Echocardiographic assessment of cardiac and pulmonary manifestations in patients with systemic sclerosis

Summary of Ph.D. Thesis

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INTRODUCTION

Systemic sclerosis (SSc) is a connective tissue disorder characterized by widespread vascular lesions that culminate in systemic fibrosis.

The clinical manifestations and the prognosis of SSc vary with the majority of patients having skin thickening and variable involvement of internal organs. Organ manifestations of SSc can be particularly problematic when they are present in the lungs, kidneys or heart. Among the rheumatic diseases, SSc carries the highest case-based mortality.

The cardiac manifestation of systemic sclerosis is particularly problematic in the clinical practice. In the majority of patients, cardiac manifestations are subclinical. Cardiac involvement can develop very early in the course of the disease, even years before becoming clinically evident. The development of overt myocardial manifestations are recognized as powerful adverse prognostic factors. When clinically evident, these features are often associated with increased mortality. All cardiac structures may be involved, potentially leading to heart failure. Primary myocardial involvement, without systemic or pulmonary hypertension and without significant renal or pulmonary involvement, implicates different pathophysiological mechanisms, including the

characteristic vascular lesions and fibrosis deposition, which may impair coronary microcirculation and myocardial function.

Pulmonary involvement is a prominent feature of the SSc and occurs more frequently in SSc than in any other connective tissue diseases. The most frequent types of lung involvement are interstitial lung disease and pulmonary artery hypertension.

Systemic sclerosis-related pulmonary hypertension is the result of an isolated pulmonary arteriopathy, but in these patients, elevated pulmonary pressure may occur also as a consequence of interstitial lung disease or left ventricular systolic and/or diastolic dysfunction. Pulmonary hypertension is a severe vascular complication of the SSc, and it has a dramatic impact on the clinical course and overall survival of the patients. It is the single most common cause of death in patients affected by this syndrome. The poor outcome of pulmonary hypertension in SSc may be partially explained by disease-related co-morbidities but also by delayed establishment of the diagnosis. Signs and symptoms of SSc related pulmonary hypertension are generally aspecific and thus often underestimated. The establishment of the diagnosis is frequently delayed till the advanced phases of the pathological process, characterized by structural and not reversible damage to the pulmonary vasculature. Therefore, efforts to promote an early recognition of pulmonary hypertension have been expended in the past few years.

METHODS

From May 2007 to January 2010, 220 consecutive patients affected with SSc were admitted to the Department of Rheumatology. In the substudy regarding myocardial involvement 42 age and gender-matched control subjects were selected.

1. Study of cardiac manifestation

   All patients underwent comprehensive two-dimensional transthoracic echocardiography examination. Beside the conventional diastolic parameters such as pulsatile Doppler and tissue Doppler methods, two-dimensional speckle tracking echocardiography was also used. The tracking settings allow us to distinguish three left atrial strain values. If the reference point is set at the onset of the QRS, we can measure positive peak atrial longitudinal strain ($\varepsilon_{pos\ peak}$), which corresponds to the left atrial reservoir function. If the reference point is set at the onset of the P wave, we can measure both negative atrial longitudinal strain ($\varepsilon_{neg\ peak}$), which mirrors the left atrial pump function and a second, positive peak atrial strain (sec $\varepsilon_{pos\ peak}$), which corresponds to left atrial conduit function.

2. Exercise stress echo

   Exercise stress echo was conducted by using a graded semisupine bicycle ergometer. Echocardiography monitoring was performed

throughout the exercise stress test. Tricuspid Doppler tracing and right ventricular outflow tract time-velocity integral were estimated at peak exercise, while the patient was still pedaling. Immediately after that, while the patient was stopping pedaling, left ventricular outflow track time-velocity integral and measurements of left ventricular and right ventricular functions were performed because pulmonary artery systolic pressure and cardiac output return rapidly back to normal after exercise, although less relevant for cardiac output. A cut-off value of pulmonary artery systolic pressure ≥50 mmHg at peak exercise was considered to be a significant exercise-induced increase in pulmonary pressure. A cut-off value of peak pulmonary vascular resistance ≥3.0 Wood Units was considered to be a significant increase in pulmonary vascular resistance.

3. Follow up study of the exercise echocardiography group

   In the subgroup of SSc patients with normal resting pulmonary artery systolic pressure (<40 mmHg), who had developed exercise-induced pulmonary artery systolic pressure increase at a previous graded bicycle semi-supine exercise Doppler echocardiography, underwent the same examination after 21 ± 12 months. Patients discovered with a resting pulmonary artery systolic pressure > 40 mmHg did not perform the exercise.

