Assessment of lung involvement

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ABSTRACT
The aim of the subcommittee was to identify a core set of feasible variables reflecting the occurrence of interstitial and/or vascular lung disease. After extensive review of published studies and critical assessment of candidate variables, the subcommittee identified the minimal requirements to assess lung disease. Two core sets of variables are provided: the first concerns inter-stitial lung disease; the second pul-monary vascular disease.

Introduction

Pulmonary complications are the most common cause of death in systemic sclerosis (SSc) (1, 2). The two major features of lung involvement are inter-stitial lung disease (ILD) and pul-monary hypertension (PAH), the latter occurring as an isolated event or secondary to advanced ILD. The aim of our work was to identify and select clinical, laboratory and instrumental inve-stigations suitable to study lung invol-vement.

INTERSTITIAL LUNG DISEASE

The involvement of the lung intersti-tium in SSc (ILD) is characterized by early alveolar inflammation (alveolitis) evolving slowly or rapidly to pul-monary fibrosis.

Candidate variables

Clinical features

Symptoms and objective abnormalities occur at a relatively late stage in the course of ILD because the lungs have great reserve capacity.

Dyspnea. This symptom occurs in about 55% of patients (3). Dyspnea is usually first noted on exertion, and be-comes evident at rest only in advanced lung disease. Standardized assessment of dyspnea should be performed both in individual patient management and in clinical trials. Three methods of staging dyspnea are widely used: i) NYHA functional class; ii) the method of Mahler *et al.* (4), which includes two instruments, the baseline dyspnea in-dex and the transition dyspnea index; and iii) the Borg Dyspnea Score (5).

Cough. Cough is infrequently reported, usually non-productive (dry), and found in patients with moderately severe ILD. Cough has not yet achieved a satisfy-ing degree of reliability. It may be assessed in terms of severity, frequency and the production of phlegm using a standardized instrument developed by Petty *et al.* (6). Because of the non-fea-sibility of the measure, cough assess-ment was not chosen as a candidate variable.

Bilateral basal fine inspiratory crack-les. The presence of "velcro rales" is the most commonly reported physical finding. At present, however, no data are available regarding its validity and reliability.

Smoking history. The classification of patients as ever, previous and current smokers generally suffice in clinical in-vestigation in general. In a study pri-marily designed to analyse lung func-tion, the total intake of cigarettes, recorded as pack-years (1 pack-year = 1 pack of 20 cigarettes per day for 1 year), should be specified.

Laboratory investigations

Blood gas measurements may reveal a reduced PaO_2 with a normal $PaCO_2$. In more advanced cases, the $PaCO_2$ may be reduced because of the increase in ventilatory drive.

Serum collagen metabolites. Serum levels of PIIINP, reflecting collagen synthesis, were predictive of ILD as de-fined by high resolution computed tomography (HRCT) and pulmonary function tests (PFT) (7). PIIINP levels were significantly higher in patients with ILD (as assessed by PFT, i.e. forced vital capacity (FVC) < 80%) but were not increased in patients with ILD on chest radiograph (8). Cross-linked carboxyterminal telopeptide of colla-gen I (ICTP), a marker of collagen catabolism, and PIIINP correlated neg-atively with diffusing lung capacity for

CO (DLCO) (9). These markers are not valid measures since they could reflect fibroblast activation in sites other than the lungs (mainly the skin) and are not feasible since they are not routinely performed.

Soluble adhesion molecules. Previous studies have shown relationships between circulating levels of some adhesion molecules and pulmonary function (10, 11). Unfortunately there is poor specificity, as adhesion molecules may also reflect endothelial cell dysfunction and have been detected in a variety of inflammatory and neoplastic conditions.

KL-6 and surfactant proteins. KL-6 is a glycoprotein produced by alveolar type II epithelial cells. Fukaya *et al.* (12) found that serum KL-6 levels were significantly higher in patients with ILD, correlated positively with the extent of the pulmonary fibrosis (percentage of the area of pulmonary fibrosis on chest x-ray), and decreased after clinical improvement following treatment. In a study by Sato *et al.* (13), elevated KL-6 levels were associated with the presence of pulmonary fibrosis and correlated inversely with DLCO and FVC. K. Yamane *et al.* (14) found that serum KL-6 levels were significantly higher in patients with ILD compared to those without ILD and that DLCO and FVC were decreased in patients with elevated KL-6 levels.

