DIAGNOSIS AND MECHANISMS OF CARDIAC INVOLVEMENT IN PATIENTS WITH SYSTEMIC SCLEROSIS

Ph. D. thesis

by

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1 Introduction

Systemic sclerosis (SSc) is characterized by fibrosis and vascular abnormalities of skin and internal organs. Cardiac involvement in SSc includes coronary artery disease (CAD), pulmonary arterial hypertension (PAH) related right ventricular changes and microvascular disease (MVD). The clinical presentation of these conditions is often atypical, making their distinction difficult. Recent epidemiological studies suggest that besides pulmonary involvement cardiovascular disease produces the highest mortality in SSc, as cardiovascular deaths are consistently reported to be responsible for 20-30% of all premature deaths. Myocardial involvement in SSc (SScMI) has been hypothesized to be provoked by ischemia; however, the underlying mechanism is not fully elucidated. The potential mechanisms include macrovascular and microvascular damages. Arteriolar vasospasm that is analogous to Raynaud phenomenon (RP) may lead to reversible attacks of ischemia in response to cold provocation. Alterations of the microvasculature may play a crucial role in the development of SScMI. Observations suggest that coronary flow reserve (CFR) is reduced in SSc despite the lack of atherosclerotic CAD. Recent studies confirmed this finding among SSc patients; however, mechanisms leading to the restriction of adaptive capacity are still not clear. Short-term beneficial effect of vasodilator treatment in terms of better myocardial perfusion and improvement in contractility also supports the concept that reversible ischemia plays a possible role in SScMI and these agents have recently been found to be protective against left ventricular dysfunction. Despite the promising data, it is unclear which mechanisms lead to restriction of the CFR, and thus how the pharmacotherapy may target these.

The right heart catheterization is a widely accepted method to confirm the presence of PAH. The coexistence of coronary artery disease and microvascular abnormalities in symptomatic patients has not been previously investigated.

2 Aims

Our goal was to design and execute a prospective screening program for SSc patients that included classical, non invasive screening investigations as well as invasive methods for characterization of cardiopulmonary circulatory parameters among high risk cases. We aimed

- to estimate the prevalence of pulmonary hypertension, atherosclerotic coronary artery disease and microvascular dysfunction among SSc patients

- to characterise the proportion and distribution of these alterations behind the overlapping symptoms

- to investigate the mechanisms of the microvascular impairment by means of analyzing the myocardial resistance of SSc patients compared to patients with angina pectoris having mild coronary artery disease

3 Cross-sectional study of SSc patient for elucidation of the prevalence of cardiopulmonary involvement

3.1 Patients and methods

A total of 120 consecutive SSc cases were enrolled in the study. SSc was diagnosed by standard criteria and the patients were asked to provide informed consent before the entry. Each patient underwent a baseline physical examination; electrocardiogram, echocardiography and a 6-min walk test were also performed. Cardiac catheterisation was initiated in the presence of abnormalities suggestive of PAH (''suspected PAH'' group) or suggestive of CAD (''suspected CAD'' group). Right heart catheterisation (RHC) and coronary angiography, supplemented with thermodilution coronary flow reserve (CFR) assessment, were performed at the same time.

3.1.1 Coronary angiography

Angiograms were recorded digitally. Coronary lesions were assessed by quantitative angiography (QCA). The SYNTAX score was used to describe the extent of the CAD. The target artery was instrumented with an intracoronary pressure wire. After baseline measurements of aortic pressure (Pa), distal coronary pressure (Pd) and mean transit time of a room temperature 3 ml bolus of saline, measurements were performed in triplicate in the presence of maximal hyperemia induced by intracoronary papaverine (12 mg bolus). Fractional flow reserve (FFR) was calculated as Pd/Pa ratio during hyperemia. CFR was calculated from the ratio of the mean transit times in hyperaemia and at rest. MVD was defined as reduced flow reserve (CFR<2) in the absence of significant stenosis (FFR>0.75). Coronary flow velocity was assessed by the ''Thrombolysis in Myocardial Infarction (TIMI) frame count''.

