Pulmonary function tests

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Systemic sclerosis-associated interstitial lung disease (SSc-ILD) is the leading cause of morbidity and mortality in SSc patients. In autopsy studies, up to 70% of the SSc patients show histological evidence of lung involvement. In surgical lung biopsies from SSc-ILD patients, a pattern of non-specific interstitial pneumonia is present in a majority, while usual interstitial pneumonia is found in a more variable proportion of patients. Up to 90% of the SSc patients have lung function abnormalities, especially with respect to gas transfer. Pulmonary function testing, therefore, is a major tool of investigation of lung involvement in SSc.

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Introduction

In general, pulmonary function testing (PFT) is employed to measure lung volumes, bronchial obstruction, gas exchange, lung compliance and ventilatory capacity. Interstitial lung diseases (ILDs) are characterized by reduced lung volumes (restrictive ventilatory impairment), reduced (static) lung compliance, reduced diffusion capacity [routinely measured as single-breath CO transfer factor (TLco)], and, as a consequence, hypoxaemia at rest or during exercise, whereas bronchial obstruction is typically absent in SSc-associated ILD (SSc-ILD) [1]. The pattern of lung function impairments does not allow a specific diagnosis to be made, but rather enables one to assess the presence or absence and the severity of lung involvement. The pattern and quantitative relationships of the impairments of lung volumes and diffusing capacity also allow some further extrapolations regarding coexisting diseases like pulmonary hypertension, chronic obstructive pulmonary disease (COPD) and emphysema [1, 2]. Serial lung function testing provides objective evidence of improvement or deterioration of lung involvement and is, therefore, of crucial importance for the management of SSc patients, providing a quantitative assessment of treatment effects.

Diagnostic tools in the lung function lab

The following gives an overview of different pulmonary function tests and the clinically relevant parameters in the context of ILD (summarized in Tables 1 and 2).

Spirometry

Spirometry is a simple test to measure static lung volumes at rest—slow (inspiratory or expiratory) vital capacity (sVC), forced vital capacity (FVC)—and dynamic volumes—forced expiratory volume in 1 s (FEV1), flow-volume loops. The technical equipment is simple and robust, but the correct performance of the breathing manoeuvres and full cooperation of the patient is crucial and special training of the investigator is warranted. Specific attention needs to be paid to the consistency of the machine and technician doing the test and these should be the same over time. Of note, a reduction of the vital capacity is not direct evidence of a restrictive ventilatory pattern, as VC may be reduced in COPD and emphysema, due to expansion of the residual volume, which is not measurable with spirometry. Differentiation of a true restrictive impairment from reduced FVC in favour of residual volume is possible if the FEV1/FVC ratio is <0.7, indicating bronchial obstruction, which usually accompanies COPD and emphysema, whereas reduced FVC with normal or even increased FEV1/FVC ratio is indicative of a restrictive defect as is found in ILD and pulmonary fibrosis. Flow-volume loops showing an early drop of expiratory flow also identify COPD. Thus, spirometry provides clinically relevant parameters of the functional status of the patient. Highly reproducible acquisitions of these lung function parameters are advantages of spirometry with the caveat noted above and are especially valuable in serial measurements.

Diffusing capacity of the lung

The diffusing capacity of the lung is routinely measured as the single-breath TLco. The principle of this measurement is based on two physically different gases: (i) CO (FiCO 0.2–0.4%), which rapidly diffuses from the alveolar air to the blood, where it binds to haemoglobin; and (ii) helium (FiHe 4–8%), which does not leave the alveolar space after inhalation. The results of this measurement are reported as TLco or diffusing capacity of the lung for CO (DLCO). The diffusion coefficient (Kco) is calculated from DLco by division by the volume ventilated (V1) and more specifically represents diffusion, since the transfer factor is clearly related to available lung surface represented by V1. Additionally, the residual volume can be calculated from helium dilution.

A new approach to differentiate alveolar and vascular/capillary pulmonary diseases is the combined measurement of DLco and DLno (diffusing capacity for nitric oxide). Preliminary data suggest that the DLno is less dependent on pulmonary blood flow than the DLco. Consequently, the DLno/DLco ratio is higher in pulmonary vascular disease as compared with diffuse lung parenchymal disease.
Additionally, the DLCO is modified by the haemoglobin and the DLCO compensated for the haemoglobin factor must be included in the reporting of the DLCO.

Like the lung volumes, the DLCO is highly machine and technician dependent and has the highest coefficient of variation of all the measurements.

Static lung compliance

Measurement of static lung compliance ($C_s$) necessitates the placement of an oesophageal balloon to report oesophageal pressure as a surrogate of pleural pressure ($P_{pl}$). Simultaneously, the lung volume changes are measured with $C_s$ being expressed as $\Delta V/\Delta P_{pl}$. The sensitivity of $C_s$ to detect SSC-ILD is, however, lower when compared with DLCO. There is no evidence to support added clinically useful information from $C_s$ that exceeds that of the combined use of spirometry/BPG and single-breath diffusing capacity. As measurement of $C_s$ is relatively time-consuming and involves some discomfort for the patients, it is not used for routine assessment of SSc patients in many pulmonary function laboratories.

Cardiopulmonary exercise testing

Cardiopulmonary exercise testing (CPET) is a very complex and demanding diagnostic procedure, which allows one to measure ventilatory, circulatory and gas exchange capabilities. There are also features that eventually allow one to differentiate between disorders of the pulmonary vasculature and parenchyma. Ventilatory equivalents for $\text{CO}_2$ and $\text{O}_2$, dead space ventilation and oxygen uptake are all parameters that give diagnostic guidance in this context. Peak oxygen uptake as well as systemic systolic blood pressure have been identified as potential prognostic markers in PAH [3]. This procedure is also capable of giving a measure of exercise capacity and muscular conditioning and, in the right hands, help separate cardiac from peripheral muscle disease or deconditioning. It is complex, expensive and highly technician dependent, not done reliably in many centres, if done at all.

