait dynamics, permitting a more accurate estimate of the externally applied work [58]. In contrast, a relevant advantage of treadmill testing is that walking and running are more familiar activities for most patients. Peak $V_{\text{O2}}$ is ~5–10% higher with treadmill than with cycle ergometry, probably because of the involvement of more muscle compartments [59].

Testing can be performed incrementally or at a constant work rate. Incremental exercise testing involves a gradual increase in work load in a continuous or stepwise mode over time. Exercise is usually continued until volitional fatigue is reached, unless medical complications, such as angina, ECG ischaemic changes, uncontrolled blood hypertension (systolic blood pressure >250 mmHg, diastolic blood pressure >120 mmHg), marked oxygen desaturation (<80%), dizziness or mental confusion impose to terminate the challenge. Commonly, a test lasting 10–12 min is considered ideal, being long enough to provide useful
physiological information, yet not so long as to be burdensome for the patient [60]. Incremental testing provides information on maximal exercise performance and potential mechanisms limiting exercise capacity. A typical protocol for constant work rate testing is instead to start with a 1–3 min warm-up, followed by a workload brusquely increased to a high percentage (usually 75–80%) of that patient’s maximal work rate [61]. The constant work test is generally continued to a symptom-limited maximum, and is mainly used for monitoring disease evolution over time and determining responses to pharmacological and nonpharmacological therapeutic interventions [62].

Although CPET has been available for decades and provides extremely valuable and reliable physiological information on the integrated cardiopulmonary response to exercise in health and disease, its application in ILD has remained confined until recent years. Increasing evidence is emerging in the literature supporting the usefulness of CPET investigation in these patients.

In order to examine whether the relationship between inspiratory neural drive to the diaphragm and exertional dyspnoea intensity was different between ILD and chronic obstructive pulmonary disease (COPD), Faisal et al. [63] assessed diaphragmatic electromyography (EMGdi) and respiratory pressure measurements during incremental cycle exercise. The study population included ILD, COPD and healthy control subjects (n=16 for each group). In ILD and COPD patients, the oxygen uptake, work rate and ventilation at peak exercise were significantly lower than in healthy subjects. Moreover, EMGdi, respiratory effort and ventilation were higher, both at rest and during exercise, in ILD and COPD patients than in controls. However, each of these measurements was similar in the ILD and COPD groups. The authors concluded that disease-specific differences in mechanics and respiratory muscle activity did not influence the key association between dyspnoea intensity and inspiratory neural drive to the diaphragm. Although CPET has not yet proven to be diagnostic in ILD, reduced VO2peak and maximal achievable workload on incremental exercise testing represent disease hallmarks [17, 30]. Typical CPET findings in ILD include very elevated fR (often >55 breaths·min$^{-1}$), high VE with little or no breathing reserve, a failure to reduce VD/VT, oxygen desaturation and elevated ventilator equivalents for carbon dioxide (table 2). A recent observational study, aimed to describe the physiological profile and limiting factors during CPET among 34 IPF patients, showed reduced aerobic capacity (mean VO2peak 62% pred) associated with the presence of abnormalities in pulmonary gas exchange, desaturation, circulatory impairments, inefficient ventilation and skeletal muscle dysfunction [64].

In addition, CPET can be useful for monitoring changes in exercise capacity over time [65]. This requires an understanding of the magnitude of change that would be considered clinically significant (minimal important difference (MID)). MID refers to the smallest change that patients and clinicians would consider important enough to warrant a change in treatment plan [66]. To date, a MID for CPET has not been identified in patients with ILD; however, some data are available to guide assessment from changes in 6MWD [67–69]. Further work is sought to identify clinically relevant thresholds for changes in exercise capacity in people with ILD [70].

**TABLE 2** Common cardiopulmonary exercise test features at peak exercise in interstitial lung disease (ILD) patients compared to healthy subjects

| Feature                        | Healthy subjects | ILD patients | Cause                                                                 |
|-------------------------------|------------------|--------------|----------------------------------------------------------------------|
| Peak VO$_2$, L·min$^{-1}$     | ≥85%             | <85%         | Hypoxia, ventilatory limitation, deconditioning                      |
| Maximum work W                | ≥85%             | <85%         | Hypoxia, ventilatory limitation, deconditioning                      |
| Heart rate beats·min$^{-1}$   | ≥85%             | <85%         | Ventilator limitation to exercise, deconditioning                   |
| Oxygen saturation              | Preserved        | Reduced      | Increased V/Q mismatch, diffusion limitation, shunt, reduced mixed venous oxygen concentration | Respiratory muscle elastic loading, stimulation of peripheral mechanoreceptors |
| Respiratory frequency breaths·min$^{-1}$ | <50          | >50          | Respiratory muscle elastic loading, stimulation of peripheral mechanoreceptors |
| VT L                           | Increased        | Reduced      | Reduced lung compliance                                             |
| VE L·min$^{-1}$               | 50–80% of MVV   | >90% of MVV  | Ventilator limitation to exercise                                    |
| V0/Vt                         | Reduced          | Unchanged or increased | Increased V/Q mismatch, rapid, shallow breathing pattern |
| VE'/VCO$_2$ slope             | 25–35            | >35          | Increased V/Q mismatch                                              |
| Anaerobic threshold L·min$^{-1}$ | >45% peak VO$_2$ | <45% peak VO$_2$ | Hypoxia, pulmonary hypertension                                     |