3.2 Results

Of the 120 cases, 2 patients were excluded due to severe pulmonary fibrosis. Cardiac catheterisation was performed in 30 cases. In all, 20 patients were included in the ''suspected PAH'', and 10 cases in the ''suspected CAD'' group. Among the 120 patients with SSc, the prevalence of PAH was 11.6% (14/120), while the prevalence of verified CAD and of severe CFR reduction were 12.5% (15/120) and 8.3% (10/120), respectively. Normal coronary vessels and pulmonary pressure, as well as preserved CFR, were found in eight cases. There was a considerable overlap among these groups. In all, 12 patients in the ''suspected PAH'' group and 2 in the ''suspected CAD'' group had PAH. Coronary angiography was positive in 9 cases in the ''suspected PAH'' group. Severely reduced CFR was found in seven cases in the ''suspected PAH'' and in three patients in the ''suspected CAD'' group (fig 1).
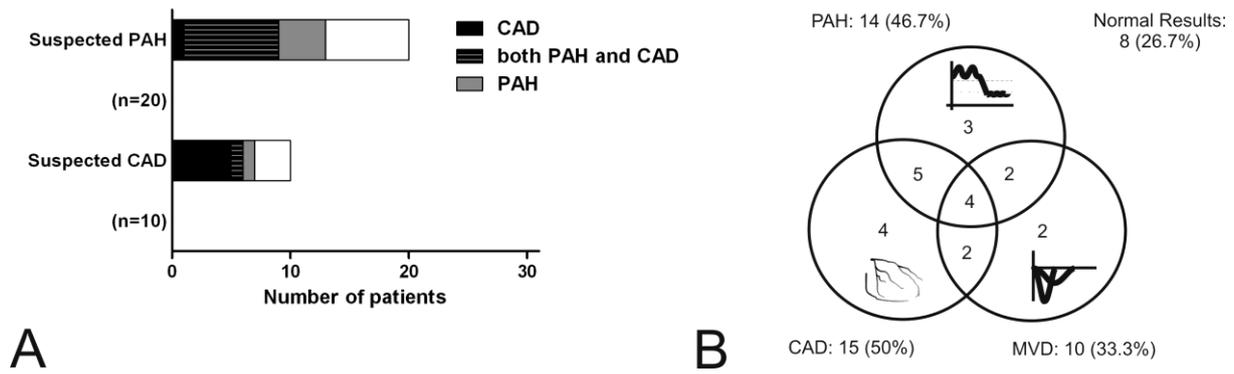
Figure 1: Catheterization findings in 30 systemic sclerosis patients. Panel A shows the frequency of coronary artery disease (CAD) and pulmonary hypertension as indications for catheterization. Panel B illustrates the considerable overlap found between abnormalities of the pulmonary circulation and the coronary micro- and macrovasculature. Abbreviations: PAH: pulmonary arterial hypertension, CAD: coronary artery disease, MVD: microvascular disease

Significant correlation was found between the coronary flow velocity and flow reserve values, indicating better CFR in patients with slower resting flow ($p<0.01$, $r2=0.24$). Of the 15 patients with coronary lesions detected by morphological and functional assessment, 8 underwent revascularisation (1 bypass grafting, 7 percutaneous coronary stent implantations). These procedures resulted in improvement in the patients' physical activity (Figure 2).
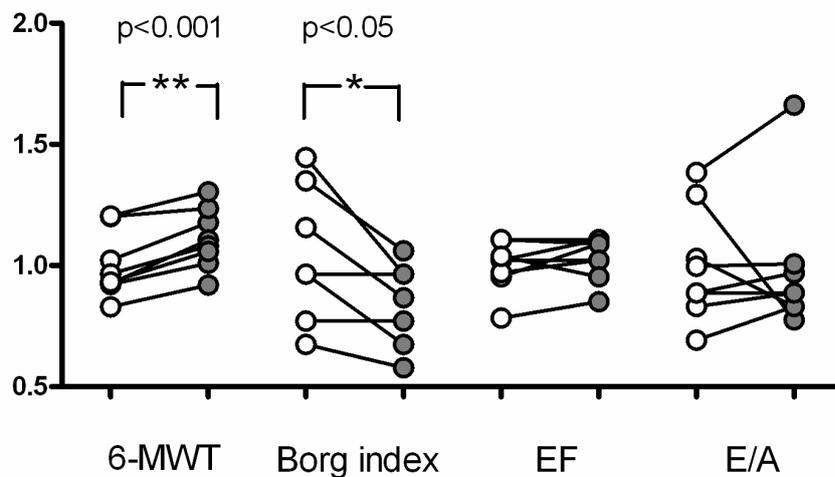
Figure 2: Effect of coronary revascularization on physical competence and echocardiographic parameters. Dots represent percentage relative to initial mean values. Open circles show baseline state, while grey circles refer to 30-day evaluation after coronary intervention. Revascularization improved walking distance in 6-minute walk test (6-MWT, p<0.001) and decreased Borg dyspnoea index in 8 SSc patients (p<0.05). Ejection fraction (EF) and E/A values representing systolic and diastolic left ventricular function did not show significant difference between time points.

