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**Title:** Pulmonary structure and function analysis in systemic sclerosis : clinical assessment of complicating interstitial lung disease and pulmonary vasculopathy  
**Issue Date:** 2015-12-15
Chapter 1

Introduction
Introduction to systemic sclerosis

Systemic sclerosis (SSc) is a systemic autoimmune disease that is characterised by endothelial dysfunction resulting in a small-vessel vasculopathy, fibroblast dysfunction with resultant excessive collagen production and fibrosis. The classification of SSc is based on the extent of skin involvement into diffuse cutaneous sclerosis (dcSSc) and limited cutaneous sclerosis (lcSSc) (1). Mortality in SSc is high; in a systematic review and a meta-analysis of the literature (2) including 2,691 SSc patients in 9 cohort studies, the pooled Standardized Mortality Ratio was (SMR) was 3.53. Among 732 deaths, heart involvement was the most frequent cause of death (29%), followed by lung involvement (2). In the EULAR Scleroderma Trials and Research group (EUSTAR) database (3), 55% of deaths were due to SSc, whereas 45% of deaths were thought to be unrelated to SSc. Of the SSc-related deaths, 26% were cardiac (predominantly heart failure and arrhythmias), whereas 29% of non-SSc related deaths were due to cardiac causes.

Pulmonary involvement in systemic sclerosis

While virtually any organ system may be involved in the disease process, fibrotic and vascular pulmonary manifestations of SSc, including interstitial lung disease (ILD) and pulmonary hypertension (PH), are the leading cause of death (4).

In SSc, the two most common types of direct pulmonary involvement are ILD and PH, which together account for 60% of SSc-related deaths (5). While certain pulmonary manifestations may occur more commonly in a subset of SSc (i.e. ILD is more common in dcSSc while PH is more common in lcSSc) (6), all of the known pulmonary manifestations reported have been described in each of the subsets of disease. In the following text, these two complications are further discussed.

Interstitial lung disease

Interstitial lung disease is very common in SSc. In early autopsy studies, up to 100% of patients were found to have parenchymal involvement (7;8). As many as 90% of patients will have interstitial abnormalities on high-resolution computed tomography (HRCT) (9;10) and 40–75% will have changes in pulmonary function tests (PFTs) (11-13). Parenchymal lung involvement often appears early after the diagnosis of SSc, with 25% of patients developing clinically significant lung disease within 3–5 years (11). Symptoms and complaints include dyspnea (at rest and at exertion), chest tightness and non-productive cough. Risk factors for
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its development include African–American ethnicity, skin score, hypothyroidism and cardiac involvement (14;15). Genetic factors, specific serological findings (anti-topoisomerase and anti-endothelial cell antibodies predict the presence of lung involvement) and the pattern of skin disease (patients with dcSSc have a higher incidence of interstitial disease) all contribute (16;17). Predictors of severe restrictive lung disease (defined by a forced vital capacity (FVC) less than 50% predicted) include African–American ethnicity (18), male sex, the degree of physiological abnormalities at diagnosis (FVC and diffusing capacity of the lung for carbon monoxide (DLCO)) and younger age (18;19).

Role of pulmonary function tests in ILD

Screening pulmonary physiology shows a reduction in FVC in 40–75% of patients, with 15% having a severe reduction (12;18;20). DLCO is reduced in almost all patients with other PFT abnormalities (21;22) and correlates with the extent of lung disease on HRCT(22). DLCO is lower in patients with UIP on biopsy (21) and, although FVC and DLCO are both identified as adverse prognostic markers (18;19), a declining DLCO is the single most significant marker of poor outcome (21).