Relevance and interpretation of PFTs

From the literature, the FVC and DLCO are the most important and most commonly used diagnostic markers in ILD. In the absence of bronchial obstruction or emphysema, and in reliable laboratories, FVC is a marker of restrictive ventilatory pattern, which is associated with fibrosis, whereas DLCO is an indicator of alveolitis, ventilation-perfusion mismatch, vascular involvement and fibrosis when examined relative to spirometry and lung volumes. Presently, static compliance is used only as an adjunct diagnostic tool to detect increased stiffness of the lungs, as a consequence of fibrosis and/or inflammation. CPET is useful in differentiating circulatory from respiratory exercise limitation and to assess exercise capacity ($W_{max}$, VO$_2$peak), which has been shown to be linked to survival. Technical and standardization problems limit the reproducibility and interpretation of CPET in clinical trials.

In general, the reproducibility of FVC is better than that of DLCO. In serial lung function measurements, therefore, changes of 10% in FVC and of 15% in DLCO are generally regarded as significant [4].

Lessons from idiopathic interstitial pneumonia

In idiopathic non-specific interstitial pneumonia (NSIP) and usual interstitial pneumonia (UIP), a decline of FVC by 10% from baseline during a period of 6 or 12 months has been shown to be predictive of increased mortality, whereas stability or an increase of FVC was associated with a favourable prognosis [5, 6]. Similarly, a decline of DLCO by ≥15% from baseline was linked to increased mortality in another study [7]. Interestingly, in these studies, longer term survival was not linked to the underlying histological pattern of disease (i.e. NSIP or UIP) but was solely dependent on the changes of lung physiology [6, 7]. Of note, these studies were performed prospectively and retrospectively and most of the patients (>80–90%) included in these evaluations were given anti-inflammatory therapy with prednisone and/or with a combination of prednisone plus a cytotoxic agent (i.e. cyclophosphamide or AZA) [5–7]. Consequently, these results do not reflect the untreated course of the disease. Moreover, comparable data specifically derived from SSC-ILD populations are not available yet.

Clinical relevance of lung function impairment in SSC-ILD

Up to 40% of SSc patients show at least a moderate restrictive pattern in spirometry (FVC 50–70% of predicted) and 15% have severe restriction (FVC <50% of predicted) without obstruction [8]. In several studies, the extent of restriction at diagnosis has been linked to disease progression and prognosis [8, 9]. In general, DLCO is more sensitive in detecting lung involvement when compared with FVC, but it is also less specific with respect to ILD as pulmonary vascular disease and coexisting fibrosis and/or COPD/emphysema may also lead to decreased DLCO. Moreover, a moderate, isolated reduction of DLCO (55–80% of predicted) may also indicate subclinical alveolitis, potentially associated with ground glass pattern on high-resolution computer tomography (HRCT) [2]. Finally, a reliable change in DLCO may occur very slowly and requires up to years to change [11, 13]. In this situation, disease progression and clinical symptoms are neither necessarily concomitant nor correlated. Consequently, isolated mild to moderate DLCO reduction does not warrant immediate treatment, but the patient should be evaluated for the presence of pulmonary hypertension and closely followed up. In addition, the combination of well-preserved lung volumes and very low DLCO (VC% predicted/DLCO% predicted >1.4–1.8) has been postulated to be indicative of the presence of pulmonary hypertension [2, 10].

Impact of serial lung function measurements in SSc-ILD

A majority of studies demonstrate that idiopathic NSIP and UIP show a more progressive course when compared with CTD and especially scleroderma-associated forms [11, 12]. However, there are also data indicating that long-term prognosis is relatively independent of the underlying histological disease pattern [13]. In serial measurements, declines of FVC and DLCO have had a
negative impact on prognosis [13]. Importantly, small changes of FVC and DLco within the first 6–12 months of observation may translate into major survival differences during long-term follow-up over 5 and 10 yrs. Although most of this knowledge is derived from studies in patients with idiopathic interstitial pneumonias, the similarities between idiopathic and SSc-associatedILD suggest that these general observations are probably also true for the SSc population, however, at a somewhat slower pace.

Recent placebo-controlled treatment trials involving anti-inflammatory therapy with cyclophosphamide and AZA have suggested that there is a modest but significant positive effect on the decline of FVC in SSc-ILD, which continues for up to another 6 months after cessation of a 1-yr treatment course and returns to the placebo level after a full year of treatment pause [14, 15]. Interestingly, patients with more progressed fibrosis had the biggest benefit from this therapy in the Scleroderma Lung Study [14]. Serial FVC measurements have allowed one to measure this small effect, which is potentially of clinical relevance, especially for the most severely impaired patients. The value of serial lung function measurement has been clearly evidenced in these trials.

Rheumatology key messages

- Lung involvement in SSc is frequent and leads to significant morbidity and mortality.
- Lung function assessment should be performed in every newly diagnosed patient with SSc and once yearly during follow-up in the absence of abnormal findings.
- Lung function assessment should include spirometry and single-breath diffusing capacity as a minimum; additionally, BPG and CPET significantly add to comprehensive functional characterization of the SSc patients.
- Serial PFTs, especially FVC and DLco, are helpful to follow up the course of the disease and to monitor treatment effects.

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