3.3 Conclusion

PAH, CAD and reduced CFR all show a considerable overlap in symptomatic patients with SSc. The current non-invasive investigations are neither sensitive nor specific enough to make an appropriate distinction between these different disease manifestations. A more invasive approach, such as coronary angiography at the initial catheterization, is required to properly characterize and treat the different forms of cardiac involvement in SSc.

4 Investigation of coronary microcirculatory parameters and mechanisms of coronary microvascular dysfunction in SSc

4.1 Patients and methods

Diffuse and limited subset of SSc cases were diagnosed by the commonly used criteria. The methods applied during the study have been explained in details in chapter 3.1. and 3.1.1. Duration of Raynaud's phenomenon (RP) at the time of the study entry was evaluated by clinical interview, while duration of SSc was determined from the time of the onset of the first SSc-related non-Raynaud symptom. Cardiac catheterization was initiated in the presence of abnormalities, which were suggestive of pulmonary arterial hypertension (PAH) or of coronary artery disease. Coronary angiographic findings and coronary flow reserve data of the first ten consecutive patients were included in our previous publication. Subsequent seven SSc patients were enrolled according to the same protocol for investigation of the myocardial resistance levels. The Ca-antagonist therapy was stopped for more than twenty four hours before cardiac catheterization. Right heart catheterization (RHC) and coronary angiography, supplemented with thermodilution CFR assessment were performed at the same time. Intracoronary pressure-wire measurements of 17 patients with intermediate coronary lesions were used as control.

4.1.1 Coronary angiography

The coronary arteriography was performed as described in chapter 3.1.3. IMR was calculated as a product of mean transit time and Pd, in hyperemia and at rest. (Figure 3)

$$(A.) \quad FFR = \frac{Pd_{hyp}}{Pa_{hyp}} \qquad (B.) \quad CFR = \frac{Tm_{bas}}{Tm_{hyp}}$$

$$(C.) \quad IMR_{bas} = Tm_{bas} \times Pd_{bas}$$
$$IMR_{hyp} = Tm_{hyp} \times Pd_{hyp}$$

Figure 3: Calculation of hemodynamic parameters. During the pressure-wire measurements aortic pressure at the coronary orifice (Pa), distal coronary pressure at the tip of the wire (Pd) and mean transit time of 3 ml room temperature saline (Tm) were measured at basal conditions and during hyperemia (subscript 'bas' and 'hyp', respectively) A: Fractional flow reserve (FFR) was calculated as a Pd/Pa ratio during hyperemia. B: coronary flow reserve (CFR) was calculated from the ratio of the mean transit times in hyperemia and at rest. C: Index of myocardial resistance (IMR) was calculated as a product of mean transit time and Pd, in hyperemia and at rest.

4.2 Results

Demographics, cardiovascular treatment and echocardiographic characteristics of the included patients are showed non-significant differences.

