Blunted coronary flow reserve in systemic sclerosis

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Objectives. We investigated whether the non-invasive determination of coronary flow reserve (CFR), as evaluated by transthoracic Doppler echocardiography, might be a potential method to detect early dysfunction of cardiovascular system in patients affected by systemic sclerosis (SSc) without clinical signs or symptoms of cardiac impairment. The possible correlations between the CFR values and the duration of the disease, specific autoantibodies and cutaneous involvement subsets were investigated.

Methods. Forty-four consecutive patients affected by SSc were analysed. The CFR was detected in the distal left anterior descending coronary artery by contrast-enhanced transthoracic second harmonic Doppler in all SSc patients and in 16 healthy controls. CFR was assessed at rest and during hyperaemia induced by administration of adenosine at 0.14 mg/kg min over 5 min. The CFR was calculated as the ratio between hyperaemic (peak adenosine infusion) and resting peak diastolic velocity (PdvCFR) and resting velocity time integral (VtiCFR). Past medical history was carefully investigated.

Results. Both PdvCFR and VtiCFR were significantly reduced in SSc patients when compared with controls (P < 0.0001). In particular, both PdvCFR and VtiCFR were significantly lower in patients with dSSc when compared with patients affected by ISSc (P < 0.02 and P < 0.04 respectively). No statistically significant correlation was found between CFR values and history of smoking, serum levels of cholesterol or triglycerides, blood pressure, age of patients, duration of SSc and serum autoantibody positivity for ANA, ACA and Scl70.

Conclusions. CFR is often reduced in SSc patients. CFR was lower in patients with dSSc than in those affected by ISSc. A reduced CFR value should be considered an indirect sign of heart involvement in scleroderma, but its clinical and prognostic implications need to be clarified.

Key words: Systemic sclerosis, Coronary flow reserve, Heart disease, Doppler echocardiography.

Systemic sclerosis (SSc) is a clinically heterogeneous and generalized disease that affects the connective tissue of the skin and internal organs, such as the gastrointestinal tract, lungs, kidneys and heart. SSc is characterized by disturbances of the immune system, alterations of the microvasculature, and massive deposition of collagen and other extracellular matrix proteins in the connective tissues [1–3]. SSc-related mortality might be associated with cardiovascular impairment and in particular with heart failure. Although the main cause of death is related to the cardiopulmonary or renal involvement, cardiac damage is often present but is rarely of clinical significance [4]. Chest pain and dyspnoea are related mainly to the involvement of other organs, such as the oesophagus or the lung. In addition, myocardial fibrosis may be due to other concomitant diseases (such as diabetes and hypertension) and it may be difficult to establish the specificity of cardiac involvement as restricted to SSc itself [1].

Clinically manifested symptoms of heart involvement have been described in 20–25% of SSc patients, although autopsy studies have revealed alterations such as myocardial fibrosis and pericardial effusion in 30–80% of patients [5]. Moreover, conduction system disturbances, arrhythmias, hypokinetin alterations of the left ventricle, signs of infarction and non-specific ST- and T-wave changes have been described recurrently [6–11].

The impaired relaxation of the left ventricle is a recently reported feature of scleroderma heart disease [12]. The diastolic dysfunction, which might depend on myocardial fibrosis and/or myocardial ischaemia, has been described in association with a defective cardiac functional reserve, the clinical and prognostic significance of which remains to be clarified [13].

SSc patients often show angiographically normal epicardial coronary arteries and normal left ventricular function, despite decreased coronary flow and resistance reserve [14, 15]. Therefore, we investigated whether the non-invasive determination of coronary flow reserve (CFR), as evaluated by transthoracic Doppler echocardiography, might represent a potential method of detecting early dysfunction of the cardiovascular system in patients without clinical signs or symptoms of cardiac impairment. Furthermore, the possible correlations between the CFR values and the duration of the disease, specific serum autoantibodies and cutaneous involvement subsets were investigated in all the patients.

Patients and methods

Patients

Forty-four consecutive patients, who complained of no signs or symptoms of cardiac disease, [three males, 41 females, mean age 54 ± 14 (S.D.) yr affected by SSc according to the American College Rheumatology criteria [16, 17], were recruited from our Service for the Diagnosis and Treatment of Connective Tissue Diseases during

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a period of 6 months. Patients complained of no serious diseases other than SSc. Exclusion criteria included cardiac involvement.

The presence of limited cutaneous SSc (lSSc) (skin involvement of the fingers, hands, forearms, toes, feet, legs, neck and face) or diffuse cutaneous SSc (dSSc) (skin involvement of arms, thighs, chest, abdomen and back) according to the guidelines of LeRoy et al. was carefully investigated [18].

All patients who were enrolled reported the presence of Raynaud’s phenomenon (RP). The age of onset of both SSc and RP was investigated in all patients. The duration of SSc at the time of study entry was evaluated by clinical interview and/or from clinical file data. In particular, the duration of SSc was calculated from the time of the onset of the patient’s complaining of clinical signs or symptoms clearly related to SSc or from the time of instrumental and/or serological examinations specific for SSc.