Recently, other "lung specific" markers have been identified, e.g. the surfactant proteins A and D (SP-A and SP-D) which are produced and secreted by alveolar type II epithelial cells and Clara cells. Takahashi *et al.* (15) found that serum levels of SP-A and SP-D were significantly higher in patients with ILD as established by HRCT. SP-D sensitivity for ILD detected by HRCT was 77%, whereas SP-A sensitivity was 33%. Specificity of SP-A and SP-D for the CT-negative ILD group were 100% and 83% respectively. Asano *et al.* (16) detected higher levels of SP-D in SSc patients with ILD and those with elevated SP-D levels showed greater frequencies of reduced DLCO and FVC. In addition, SP-D levels were significantly correlated with KL-6 and both showed a similar sensitivity and specificity in the diagnosis of ILD (68% vs. 73% and 70% vs. 74%, respectively). The main advantage of KL-6, SP-A, and SP-D in comparison with the other above-mentioned markers is their specificity for the lung.

The cut-off value to distinguish normal from abnormal findings should be defined. We consider normal values of FVC, DLCO and DLCO/alveolar volume (VA) (expressed as percentages of the predicted value based on age, sex, height and ethnic origin) to be greater than 80% of the predicted values. PFTs abnormalities in SSc are related to the presence, in varying degree, of interstitial fibrosis, producing restriction and obliteration of pulmonary vascular bed increasing ventilation-perfusion inequalities. FVC has been used as the main para-meter of restrictive lung disease and DLCO as a marker of capillary surface area and pulmonary capillary blood volume. The typical picture of ILD is a restrictive pattern with a proportionate reduction in FVC and DLCO. Forced expiratory volume in the first second (FEV_1), residual volume, and total lung capacity may also be reduced. A low DLCO, without reduction of FVC, is the earliest and most sensitive pulmonary functional abnormality in SSc (17, 18). This finding may suggest pulmonary vascular disease and should be clarified. In most patients the DLCO/VA is also reduced but does not generally add to sensitivity. Moreover, the gas transfer reduction is not purely attributable to a loss of lung volume, but also reflects impaired capacity to exchange gas in the remaining lung.

In SSc, in contrast to other ILDs, there often exists an "intrinsic" pulmonary vascular disease which, by altering the effective pulmonary blood flow, may affect the measurements of gas transfer. Thus, DLCO impairment in SSc could be due to destruction of alveolar-capillary bed by interstitial fibrosis or, alternatively, pulmonary vascular disease. A markedly low DLCO, particularly when it occurs in the absence of substantially reduced lung volume, is considered attributable either directly or indirectly to pulmonary vascular disease.

Lung function should be made sequentially to assess disease progression. Recent data show that the period of most rapid decline in lung function is the first 4 years, and particularly the first 2 years, after disease onset (19).

FVC and DLCO measurements will usually suffice, and it is usually unnecessary to perform exercise tests which are difficult to standardise. Additional information may be obtained by determining the alveolar-capillary oxygen gradient but this requires simultaneous measurement of arterial blood gases. This can be routinely performed using arterialised capillary samples taken from the ear lobe. Peripheral arterial punctures are best avoided in SSc patients with significant digital arterial disease with Raynaud's phenomenon. A significant airway obstruction, although rarely, could occur. Therefore, the number of patients with an FEV1/ FVC ratio lower than 75% could be specified.

Chest radiography. Routine chest radiographs may show linear shadows and, in more advanced cases, a "honeycomb" reticular appearance. These changes occur particularly at the periphery of the lung and at the bases. This chest radiograph abnormality is included in the criteria for the classification of SSc. However, it is often normal early in the course of disease (20). Its main usefulness is for the exclusion of other etiologies of lung disease. High kV films may be more sensitive for detecting early interstitial changes in the lung fields.

Chest high resolution computed tomography (HRCT). HRCT is more sensitive than conventional chest radiography, and it may often be abnormal even when the plain chest radiograph is normal, making it the preferred modality for early diagnosis (22, 23). HRCT abnormalities have been demonstrated in about 90% of patients, a percentage similar to that found in autopsy studies (20). HRCT using 1 mm slices is a useful diagnostic tool for ILD, providing a non-invasive and inexpensive alternative to bronchoalveolar lavage (BAL) and open lung biopsy. Areas of "ground-glass" attenuation correlate with active cellular infiltration, whereas subpleural lines, parenchymal bands, and honey-

combing correspond to areas of irreversible fibrosis (23-27).