The control group was matched for gender and age. Cardiovascular risk profile was similar except for the more frequent diabetes in control group. All SSc patients but none of the controls reported the presence of Raynaud's phenomenon (RP). Regarding therapy, the patients in the control group used significantly less calcium channel blockers, pentoxyphylline, cyclophosphamide and corticosteroids. Baseline hemodynamic data were similar between the two groups. The severity of coronary atherosclerosis as expressed by the QCA and SYNTAX scores did not differ significantly (P=0.830, and P=0.821, respectively). The SSc patient group and the control group were similar with regard to TFC, FFR and CFR (P=0.604, P=0.651 and P=0.117, respectively).

The IMR_{bas} was not significantly higher in the SSc group (P=0.207), and in response to maximal vasodilatation there was no significant difference between SSc patients and controls (P=0.731) (Fig.4).
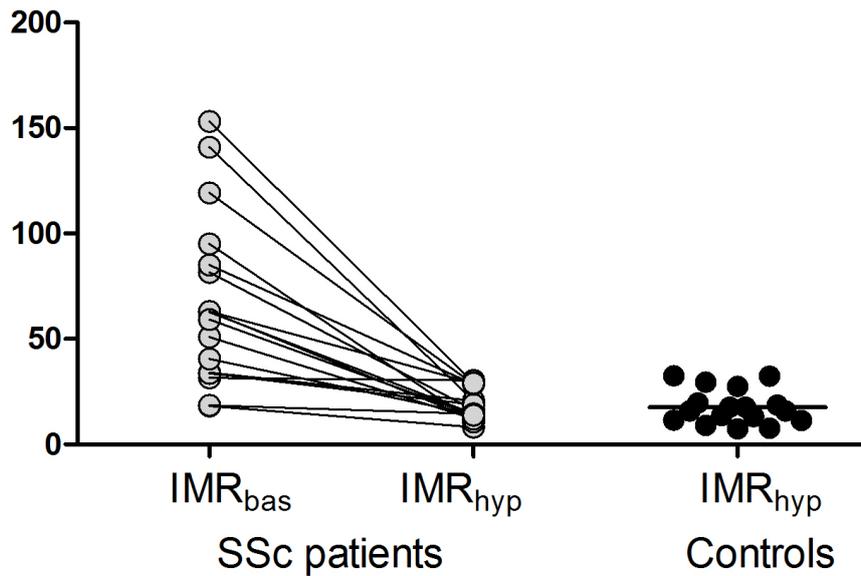
Figure 4: In systemic sclerosis (SSc) patients the myocardial resistance at maximal vasodilatation (IMR_{hyp}) was not significantly different from controls (p=0.99). The difference of the magnitude of the response to vasodilatation (i.e. the coronary flow reserve) is dominated by the differences in the resting resistance (IMR_{bas}) i.e. in the vascular tone.

CFR values lower than 2 were detected in six SSc patients. These patients had higher basal coronary flow velocities than SSc patients with normal CFR (10.63 ± 5.1 vs. 27.53 ± 14.8 p<0.05) (Figure 5).
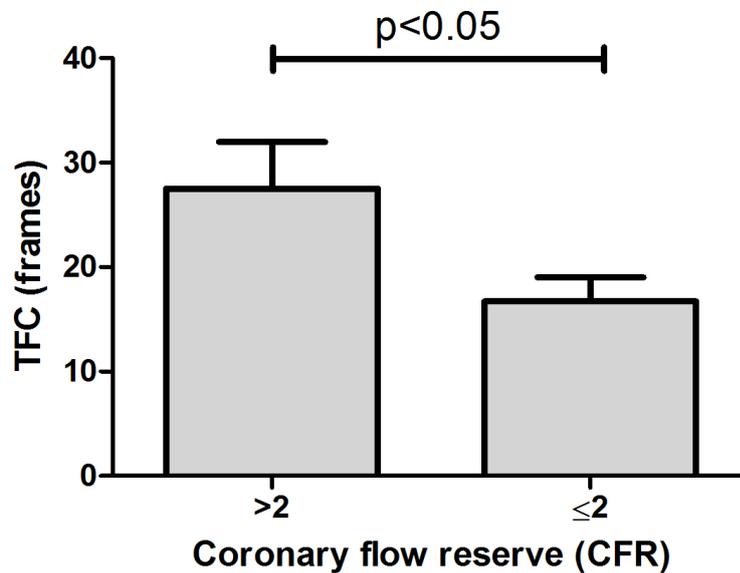

Figure 5: TIMI frame count (TFC) of SSc patients with normal CFR were significantly higher, than in SSc patients with decreased CFR, which indicate accelerated coronary flow among patients with restricted coronary reserve.