PRIMARY GOALS OF THE THESIS

1. To assess whether two dimensional speckle tracking echocardiography parameters may detect early alterations in left atrial function in SSc patients.
2. To evaluate the clinical and echocardiographic determinants of exercise-induced increase in pulmonary artery systolic pressure in a large population of patients with SSc.
3. To evaluate whether increase in exercise-induced pulmonary artery systolic pressure may predict increase in resting pulmonary artery systolic pressure in a population of SSc patients.

RESULTS

1. SSc patients did not show significantly different left atrial indexed volumes (Group 1 = 24.9 ± 5.3 ml/m^2 vs. Group 2 = 24.7 ±4.4 ml/m^2, p = .8), but showed significantly different left ventricular diastolic and left atrial longitudinal strain parameters. E/e' ratio was higher in SSc patients (Group 1 = 7.6±2.4 vs. Group 2 = 6.5±1.7, p < .05) and $\varepsilon_{\text{pos peak}}$ and sec $\varepsilon_{\text{pos peak}}$ were significantly decreased (Group 1 = 31.3 ± 4.2% vs. Group 2 = 35.0 ± 7.6%, p < .01 and Group 1 = 18.4 ± 4 % vs. Group 2 = 21.4 ± 7.6%, p < .05). Interestingly, we found significant correlation between $\varepsilon_{\text{pos peak}}$ and age, but only in the control group (R = -.59, p < .001) and not in SSc patients (R = -.09, p = .57).
2. Among the 164 patients who underwent exercise Doppler echocardiography study, 69 (42%) patients showed a pulmonary artery systolic pressure of ≥50 mmHg at peak exercise. Univariate analysis showed that age, presence of interstitial lung disease, values of resting pulmonary artery systolic pressure, and both right and left diastolic dysfunctions were predictors of pulmonary artery systolic pressure elevation over ≥50 mmHg. According to observation, peak pulmonary artery systolic pressure was higher in patients older than 50 years (52 ± 14 mmHg vs. 43 ± 8 mmHg, p< .001), with left ventricular E/e′ >8 (59 ± 17 mmHg vs. 48 ± 13 mmHg, p< .01), with right ventricular E′/A′ <0.8 (52 ± 11 mmHg

vs. 44 ± 9 mmHg, p< .001), and with interstitial lung disease (54 ± 14 mmHg vs. 48 ± 12 mmHg, p< .05). In a subgroup of 89 patients, noninvasive hemodynamic parameters also measured (pulmonary vascular resistance cardiac output). Peak pulmonary vascular resistance ≥3 Wood Unit was present in 11% of patients with peak pulmonary artery systolic pressure of ≥50 mmHg, which represents about 5% of the total population. Univariate analysis showed that none of the parameter predictors of peak pulmonary artery systolic pressure ≥50 mmHg were predictors of pulmonary vascular resistance ≥3 Wood Unit.

3. Mean follow-up time between the two exercise Doppler echocardiography study was 21 ± 12 months, during which two deaths occurred. Seven patients (19%) developed an increase in resting pulmonary artery systolic pressure, which may suggest that the previous abnormal response to exercise in these patients predicted subclinical pulmonary hypertension. Twenty-four patients (65%) showed the same behavior as previous to the examination, 2 patients (7%) died and 4 patients (11%) did not confirm the exercise-induced pulmonary artery systolic pressure increase.

NEW OBSERVATIONS

1. Two dimensional speckle-tracking echocardiography is a sensitive tool to assess impairment of left atrial mechanics, which is detectable in absence of changes in left atrial size and volume and may represent an early sign of cardiac involvement in patients with SSc.
2. Exercise-induced increase in pulmonary artery systolic pressure occurs in almost one-half of patients with SSc with normal resting pulmonary artery systolic pressure. Peak exercise pulmonary artery systolic pressure is affected by age, interstitial lung disease, and right and left ventricular diastolic dysfunction and, only in 5% of the patients, it is associated with an increase in pulmonary vascular resistance during exercise, suggesting heterogeneity of the mechanisms underlying exercise-induced pulmonary hypertension in SSc.
3. Exercise Doppler echocardiography study is a feasible test to track serial changes over time in pulmonary artery systolic pressure in patients at high risk of developing pulmonary hypertension. An increase in exercise-induced pulmonary artery systolic pressure is frequently associated with poor outcome or the development of an increase in overt resting pulmonary artery systolic pressure.

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