Data are presented as n, unless otherwise stated. VO$_2$: oxygen uptake; VT: tidal volume; VE: minute ventilation; V0: dead space volume; VCO$_2$: carbon dioxide production; MVV: maximal voluntary ventilation; V/Q: ventilation/perfusion.
Furthermore, CPET has proved to be useful in distinguishing between ILD patients with and without pulmonary hypertension. In the retrospective study of Armstrong et al. [71], ILD patients with pulmonary hypertension demonstrated significantly lower end-tidal carbon dioxide tension \( P_{ETCO_2} \) and mixed expired carbon dioxide pressure \( (P_{ECO_2}) \) during exercise with a distinctive activity pattern for \( P_{ECO_2}/P_{ETCO_2} \). Degani-Costa et al. [72] aimed to determine the functional significance of abnormal pulmonary arterial pressure \( (PAP) \) responses to exercise in 27 ILD patients and 11 age-matched controls using invasive cardiopulmonary exercise testing. Mean \( (mPAP) \) was indexed to cardiac output \( (Q') \) during exercise, with a mPAP–Q’ slope \( \geq 3 \text{mmHg·L}^{-1} \) defined as an abnormal pulmonary vascular response. Peak oxygen consumption was significantly lower in patients with ILD and pulmonary vascular disease \( (PVD) \) compared to those without PVD and controls. Patients with ILD and PVD also showed increased \( V_d \) and \( V/E/V^{CO_2} \) at the anaerobic threshold.

Although exercise intolerance is a cardinal feature of ILD, few treatments have been shown to influence exercise capacity. Exercise outcomes have been measured in trials of both pharmacological and nonpharmacological interventions, but with inconsistent results. Two studies have assessed the acute effects of oxygen therapy in patients with a variety of ILDs [29, 36]. Compared to exercise on room air, high-flow oxygen substantially improved endurance time in both studies. The greatest gains were seen in patients who desaturated during exercise [29]. However, only one study found a significant effect of oxygen on \( V^{O_2}_{peak} \) and maximum work rate [36]. However, to date no study has examined the long-term effects of oxygen therapy on exercise capacity in patients with ILD and thus it is not known whether there are survival and quality-of-life benefits from oxygen therapy [73]. A number of randomised controlled trials have examined the effects of pharmaceutical treatments on exercise capacity in IPF. Small but nonsignificant changes in peak exercise capacity were found in a large placebo-controlled trial of N-acetylcysteine [74]. A large trial comparing pirfenidone to placebo did not find a difference in nadir oxygen saturation on a 6-min treadmill test after 6 months, despite improvements in vital capacity and a reduced rate of acute exacerbation in the treatment group [75].