We found a trend for lower IMR_{bas} values in these patients (43.8±23.6 vs. 80.7±42.5, P=0.07). IMR_{hyp} differed significantly neither from the SSc patients with normal CFR nor from the control group (21.68±6.61, 17.23±7.83 and 17.80±8.17, respectively, P=0.292 and P=0.308). The IMR_{bas} correlated to the coronary flow velocity (R=0.56, p<0.05) (Figure 6).
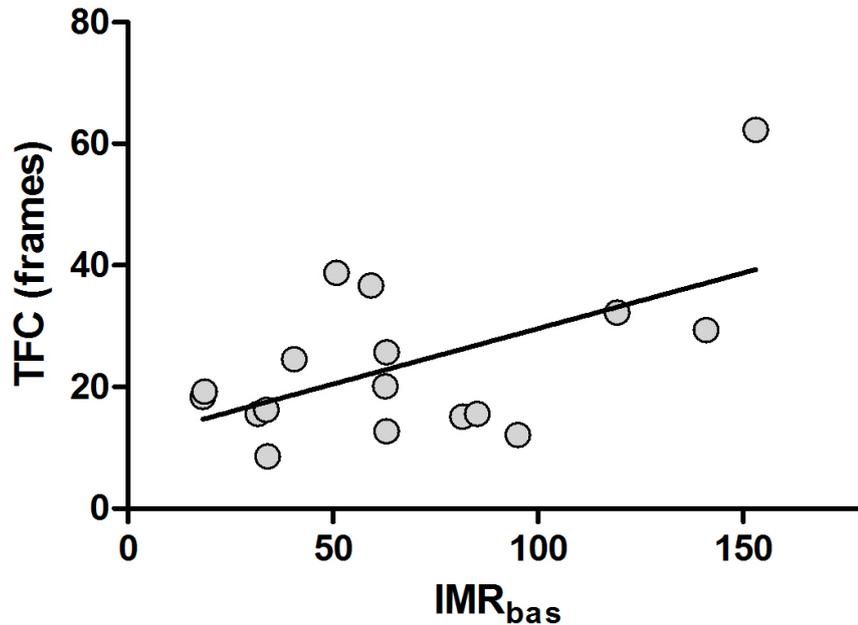
Figure 6: The baseline myocardial resistance shows significant linear correlation with the coronary flow velocity – assessed by the TFC. ($R_{Pearson}$=0.56, p<0.02)