A few patients were treated with vasodilators (i.e. buflomedil or prostanoids), or with non-steroidal anti-inflammatory drugs. In these cases, a washout period of 1 month was performed before instrumental cardiac examination. Patients were not taking corticosteroids, d-penicillamine or immunosuppressive agents and had not previously taken cardiotoxic agents.

Any history of smoking and blood pressure values were carefully evaluated in all SSc patients. The lipid profile and serum glucose levels were investigated by routine examinations. A few healthy subjects were recruited as controls [three males, 13 females, mean age 52 ± 8 (S.D.) yr].

Informed consent was obtained from all patients and controls before entry to the study, and ethical approval was obtained for this study.

Electrocardiography and echocardiography

Surface electrocardiography (ECG) and transthoracic echocardiography were performed in all patients.

Echocardiography was performed with an Acuson Sequoia™ ultrasound unit (C256 Echocardiography System; Acuson Corporation, Mountain View, CA, USA) using a broadband transducer with second harmonic capability (3V2c) over a wide range (from 2.0 to 3.5 MHz) in both B-mode and Doppler modality.

Coronary flow reserve

The only enrolment criterion was that the patient was eligible to receive intravenous echo-contrast injections. The most important exclusion criteria were pregnancy and a poor image quality or limited acoustic windows.

Leovist® (Schering, Berlin, Germany) was used as the ultrasound contrast agent, and was administered by infusion using an infusion pump (IVAC P6000 Anaesthesia Syringe) connected over a special 50 cm connector tubing (Medrad®; Indianola, PA, USA) to an i.v. cannula inserted into an antecubital vein. A concentration of 300 mg/ml was used with a velocity infusion in a range of 0.5–2 ml/min, based to achieve optimal Doppler signal in the distal left anterior descending coronary (LAD).

Flow velocity was measured using a new non invasive method recently developed and validated (transharmonic contrast enhanced second harmonic Doppler) [19, 20].

The CFR, expressed as the ratio between hyperaemic (peak adenosine infusion) and resting peak diastolic velocity (PdVCFR) and resting velocity time integral (VtCFR), was assessed non-invasively in the LAD.

The Doppler image was sampled using pulse-wave Doppler at a gate size of 2.5. Due to the absence of ventricular contraction in diastole, the sample volume was positioned in the diastolic position of the vessel and the spectral trace of coronary flow velocity was characterized by a biphasic flow with a prevalent diastolic component (Fig. 1).

Blood flow Doppler recording in the LAD was attempted at baseline (with and without contrast enhancement). Then, during contrast infusion, intravenous adenosine (140 μg/kg/min over 5 min) was started using a separate intravenous line. Hyperaemic flow velocity by pulse-wave Doppler was recorded within 3 min after the beginning of adenosine administration and continued, if well tolerated, until the end of the infusion. The peak and rest Doppler spectra were obtained in all patients enrolled in the study and in the control group.

Autoantibody detection

Serum antinuclear antibodies (ANA), antitopoiso merase 1 antibodies (Scl70) and anticentromere antibodies (ACA) were sought in all patients.

ANA were detected by indirect immunofluorescence using HEP-2 cells as substrate (Euroimmun, Luebeck, Germany). ACA and Scl70 were measured using an enzyme-linked immunosorbent assay (ELISA) (Euroimmun).

Statistical analysis

Statistical analysis was performed by analysis of variance and the non-parametric Mann–Whitney U-test to compare continuous variables with nominal variables. Regression tests were used to evaluate any possible relation between continuous variables. Categorical data were evaluated with the \( \chi^2 \) test. \( P \) values lower than 0.05 were considered statistically significant.

Results

Nineteen patients [mean age 50 ± 14 (S.D.) yr] and 25 patients [mean age 57 ± 14 S.D. yr] were affected by dSSc and lSSc respectively. Electrocardiographic examination revealed sinus rhythm in all
study patients, and no other major abnormalities (such as conduction defects, left and right hypertrophy, prominent P wave and low voltage) were found. All echocardiographic parameters were in the normal range. Left and right ventricular ejection fraction was normal and there was no pericardial effusion. The systolic pulmonary pressure, determined by the peak flow velocity of tricuspid regurgitation, was normal in all enrolled patients.

Twenty-four out of 44 SSc patients showed reduced CFR when compared with the normal range of age- and sex-matched healthy subjects, as observed in previous studies (normal CFR >2.00) [20].

