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Chapter 9

Summary
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This thesis describes the clinical assessment of complicating interstitial lung disease (ILD) and pulmonary vasculopathy (PV) in patients with systemic sclerosis (SSc). In chapter 2, 3 and 4 exercise test derived and echocardiographic parameters for the presence of ILD and/or PV are described. In chapter 5 and 6 patient-reported dyspnea and exercise intolerance are studied and in chapter 7 lung densitometry is performed to assess the lung function-structure relationship in SSc.

Systemic sclerosis 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). While virtually any organ system may be involved in the disease process, fibrotic and vascular pulmonary manifestations of SSc, including ILD and pulmonary hypertension (PH), are the leading cause of death. Better ascertainment of lung and cardiac involvement is of particular interest, since treatment allocation has been traditionally based on the extent and type of its involvement.

In chapter 2 the oxygen pulse slope (VO$_2$/HR) is studied in patients with SSc during cardiopulmonary exercise testing (CPET). The oxygen pulse normalizes oxygen consumption for heart rate and is widely used as an indirect measurement of cardiac stroke volume (SV). In our experience, SSc patients may show an abnormal VO$_2$/HR slope containing a breakpoint despite normal pulmonary pressures measured at rest using Doppler echocardiography (DE). We hypothesized that a compromised pulmonary vasculature may lead to an increase in pulmonary pressures and an decreased oxygen uptake. The resulting heart rate increase as a function of the oxygen uptake (VO$_2$/HR) may therefore show a breakpoint in the slope reflecting a disproportional heart rate increase. In two SSc patient populations (Graz, Austria and Leiden, the Netherlands) VO$_2$/HR slopes were analysed for breakpoints. In the Austrian SSc population simultaneous right heart catheterisation was performed allowing direct comparison between heart rate and pulmonary pressure increase as a function of oxygen uptake during exercise. In the Austrian CPETS a breakpoint in the V'O$_2$/mPAP preceded the breakpoint in the V'O$_2$/HR slope. In the Leiden CPETs peak oxygen uptake was significantly lower CPETs containing a V'O$_2$/HR breakpoint. Furthermore, several pathologic V'O$_2$/HR slopes were observed despite normal resting pulmonary pressures measured by DE. Whether these patients will develop pulmonary hypertension at rest is an interesting focus for further research.
Chapter 3 and 4 describe the use of a new available echocardiographic tool to assess the myocardial velocity and deformation (strain) by tissue Doppler imaging. This two-dimensional speckle-tracking strain analysis has been proposed for the evaluation of left ventricular (LV) regional and global strain in 3 orthogonal directions (longitudinal, circumferential and radial). Right ventricular (RV) function was assessed by speckle-tracking derived RV free wall strain. The relation between LV systolic dysfunction as measured by this technique and functional capacity (peak oxygen uptake during CPET) as well as ventricular arrhythmias was evaluated in chapter 3. Each strain was independently associated with peak oxygen uptake. Furthermore each strain was associated with abnormal Holter electrocardiography results. In chapter 4 the potential role of pulmonary fibrosis and pulmonary hypertension (PHT) in the development of RV dysfunction was evaluated. Compared to controls SSc patients without pulmonary fibrosis and PHT had an impaired RV free wall strain. Both pulmonary fibrosis and PHT were independently associated with impaired RV free wall strain and therefore RV dysfunction. The findings of both LV and RV strain analysis in SSc should be explored in larger prospective studies to assess the prognostic value of these measures.

In chapter 5 and 6 frequently reported problems by SSc patients are described: dyspnea and exercise intolerance. Dyspnea may arise in SSc by complicating interstitial lung disease and/or pulmonary hypertension. An increased respiratory impedance, which is influenced by the lung and chest wall compliance as well as respiratory flow resistance, is recognized as the most frequent cause of dyspnea. To assess dyspnea in SSc, mouth occlusion pressures as an index of central respiratory output (i.e. the respiratory drive), were measured in chapter 5. In addition, they were obtained during CO₂ rebreathing and related to pulmonary function tests. Normal values of mouth occlusion pressures (V’E/P0.1>8 l/min/cm H₂O) are independent of age and sex. Furthermore, the technique has a high reproducibility within each subject. In SSc patients an abnormal V’E/P0.1 response provided a better correlation with severity of dyspnea than traditional lung function parameters. Furthermore, in these patients, ∆P0.1/∆PetCO₂, as an index of the central chemoreceptor response to hypercapnia, was significantly higher than in SSc patients with normal mouth occlusion pressure responses. Since it sharply demarcates a normal from a high (i.e. abnormal) impedance of the respiratory system, mouth occlusion pressures (V’E/P0.1) can be easily assess as a first diagnostic test in the outpatient clinic. In chapter 6 the peripheral chemoreflex drive is studied in SSc in relation to patient-reported exercise intolerance. The peripheral chemoreflex drive plays an important role in the control of breathing at rest and during exercise. Activation of this
drive has been implicated in the ventilatory compensation for metabolic acidosis during exercise. This activation is reflected by an sharp increase in the ventilator equivalent for CO₂ at the end of the isocapnic buffer phase and decrease in end-tidal pCO₂. In addition to an exercise test, the peripheral chemoreflex drive is assessed by the difference between the euoxic and hyperoxic ventilatory response to hypercapnia (eVHR-hVHR). Since SSc is primarily a microvascular disorder, SSc-related inflammatory and fibrotic responses in the carotid body may cause a diminished peripheral chemoreflex. In all SSc patients, respiratory compensation for metabolic acidosis occurred. However, eVHR-hVHR differed significantly between limited cutaneous and diffuse cutaneous patients, suggesting an altered control of breathing in these patients. This may help the clinician to better understand reported exercise intolerance and exertional dyspnea in diffuse cutaneous SSc patients.

In chapter 7 lung structure and lung function relationship is studied by lung densitometry and pulmonary function tests. Data from a high-relation CT scan of the thorax (HRCT) 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 than visual scoring as currently is done by the radiologist. In SSc, we evaluated the optimal percentile density score in SSc by quantitative CT densitometry, against pulmonary function. Lung volumes and the n° percentile density (between 1 and 99%) of the entire lungs were calculated from CT histograms. The n° percentile density is defined as the threshold value of densities expressed in Hounsfield units. A prerequisite for an optimal percentage was its correlation with baseline DLCO% predicted. Regression analysis for the relation between DLCO% predicted and the n° percentile density was optimal at 85% (Perc85). There was significant agreement between Perc85 and DLCO % predicted and FVC % predicted. Of interest, two patients showed a marked change in Perc85 over a two year period, but the localisation of change differed clearly. We conclude that we identified Perc85 as optimal lung density parameter, which correlated significantly with DLCO and FVC, confirming a lung parenchymal structure-function relation in SSc. This provides support for future studies to determine whether structural changes do precede lung function decline.