Pulmonary hypertension

PH can occur in all forms of SSc and is associated with early mortality. First symptoms and complaints include dyspnea at exertion, palpitations and chest discomfort. Patients with SSc have the highest prevalence of PH among patients with a collagen vascular disease (CVD) (23). The updated clinical classification of PH divides patients into five groups based on the aetiology of their PH (24). SSc patients may fall into group 1 (isolated PAH, defined as a resting mean pulmonary artery pressure (mPAP) ≥25 mmHg with a pulmonary capillary wedge pressure ≤15 mmHg (25), group 2 (PH resulting from left ventricular involvement or diastolic dysfunction) and group 3 (PH resulting from ILD/hypoxaemia). Furthermore, patients can have combinations of these forms of PH. The prevalence of PH in SSc (SSc-PH) is variable and depends on the method of detection and the population studied. Using transthoracic Doppler echocardiography to screen SSc patients, the prevalence of PAH has been reported to range from 13% to 35% (26). However, when right heart catheterisation (RHC) is performed on “high-risk” SSc patients (defined as a combination of abnormal echocardiography findings, reduced DLCO in the absence of pulmonary fibrosis, a fall in DLCO and/or unexplained dyspnoea), a prevalence of 7–13% is found (27). PH can develop anytime during the course of SSc (28) and is more common in lcSSc when compared to
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diffuse disease (29). In the European League against Rheumatism (EULAR) Scleroderma Trials and Research database, a multinational open scleroderma cohort with over 3,000 patients, isolated PH was seen in 9.2% of lcSSc and 5.8% of dcSSc patients. Multiple risk factors have been identified including increased age at diagnosis (30), more severe Raynaud’s phenomena (31), the presence of digital tip ulcers (32), a diagnosis of lcSSc, decreased nailfold capillary density (33) and increased numbers of teleangiecitasias on examination (33). Specific autoantibodies, including the presence of anti-U3 ribonucleoprotein antibodies (34), anti-topoisomerase Ila antibodies and anti-centromere antibodies (35), appear to be associated with a higher risk of PH. The presence of anti-Scl70 antibodies is associated with progressive ILD and appears to be less associated with PH (31). Patients with SSc-PH are older, more severely ill and more likely to be female when compared to idiopathic PH (36).

Role of echocardiography in PH
Transthoracic echocardiography is the most widely used tool to screen for PH in SSc. The performance characteristics of echocardiography depend on the population evaluated and the cut-off used. Studies show that 55–86% of patients with an echocardiography suggestive of PH (right ventricular systolic pressure (RVSP) 30–40 mmHg or higher with or without symptoms) will have PH on RHC (37). Higher cut-off points for RVSP as well as other characteristics of increased pulmonary pressures, such as increased right atrial or right ventricular size, decreased right ventricular function, increases the specificity of echocardiography for the diagnosis of PH. False positive and false negative results regularly occur in patients with mild disease. False negative results have been reported in patients earlier in the course of disease (38).

Role of pulmonary function tests in PH
Reductions in DLCO are very common in SSc. In 19% of all SSc patients isolated reductions in DLCO were found (39), but only a minority developed PH. However, a moderate reduction (DLCO <55% predicted) in association with an FVC/DLCO ratio >1.4% (40) or a DLCO that is low or declining in the absence of parenchymal lung disease predicts the development of PH in SSc (31). Hachulla et al. (41) found that a DLCO <60% predicted in the absence of parenchymal lung disease was significantly associated with PH (OR 9.23, 95% CI 2.73–31.15). Steen and Medsger (31) found a significantly lower DLCO in patients with PH at an average of 4.5 years before the diagnosis of PH (52% versus 81%, p<0.001). In addition, they found that a declining DLCO over 15 years strongly predicts the development of PH.
Importance of management of SSc patients at risk for PH and ILD

The prevalence of PH in SSc exceeds 10% (8–13%), its presence increases morbidity and mortality. Since effective treatments are available (42), screening for PH is appropriate. However, despite echocardiography is currently widely used as a first screening tool, it lacks sufficient sensitivity and specificity in mildly increased pulmonary arterial pressures (43). Therefore, it cannot be used to screen for developing PH, which is now recognized of increasing importance in SSc (44).

As SSc patients who develop significant and progressive interstitial lung disease lung function tests and HRCT chest imaging should be considered. In patients with measurable disease, the extent of the abnormalities identified is important as patients with mild physiological or imaging abnormalities are likely to remain clinically stable. In contrast, those with more severe disease are at increased risk for disease progression (45).