Both PdvCFR and VtiCFR, as assessed by transthoracic contrast-enhanced second harmonic Doppler, were strongly reduced in SSc patients [1.95 ± 0.55 (s.d.) and 1.76 ± 0.51 (s.d.) respectively] when compared with controls [3.10 ± 0.78 (s.d.) and 2.68 ± 0.42 (s.d.) respectively] (P < 0.0001) (Figs 2A and 3A). In particular, both PdvCFR and VtiCFR were significantly lower in patients with dSSc [1.74 ± 0.46 (s.d.) and 1.59 ± 0.38 (s.d.) respectively] when compared with patients affected by lSSc (2.11 ± 0.56 and 1.90 ± 0.56 respectively) (P < 0.02 and P < 0.04 respectively) (Figs 2B and 3B).
Glucose serum levels were within the normal range in all SSc patients. Four patients were smokers. Cholesterol was within the normal range in all SSc patients. No statistically significant correlation was found between CFR and both a history of smoking and serum levels of cholesterol or triglyceride. Moreover, no statistically significant correlation was found between CFR and blood pressure values. No statistically significant correlation was observed between CFR and the age of patients, duration of SSc, or the presence of antibodies to ANA, ACA or Scl70. Serum ACA and Scl70 autoantibodies were positive in 54% and 23% of SSc patients respectively. Serum ACA positivity was detected more frequently in patients with ISSc (64%), but the difference was not statistically significant. On the contrary, Scl70 autoantibody positivity was more common in dSSc patients (26%), once again without statistical significance.

No correlation was observed between SSc duration and both skin involvement and autoantibody positivity.

Discussion

The present study shows that SSc patients might be characterized by clinically asymptomatic heart function impairment. In particular, the CFR rate, as assessed by transthoracic contrast-enhanced second harmonic Doppler, was strongly and significantly reduced in SSc patients when compared with healthy controls. Left ventricular function (fractional shortening and ejection fraction) was normal in all SSc patients, as evaluated by M-mode and 2D echocardiography. On the other hand, no correlation was observed between CFR and serum lipid profile, glucose levels, blood pressure and smoking in these patients.

Moreover, the CFR values were significantly lower in patients with dSSc than in patients affected by ISSc. Notably, patients with dSSc were younger than those affected by ISSc, supporting the finding that the age of the patient is not important in the development of scleroderma heart disease. However, a larger study population is needed in order to confirm this hypothesis.

Patients affected by ISSc often develop clinical manifestations different from or less severe than those of patients with dSSc, and the lower CFR found in patients with dSSc seems to support this observation [21, 22]. Therefore, the present results seem to confirm previous studies showing that dSSc patients suffer more frequently from cardiac involvement [21, 22]. A recent paper reported similar results on CFR in a smaller population of SSc patients [23]. In that study, a statistically non-significant trend between CFR and disease duration was noted. In our study no statistically significant correlation was observed between CFR values and the duration of either SSc or RP. Furthermore, no statistically significant correlation was observed between CFR and the presence of specific autoantibodies, although Scl70 autoantibodies were detected more frequently in patients with dSSc and ACA more frequently in patients with ISSc. Therefore, the duration of disease and the presence of specific autoantibodies do not seem to affect the extent of the CFR.

Specific organ involvement in SSc patients is often poorly investigated. We recently demonstrated cerebral hypoperfusion and white-matter focal damage in clinically asymptomatic SSc patients [24, 25]. Furthermore, renal functional reserve was found to be impaired in patients with SSc without clinical signs of kidney involvement [26].

Echocardiography is very sensitive in detecting some heart complications of SSc, such as pericardial effusion, heart valve alterations and ventricle dysfunction, as well as early myocardial changes [6, 12, 27]. Recently a new non-invasive Doppler method has been validated based on advanced ultrasound technology (second harmonic technology) and echo-contrast agent is used. In the literature a transthoracic Doppler approach for CFR assessment in the left anterior descending coronary, without contrast or with contrast but without harmonic technology, has been reported [19, 20]. In these reports (dealing with small series of patients) the feasibility was suboptimal (79 and 89%), whereas when contrast and harmonic technology were adopted feasibility approached 100% [19, 20]. As reported by Caiati et al. [20], intra-observer and interobserver variability in tracing curve outlines are low, and intra-observer and interobserver reproducibility of blood flow velocity recording is high.

In conclusion, because the aim of the present study was to evaluate the CFR by transthoracic Doppler echocardiography in patients affected by SSc without signs or symptoms of cardiac impairment, the CFR estimation was found to be an efficient, non-invasive and reliable tool to assess cardiac involvement in SSc. A reduced CFR value should be considered an indirect sign of heart involvement in scleroderma. However, its clinical and prognostic implications need to be clarified, as the decreased CFR might be an important contributor to the pathogenesis of primary scleroderma myocardial disease. If further studies provide any evidence on the natural history of CFR in SSc, it may be useful to include the evaluation of CFR by transthoracic contrast-enhanced second harmonic Doppler among the tools used to assess disease activity in SSc patients, at least for specific screenings. Early signs of cardiac involvement might be detected, and the progression of the disease and the effects of therapies might be monitored [28]. Further studies should be performed to elucidate the prognostic value of the present findings.

The authors have declared no conflicts of interest.

References