An even more robust body of evidence shows that exercise tolerance represents a strong end-point to predict the prognosis of ILD patients [76]. In Fell et al.’s study [12], survival was retrospectively calculated from the date of the first CPET in 117 subjects with IPF. Patients with maximal oxygen uptake \(<8.3 \text{mL·kg}^{-1} \cdot \text{min}^{-1} \) had a significantly increased risk of death (hazard ratio 3.24) after adjusting for age, sex, smoking status, baseline FVC and \( DL_{CO} \). A prospective observational study evaluating 25 IPF patients, observed for a period of 9–64 months, showed that \( V^{O_2}_{peak} \) slope and \( V^{O_2}_{peak} \) rate per kg had the strongest correlation with survival [77]. Impairment in exercise capacity and abnormal ventilatory responses during CPET were confirmed to be associated with poorer survival in a study recently performed in 34 IPF subjects who were followed-up for 40 months [78]. A multicentre retrospective study to predict 3-year mortality was completed on 63 adult patients with IPF who underwent CPET with blood gas analysis [79]. 44 (70%) patients were alive without lung transplant at the end of the follow-up, while 19 patients (30%) were dead \((n=14)\) or transplanted \((n=5)\). Univariate analysis indicated that higher \( V^{O_2}_{peak} \) and \( V^{E/V^{CO_2}} \) at both anaerobic threshold and peak exercise, as well as higher \( \Delta P_{aO_2}/\Delta V^{O_2}_1 \) (mmHg·L\(^{-1} \)), \( V^{P-O_2} \), arterial oxygen tension \( (P_{aO_2}) \) and oxygen pulse at peak exercise were associated with a significantly lower survival at 3 years. The multivariate logistic regression analysis showed that \( V^{O_2}_{peak} \) <65% and \( V^{E/V^{CO_2}} \) at anaerobic threshold \( \geq 45 \) were independently associated with a lower survival at 3 years. A further sample of IPF patients was retrospectively studied by Misi et al. [80] who reported that the \( P_{aO_2} \) slope (reduction of \( P_{aO_2} \) observed during exercise testing) was the most sensitive predictor of survival rate. The authors found that \( V^{O_2}_1 \), oxygen pulse and \( V^{E/V^{CO_2}} \) at peak exercise were valid prognostic factors. The prognostic role of exercise-induced arterial hypoxaemia in ILD patients has also been assessed by Kong et al. [81] in a large study involving patients with usual interstitial pneumonia. Authors predicted survival through a combined scoring system where \( P_{aO_2} \) at peak exercise accounted for \( \sim 10\% \) of the maximum score. Elevated \( V^{E/V^{CO_2}} \) value \( (>45) \) was reported to be the only CPET parameter associated with increased systolic PAP, potentially representing a useful noninvasive marker for early detection of pulmonary vascular impairment, and therefore for a more accurate prognostic assessment in IPF patients [82].

**Exercise training and pulmonary rehabilitation in ILD**

In both healthy subjects and patients with chronic diseases, physical fitness and regular exercise have been shown to improve functional health and reduce mortality risk [83, 84]. Exercise may not only therefore represent a valuable tool for disease assessment and monitoring, but also an effective intervention for maintaining wellbeing and managing disease. Exercise training and rehabilitation programmes in patients with chronic respiratory disease have been reported to improve symptoms and exercise capacity, but the extent and duration of the effect in specific settings need to be fully clarified [85, 86]. Although the majority of data derive from studies performed in COPD subjects [87], in recent years, pulmonary rehabilitation programmes have been adopted for patients with ILDs and particularly in IPF [88, 89]. The introduction of
new drugs aimed to slow the progression of the disease in IPF patients will further increase the number of patients that, in the near future, will be suitable for and benefit from such programmes. Rehabilitation programmes in IPF patients have been shown to be safe and effective on exercise capacity, quality of life and dyspnoea [88, 90, 91]. An ongoing two-arm double-blind multicentre randomised placebo-controlled trial (HOPe-IPF study) to determine the effect of breathing a hyperoxic gas mixture with either a constant oxygen fraction of 60% or as-required oxygen up to 40% to maintain a saturation of ≥88% in 88 patients with IPF treated with nintedanib, along 8 weeks of aerobic cycle exercise training undertaken three times weekly [92]. Hopefully the trial will lead to a more comprehensive understanding of IPF exercise physiology, with the potential to change clinical practice by indicating the need for increased delivery of supplemental oxygen during pulmonary rehabilitation in patients with IPF. Guidelines currently recommend pulmonary rehabilitation for most IPF patients, although it is highlighted how programmes need to be tailored [93]. CPET therefore represents a crucial element for better selecting patients, designing personalised training and rehabilitation protocols and more accurate evaluating outcomes of response [85, 94, 95].

Conclusions
ILDs represent a heterogeneous group of pathologies which usually share a common pattern of clinical and functional abnormalities, independently of pathophysiological characteristics. In view of their poor prognosis, particularly in IPF, there is a need for early and accurate diagnosis and risk stratification. Dyspnoea is one of the most common and disabling symptoms in patients with ILD. This becomes even more evident during physical activity, negatively impacting patients' exercise capacity. Exercise testing represents an important tool for evaluating the degree of exertional dyspnoea and exercise intolerance in patients with ILD, providing additional information to data collected by diagnostic investigations performed at rest. Among available challenges, CPET represents the gold standard, since it provides useful information on underlying causes through a comprehensive evaluation of all the systems involved in the pathophysiological response to exercise. Although CPET application in ILD has remained confined until recent years, increasing evidence is emerging about its usefulness. CPET, although not diagnostic, has been proven to be greatly helpful in disease assessment, monitoring and mostly prognostic stratification. In addition, existing data prompt for a more diffuse use of CPET in the evaluation of response to pharmacological and nonpharmacological interventions, as well as in the design of personalised exercise training and pulmonary rehabilitation programmes.

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