Changes in FVC or DLCO should indicate HRCT chest imaging; evidence of disease progression should start a discussion regarding the treatment. Treatment of significant interstitial lung disease may include Cyclophosphamide (46), autologous stem cell transplantation (47) and/or Mycophenolate Mofetil (for maintenance therapy) in patients requiring treatment. A simple stratification scheme developed by Goh et al. (45) utilises HRCT extent of disease and lung function tests and provides discriminatory prognostic information. Surgical lung biopsy in these patients is not routinely necessary as the clinical course and outcome is similar between the major histopathological subsets in SSc-ILD (i.e. NSIP and UIP) (21). However, despite its feasibility, the Goh’ score remains qualitative and is subjective to limited reproducibility.

This thesis focuses on the early recognition of complicating pulmonary hypertension and interstitial lung disease. In addition, it studies the relation between structure and function using different imaging and lung function techniques. By doing so, an improved characterisation of the individual SSc patient may be achieved facilitating personalized care.

Cardiopulmonary exercise testing in the evaluation of pulmonary arterial hypertension in systemic sclerosis

Dyspnea on exertion, fatigue and reduced exercise tolerance are common symptoms in patients with systemic sclerosis. PH may develop in the course of the disease resulting from developing pulmonary vasculopathy (PV). PV impairs dilatation of pulmonary blood
vessels in rest and during exercise, giving rise to impaired blood flow. The impedance of the respiratory system is thereby affected and results from primarily the reduced compliance of the pulmonary vasculature (48). Pulmonary arterial hypertension related to SSc (PAH-SSc) is associated with high morbidity and mortality as well as poorer response to therapy and worse outcomes compared with the idiopathic form of PAH (iPAH) (49). After three years of follow-up, less than 50% of PAH-SSc patients were still alive versus 83% of iPAH patients.

There is a need to identify variables that predict disease progression early in the course of PAH-SSc. These variables must be associated with clinical outcomes and responsive to therapeutic intervention (50). Among these new variables, exercise pulmonary hemodynamics may promise major determinants of heart failure in PAH-SSc. Exercise stress in PAH-SSc as well as in patients with developing PV tests the ability of the diseased heart to increase its output and the pulmonary vasculature to respond to an increased blood flow. Failure of these adaptations will result in impaired stroke volume increase or even decrease (51). During exercise, the increase in mean pulmonary artery pressure (mPAP) in relation to oxygen uptake (V'O₂) may show either a “takeoff” or “plateau” pattern.

Patients with severe exercise induced PAH (EIPAH) and resting PAH will show a “plateau” physiology. In these patients mPAP will increase as well as the pulmonary vascular resistance (PVR) during exercise until the cardiac output is compromised and starts to fall. Eventually, with a decline in cardiac output as a result of right ventricular dysfunction, mPAP will not further increase or even fall resulting in a compensatory tachycardia. In contrast, patients with mild to moderate EIPAH showed a “take-off” physiology, suggesting pulmonary vasoconstriction during incremental exercise. In these patients, mPAP further increases in which the cardiac output does not decrease. Therefore, it seems plausible that patients with PAH of varying duration and severity will exhibit different mPAP responses to exercise (51).

Several studies have been performed to assess the occurrence and or presence of EIPAH in SSc (43;44;48;52). Combination of echocardiography and cardiopulmonary exercise testing (CPET) in these patients revealed an elevated systolic pulmonary artery pressure (SPAP) during right-sided heart catheterization and a low peak oxygen uptake. By discriminating patients during CPET using peak oxygen uptake (peak V'O₂), low oxygen pulse (V'O₂/HR), a low oxygen uptake to work rate ratio (ΔV'O₂/ΔWR) and an elevated ventilatory equivalent for CO₂ (V'E/V'CO₂) pulmonary vasculopathy could be distinguish from left ventricular disease and a normal response (48). Interestingly, several patients showed a marked decrease in their oxygen uptake to heart rate increase ratio (ΔV'O₂/ΔHR) resulting in a breakpoint
(48). Furthermore, peak oxygen uptake was significantly lower than in patients not showing this response. This breakpoint represents a change in cardiovascular response to exercise by an abrupt increase in heart rate since cardiac output cannot effectively increase by stroke volume alone. This indicates that the rise in HR is disproportionally faster than V’O₂ as work rate increases and may be related to increasing pulmonary arterial pressures. However, whether this breakpoint analysis relates to impaired aerobic capacity or impaired stroke volumes i.e. pulmonary arterial pressures is not known.