There was no significant difference between limited cutan (lcSSc) and diffuse form (dSSc) of SSc as regards CFR, IMR_{bas} and IMR_{hyp} results. Clinical complaints showed neither relation to these parameters (data not shown). Mean transit time values during the baseline conditions in SSc patients were 0.75±0.39, 0.72±0.50, and 0.67±0.41 sec, in the controls 0.56±0.37, 0.55±0.36, 0.51±0.41 sec in baseline and 0.27±0.11, 0.27±0.14, 0.22±0.10 versus 0.25±0.14, 0.22±0.12, and 0.23±0.12 sec in hyperemia. No trend for deceleration was found (Figure 7).
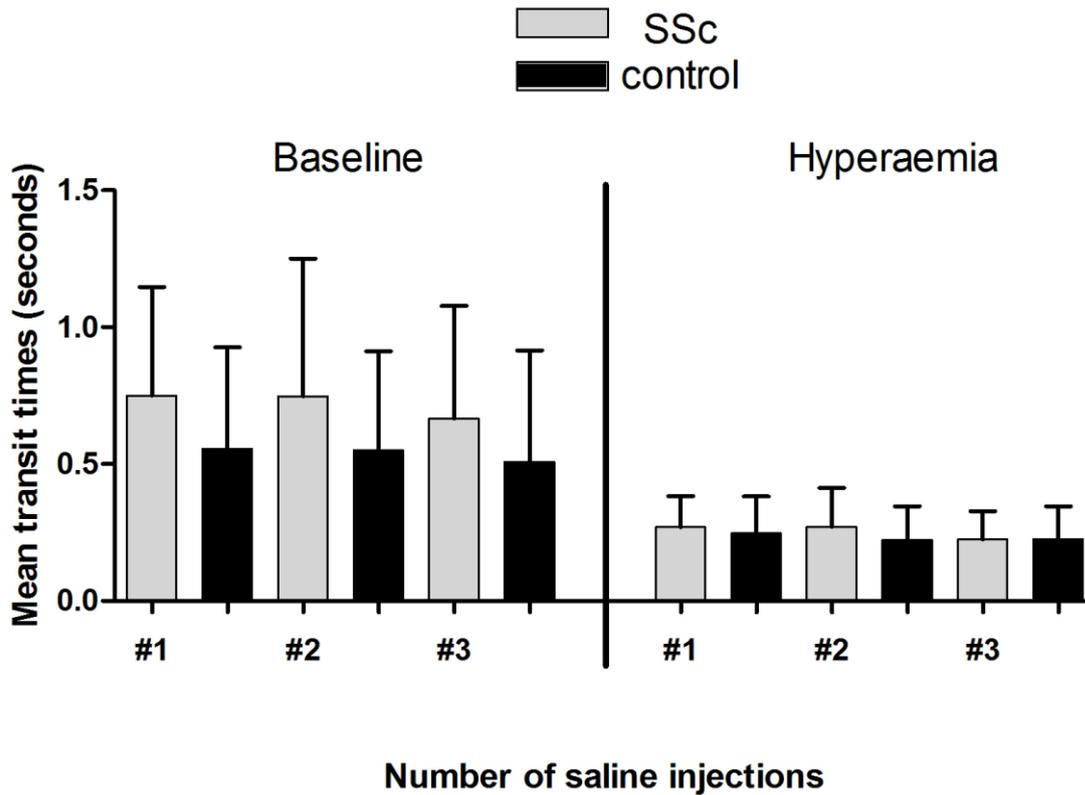
Figure 7: Mean transit time values in baseline and in hyperemia. After injection of room-temperature saline we observed longer transit times among SSc patients, however, this difference was not significant. In response to the repeated injections, lack of deceleration of the coronary artery flow suggests the absence of coronary Raynaud's phenomenon.

4.3 Conclusion

The lack of decrease in the maximal vasodilatation response indicates that there is no irreversible functional damage at the level of the coronary arterioles in SSc. In patients with reduced CFR, the decreased basal IMR and higher velocity reflect compensatory vasodilatory mechanisms probably triggered by ischemic signals deriving from abnormal myocardial microcirculation. The injection of room temperature saline into the coronaries did not provoke angina or spasm and we did not find any increase of the transit times, the hemodynamic changes caused by low temperature in the heart are not probable.

5 Novel findings of the thesis

Our studies demonstrated that coronary artery disease may mimic, and can appear in combination with PAH in patients with SSc. Patients with SSc with reduced physical capacity and exertional dyspnoea showed a considerable overlap between PAH and CAD. We found that among patients who showed signs of PAH by non-invasive investigations, the prevalence of CAD and PAH was comparable.

We found that, coronary revascularisation successfully eases symptoms and improves physical capacity. Therefore, screening for the presence of coronary artery disease by invasive methods seems to be indicated in symptomatic cases of SSc.

In our cohort coronary flow velocity showed inverse relation to the CFR, indicating that coronary flow deceleration is reversible in patients with SSc.

The index of myocardium resistance in hyperemia (IMR_{hyp}) is not increased in SSc patients compared to controls having no significant epicardial coronary artery stenosis suggesting that there is no irreversible damage at the level of the coronary arterioles in SSc.

In SSc patients with reduced CFR we demonstrated the decrease of the basal IMR, which suggests together with accelerated flow velocity the presence of a compensatory mechanism to maintain myocardial perfusion at rest already.

6 Acknowledgement