While a reticular pattern accurately predicted a fibrotic histology, a lower accuracy was found for a ground-glass pattern, which predicted at least equivalent amounts of fibrosis and cellularity (24). In subtle cases, it is important to perform both prone and supine scans to exclude the contribution of gravity, resulting in vascular and interstitial pooling in the dependent areas.

Recent data suggest that HRCT cannot reliably discriminate between nonspecific interstitial pneumonia (NSIP) and usual interstitial pneumonia (UIP) patterns of interstitial lung disease (28). The UIP pattern is associated with fibrosis. Some investigators prefer to make diagnosis of active alveolitis using BAL primarily (29).

In the setting of a clinical trial two additional main points should be addressed.

Exhaled nitric oxide. Higher exhaled NO levels were detected in patients with active BAL fluids and significantly correlated with BAL lymphocyte, but not with neutrophil, cell counts (30). A recent study showed that exhaled NO is elevated in SSc patients with no clinical or radiological evidence of ILD compared with healthy control subjects and patients with "idiopathic" ILD (31). This suggests the presence of subclinical inflammation, supported by BAL abnormalities in this group of patients. Exhaled NO may, therefore, be a sensitive marker of pulmonary inflammation in patients without overt ILD. Unfortunately, NO measurements are not readily available at this time.

Ventilation scintiscan with DTPA. This technique is intended to identify the integrity of the epithelial barrier (only in non-smoking subjects). In the early phase of lung involvement, DTPA scanning can identify those individuals who are more likely to progress to a more severe CT-stage of SSc-associated lung fibrosis (32, 33).

Bronchoalveolar lavage. BAL in SSc patients may demonstrate an increase in the total cell count by 3 to 6 fold and, in particular, an abnormal increase in neutrophils and/or eosinophils over 3%

and up to 20% in the differential cell count. An excess of lymphocytes may be also found. BAL, although invasive, may detect alveolitis in the early stage of SSc lung involvement (29,34,35). BAL is recommended in patients with dyspnea, declining lung volumes or DLCO, and HRCT scan evidence of ground glass changes.

Lung biopsy. Recent efforts to classify ILD, either idiopathic or associated with SSc, have shown that prognosis is associated with specific histologic patterns. Patients with NSIP have a better outcome than those with UIP (36). Therefore, thoracoscopic lung biopsy may help in assessing the therapeutic potential of treatments for interstitial lung disease in SSc, or for the overall prognosis in future studies. Sampling error limits the generalizability of biopsy.

PULMONARY HYPERTENSION

PAH is defined as an increase of arterial pressure in the pulmonary arterial circulation (mean pulmonary artery [PA] pressure >25 mmHg at rest or 30 mmHg with exercise) due to the involvement of the vessels and/or interstitium (37). In SSc, PAH occurs in 2 contexts: isolated PAH that is purely vascular in origin and PAH secondary to interstitial lung disease.

Candidate variables
Clinical features
Dyspnea. Dyspnea, especially on exertion, is the most common symptom. One-third of patients may be asymptomatic, particularly if they have musculoskeletal limitations which prevent them from being physically active. Typically dyspnea worsens rapidly over the course of several months. A modified NYHA dyspnea functional classification for PAH is available (37).
Physcial examination. Prominent wave of the jugular venous pulse, loud pulmonary component of second heart sound and right ventricular diastolic gallop are frequently reported in SSc patients with PAH (17). No data are available regarding their validity or reliability.

Laboratory investigations
Endothelial cells (EC) activation mark -

ers. A number of circulating molecules expressing activation/damage of EC (e.g. thrombomodulin, endothelin-1, etc) have been related to PAH (38, 39). However, these markers are not valid measures, since each could reflect EC activation in sites other than the pulmonary vasculature. Nor are they feasible measures, since they are not routinely performed.

ECG. Findings suggesting PAH on ECG include: right ventricular (RV) hypertrophy (right axis deviation, R/S >1 in V1), complete or incomplete right bundle branch block and right atrial enlargement (P pulmonale). The primary limitation of the ECG is its low sensitivity.

Chest radiography. Typical but insensitive findings are cardiomegaly (RV) and prominent pulmonary arteries.