The aim of chapter 2 is to analyse the V’O₂/HR slope breakpoint method in the detection of pulmonary vasculopathy by using an automated breakpoint detection algorithm. Furthermore, the relation between this novel analysis of V’O₂/HR slopes, pulmonary arterial pressures and peak oxygen uptake in SSc is discussed.

**Novel assessment of myocardial involvement in systemic sclerosis**

Myocardial involvement in SSc may include pericarditis, microvascular coronary artery disease, conduction abnormalities and in particular, impaired myocardial contractility or relaxation of right or left ventricle with or without heart failure (53). Myocardial dysfunction is presumably caused by myocardial fibrosis and inflammation giving rise to microangiopathy, vasospasms and poor vasodilator reserve (54). In a post-mortem study, myocardial fibrosis was detected in up to 70% of patients with SSc (54). Early diagnosis of myocardial involvement therefore plays an important role in the management of these patients.

Conventional echocardiographic assessment of left (LV) and right ventricular (RV) function is based on the LV ejection fraction (LVEF) and tricuspid annular plain systolic excursion (TAPSE) (55). However, these measurements have shown limited sensitivity for assessment of myocardial abnormalities in patients with SSc (53). Tissue Doppler imaging (TDI) assesses myocardial tissue velocities and is able to provide information on longitudinal function at the mitral valve annular level (56). Results of initial studies using tissue Doppler imaging suggested that myocardial velocity and deformation (strain) might be more sensitive than conventional measures in identifying subtle cardiac dysfunction in asymptomatic patients with SSc (57-59). Furthermore, myocardial analysis by TDI is significantly limited by angle dependency and does not allow for the evaluation of all LV segments and of different directions of myocardial deformation.
Recently, 2-dimensional speckle-tracking strain analysis has been proposed as a sensitive, non-invasive and accurate method for the evaluation of subclinical myocardial dysfunction (60). It provides measures of LV regional and global strain in three orthogonal directions (longitudinal, circumferential and radial).

The aim of chapter 3 is to assess LV dysfunction and its relation with functional capacity using this novel technique in patients with SSc and controls. Chapter 4 focuses on RV free wall strain and its association with pulmonary fibrosis and elevated pulmonary arterial pressures in patients with SSc and controls.

**Dyspnea assessment and control of breathing in systemic sclerosis**

Humans can sense a wide range of respiratory sensations such as respiratory motion, lung position, irritation, urge to cough, chest tightness and sense of effort. Among these respiratory sensations, specific aspects such as chest tightness and sense of effort are the most important contributors to the sensation of dyspnea (61). In systemic sclerosis, complicating interstitial lung disease and pulmonary hypertension may result into dyspnea (46). In SSc, an increased impedance of the respiratory system is recognized as the most frequent cause of dyspnea (62). The impedance of the respiratory system is influenced by the lung and chest wall compliance and the respiratory flow resistance (62). In progressive SSc, reduced chest wall and lung compliance may result from limited chest wall excursions and a thickened thoracic skin (63;64). Lung volumes and gas transfer studies are related to disease severity in systemic sclerosis (46). However, whether the magnitude of dyspnea relates to these function tests is not known.

To assess the respiratory drive as a function of the impedance of the respiratory system, resting ventilation (V’E) can be evaluated. However, ventilation, is an imperfect output parameter since it is affected by alterations in the impedance of the respiratory system (62). Mouth occlusion pressures (MOP) provide an excellent reproducibility and reported normal values are independent of age and sex (62). In a study of normal subjects and patients with ILD, MOP were able to distinguish between these groups (65). Furthermore, in combination with CO$_2$ rebreathing, the respiratory drive to hypercapnia provides insight into the central chemoreflex (66). These determinants of the respiratory drive may assess the dyspnea sensation more precisely than lung volumes and gas transfer studies do.
Dyspnea in SSc may also arise from an altered control of breathing (67). Specifically, an inappropriate response upon the chemoreflex drive at rest and during exercise to carbon dioxide (CO₂) may influence their control of breathing (68). The peripheral chemoreflex plays an important role in the control of breathing and therefore in the sensation of dyspnea (69). It not only ensures oxygen homeostasis, but also helps maintain CO₂ levels at rest and during exercise (68). The carotid bodies, the site of the peripheral chemoreflex to oxygen, CO₂ and pH, contain a complex microvascular anatomy in a macrovascular environment. Systemic sclerosis related inflammatory and fibrotic responses may cause a diminished peripheral chemoreflex response (70). This response may result into an increased susceptibility to exercise intolerance and consequently reported dyspnea during exercise (71).

The aim of chapter 5 was to evaluate the respiratory drive at rest and during CO₂ rebreathing by mouth occlusion pressures (MOP) and their correlation with reported dyspnea. Furthermore, the aim of chapter 6 was to assess the peripheral chemoreflex drive at rest and during exercise in healthy subjects and SSc patients.

**Quantitative analysis of interstitial lung disease in systemic sclerosis**

Clinical risk assessment of organ manifestations in systemic sclerosis (SSc) has revealed that interstitial lung disease (ILD) is present in 53% of cases with diffuse cutaneous SSc (dcSSC) and in 35% of cases with limited cutaneous SSc (lcSSC) (72). The most common pathological finding in lung biopsies of ILD in patients with SSc is nonspecific interstitial pneumonia (NSIP), although usual interstitial pneumonitis (UIP) is also occasionally found (73). However, discrimination between NSIP or UIP pathology does not improve outcome (21). Hence, the discrimination between these subtypes of ILD is limited to computed tomography (CT) scanning.

Currently, chest high-resolution computed tomography (HRCT) is the most reliable means of detecting SSc-ILD (74;75). The chest radiograph, although a valuable initial screening tool, is notoriously insensitive in the detection of SSc-ILD (76). The HRCT profile in SSc-ILD is typical of that seen in idiopathic NSIP and most commonly consists of a variable mixture of ground-glass attenuation and reticulation, without honeycomb change. However, in a minority of patients, honeycomb change is more prominent and is likely to be indicative of a histological pattern of UIP (74). Although the relative proportions of ground-glass attenuation, reticulation, and honeycombing have been quantified in several clinical studies,
this exercise does not, in general, provide clinically useful information. The exception to this rule is the occasional patient with prominent ground-glass attenuation which, in the absence of traction bronchiectasis, identifies a high likelihood of reversible inflammatory disease.

Both the severity and the extent of ILD are usually estimated by semi-quantitative scoring of a limited number of cross-sectional slices through the lungs (77;78). Clear survival discrimination was demonstrated by an easy to perform staging algorithm in combination with pulmonary function test data (45). However, despite this benefit visual scoring has limited reproducibility because of its subjective nature. In contrast, formal quantification of the extent of disease on HRCT is currently widely used in clinical studies but is insufficient for routine clinical evaluation due to its complexity and its performance with a lack of volume correction (74;79;80).

HRCT data provide a means to quantitatively analyze the structure of the whole lung, since inflammation, ground glass opacities, and fibrosis can be quantified by lung densitometry. Therefore, objective quantitative techniques by CT densitometry may provide a more sensitive measurement, similar to what has been proven in assessing progression of pulmonary emphysema by the percentile density method (81). Since these quantitative techniques are automated, it is feasible to quantify the entire lungs instead of only a limited number of slices, with a smaller chance of missing pathological changes.

Previously, Camiciotolli et al. (79) reported that lung density histogram parameters are more reproducible than visual assessment of HRCT and are more closely related to functional, exercise, and quality-of-life impairment in SSc. In their evaluation of each patient, they calculated the average global density of the lung and included kurtosis and skewness of the density histogram of the whole lung. However, this analysis did not provide a single overall score for the structure of the lungs, and lung density values were not corrected for lung volume. In a recent report, the same investigators clearly demonstrated the need for volume correction of density parameters (80). Volume-corrected lung density parameters calculated by specific software may be useful outcome measures in evaluating the progression of ILD and the response to treatment.

The aim of chapter 7 focuses is to identify the optimal percentile density threshold by using novel quantitative CT densitometry. In addition, we compared the change in percentile density score over time with changes in FVC and DLCO.
References