Echocardiography with Doppler study. When the diagnosis of PHT is suspected a transthoracic echocardiogram should be performed. If measurement of RV systolic pressure can be estimated (i.e. in the presence of tricuspid regurgitation), Doppler study is the most accurate non-invasive measure of PA pressure with a sensitivity of 90% and a specificity of 75% compared with right heart catheterisation (40).

An important point of discussion is the definition of the cut-off value to distinguish normal from abnormal PA pressure. We consider an estimated systolic PA pressure lower than 30 mmHg as normal.

Pulmonary function tests. The most common abnormality suggestive of PAH is an isolated reduction of DLCO. Indeed, it has been associated with the development of PAH. Steen *et al.* (18) found that PAH was strongly associated with an initial DLCO < 55% and with a FVC/DLCO percent predicted ratio >1.4. However, an isolated DLCO reduction was found in 20% of the patients studied, many of whom had not at that time developed PHT. For the reasons discussed above FVC, DLCO, and DLCO/VA are included among the variables useful for the assessment of PAH.

Right heart catheterization (RHC). RHC is the gold standard measure in the assessment of PAH. Although an in-

Table I. (a) Core set of variables for the assessment of interstitial lung disease.

Variable	Notes
Dyspnea	NYHA functional class*
Pulmonary function tests (FVC, DLCO, DLCO/VA)	Abnormal if < 80% of the predicted value
Chest radiography	Bilateral basilar fibrosis (yes/no)

(b) Core set of variables for the assessment of pulmonary hypertension.

Variable	Notes
Dyspnea	NYHA functional class*
Pulmonary function tests (FVC, DLCO, DLCO/VA)	Isolated reduction of DLCO (FVC/DLCO ratio > 1.4)
Echocardiogram with Doppler study	Estimated systolic PAP abnormal if > 30 mmHg

* See Table III, Page S-25.

Table II. Further investigations for the assessment of interstitial lung disease.

Variable	Notes
High resolution computed tomography	Qualitative assessment (Normal/ground-glass/fibrosis) *or* Semi-quantitative assessment (Well's or Warrick scoring system)
Bronchoalveolar lavage	Total and differential cell counts
KL-6 and surfactant proteins	see text
Exhaled nitric oxide	see text
Thoracoscopic lung biopsy	Determination of the histologic pattern

Table III. Further investigations for the assessment of pulmonary hypertension.

Variable	Notes
ECG	Abnormal/normal (look at right axis deviation; R/S > 1 in V1; RV block; P pulmonale)
Chest radiography	Abnormal/normal (look at RV megaly and prominent pulmonary arteries)
Right heart catherterization	Gold standard for measuring PAP
Endothelial cell activation markers	see text

vasive procedure, it is important to document the degree of PAH and may have great utility in hemodynamic monitoring during therapeutic intervention.

Thus, RHC allows the following: (i) precise measurement of PA pressure, right atrial pressure, and cardiac output; (ii) measurement of pulmonary vascular resistance; and (iii) acute vasodilator testing, useful in identifying patients who may respond to long term oral vasodilator treatment. The invasiveness of the method limits its use in the cases in whom PHT is suspected and the pulmonary vasoreactivity should be deter-mined, or in clinical trials specifically addressing the effects on PHT.

Discussion

Identification of core set variables
Two core sets, containing the minimal required items to be ascertained in a setting of clinical investigation, were selected (Table Ia, Ib). Tables II and III list investigations which could help the clinical researcher for specific purposes.

Rationale for the selection of the variables
The variables selected allow the clini-cal investigator to assess the presence of interstitial vascular pulmonary disease in most SSc patients. A few patients will be missed, i.e. those who have not yet developed lung function abnormalities or do not present a clear chest radiograph, but already show some alterations on high resolution lung CT scan or BAL fluid analysis. However, such a low percentage is unlikely to affect the comparability of the studies. FVC, DLCO and DLCO/VA have been selected because of their reliability and feasibility. Chest radiograph is also widely available.

Rationale for the exclusion of other variables
Other variables have been excluded either because of their low sensibility (e.g. HRCT of the lung and BAL fluid analysis are not routinely carried out in many centres) or because of the lack of feasibility and lack of standardization (e.g. exhaled NO and serum KL6).
It must be stressed that the clinician in everyday clinical practice may need to base his therapeutic decisions on one or more of the excluded variables. Nevertheless, to improve comparability among studies none of these is mandatory. In particular, lung biopsy can detect NSIP or other variables of interstitial lung disease, but is quite invasive.

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