Primary myocardial involvement in systemic sclerosis

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Systemic sclerosis (SSc) is a connective tissue disease characterized by diffuse vascular lesions and fibrosis. Primary myocardial involvement is common in SSc and, when clinically evident, appears as a poor prognostic factor. An increasing body of evidence suggests that myocardial involvement is due, at least in part, to microcirculation impairment with abnormal vasoreactivity, with or without associated structural abnormalities of the small coronary arteries or arterioles.

Using conventional methods, myocardial perfusion impairment, systolic and diastolic left ventricular dysfunction and right ventricular dysfunction have been reported in SSc. Recently, tissue Doppler echocardiography and magnetic resonance imaging have confirmed these results. Vasodilators, such as calcium channel blockers and angiotensin converting enzyme inhibitors, improve both myocardial perfusion and function abnormalities.

Systemic sclerosis (SSc) is a connective tissue disease characterized by diffuse vascular lesions and fibrosis of the skin and major organs including lungs, kidneys and heart. Although cardiac involvement is often clinically asymptomatic, myocardial involvement is common in SSc, and when sensitive tools are used it has been estimated to occur in up to 100% of SSc patients [1–3]. When cardiac involvement appears clinically evident, it is recognized as a poor prognostic factor [4].

All cardiac structures may be involved, resulting in pericardial effusion, auricular and ventricular arrhythmias, conduction system defects, valvular impairment, myocardial ischaemia, myocardial hypertrophy and heart failure. 'Primary' myocardial involvement, without systemic or pulmonary hypertension and without significant renal or pulmonary involvement, may be the consequence of the characteristic vascular lesions of this disease.

The prevalence of cardiac disease varies depending on its definition. Clinical symptoms or common investigations such as ECG, thoracic X-ray or echocardiography have been proposed as candidate variables for routine cardiac assessment [5]. In a study, only two variables independently predicted mortality, left axis deviation or large pericardial effusion [6]. Heart clinical symptoms were observed in 15% of 953 patients with the diffuse cutaneous form of the disease: in the 10-yr follow-up, cardiac involvement explained 20% of disease attributed deaths, with the greatest impact occurring in the first 5 yrs, where 44% of deaths were cardiac or renal [7]. More recently, survival was estimated in three large series of SSc patients. In a cohort of 1012 Italian patients, 35% had cardiac symptoms or arrhythmia, and cardiopulmonary deaths accounted for about 70% of the mortality, with cardiac involvement alone accounting for 36% of deaths [8]. In 309 French-Canadian patients, 11.4% of deaths involved the heart [9], and an international meta-analysis of pooled cohorts of 11 526 person-years [10] found that heart involvement was present at any time in 10% of patients (8–28% according to series). A multivariate adjusted analysis found the hazard ratio for cardiac mortality to be 2.8 (2.1–3.8), which was the strongest predictor of mortality. With the improvement in renal outcome, cardiac involvement, together with involvement of the lungs, has become the major factor in the severity of this disease.

Functional and structural abnormalities of the small coronary circulation

Characteristic SSc vascular lesions result in major impairment of the microcirculation. The frequency of atherosclerosis of the large coronary arteries appears to be similar to that of the general population. Some histological examinations have revealed diffuse patchy fibrosis, with contraction band necrosis unrelated to epicardial coronary artery stenosis [11], concentric intimal hypertrophy associated with fibrinoid necrosis of intramural coronary arteries [12]. Angina pectoris and myocardial infarction have been observed in SSc patients whose epicardial coronary arteries were normal. Repeated ischaemia-reperfusion abnormalities may lead to irreversible myocardial fibrosis. Coronary vasodilator reserve at catheterization was investigated in diffuse cutaneous SSc patients [13]: at rest, the mean coronary sinus blood flow was not significantly different compared with control subjects; in contrast, after maximal coronary vasodilation with intravenous dipyridamole, the vasodilator reserve was strikingly reduced. All the patients had evidence of established myocardial involvement, confirmed using non-invasive procedures. Their coronary arteriograms were normal; endomyocardial biopsies showed fibrotic tissue and a typical SSc vascular lesion with concentric intimal hypertrophy. Thus, despite normal epicardial coronary arteries, structural abnormalities of small coronary arteries or arterioles explained the strikingly reduced coronary reserve. Recent studies using contrast enhanced transthoracic Doppler before and after adenosine infusion have confirmed these results: 52% of 27 SSc patients [14] and 55% of 44 SSc patients [15], without clinical evidence of cardiac involvement, had impaired coronary flow reserve.

In addition to these late fixed abnormalities, vasospasm of the small coronary arteries or arterioles play a major role in the early myocardial abnormalities in SSc. Thallium-201 single photon emission computed tomography (SPECT), allowing the assessment of myocardial perfusion, provided evidence of associated reversible ischaemia. Some studies demonstrated the induction of coronary vasospasm by cold pressor tests, in 12 of 21 patients vs 0 of 8 matched controls [16] and in 10 of 12 asymptomatic patients [17]. A study evaluating patients with SSc and other connective tissue disorders showed reversible perfusion
abnormalities suggesting cold-induced ischaemia in 4 of 10 SSc patients, but in none of the patients with other rheumatic diseases [18]. Some studies compared SSc patients with those with systemic lupus or rheumatoid arthritis, using similar parameters [19]. Of the 25 SSc patients, seven had significant cold-induced myocardial ischaemia vs none in the control group. This suggested a functional ‘Raynaud’s phenomenon of the heart’ in SSc.

The mechanisms of exercise-induced myocardial perfusion defects might be different from those involved in spontaneous or cold-induced myocardial thallium-201 scintigraphic abnormalities. Exercise-induced perfusion defects observed by scintigraphy were predictive of developing subsequent cardiac disease or death [20].

Several studies demonstrating the beneficial effect of vasodilator agents on myocardial perfusion abnormalities further emphasize the potential role of coronary vasospasm. After intravenous administration of dipyridamole [21] as well as after treatment with nifedipine [2], nicardipine [22] or captoril [23], improved myocardial perfusion was seen by thallium-201 SPECT. In all these studies, some myocardial perfusion defects were reversible, whereas others remained fixed; the hypothesis is the coexistence of ischaemic lesions accessible to reperfusion after small coronary vasospasm and irreversible lesions such as organic vessel disease or fibrocardiac fibrosis. Using stress thallium-201 myocardial SPECT, decreased heart perfusion was observed in 82% of SSc patients studied [24]; the incidence of fixed or reversible defects and reverse redistribution, were significantly higher in symptomatic patients. The beneficial effect of nifedipine on myocardial perfusion and metabolism in SSc patients was also demonstrated using positron emission tomography [25]; nifedipine (20 mg, three times daily for 1 week) caused a significant increase in 38K myocardial uptake, a significant decrease in 18FDG myocardial uptake and a significant increase in the myocardial 38K/18FDG ratio, indicating improvement in both myocardial perfusion and myocardial metabolism.

Cardiovascular magnetic resonance imaging (MRI) is an accurate, quantitative method for the non-invasive assessment of myocardial perfusion [26]. MRI demonstrated subendocardial perfusion abnormalities in patients with cardiac syndrome X, with a much higher sensitivity than conventional perfusion techniques [27]. Using MRI, myocardial perfusion was investigated in SSc patients, before and after 14 days of treatment with nifedipine (60 mg/day) [28]; the results confirmed the nifedipine-induced improvement, with a mean 38% increase of the global perfusion index (Fig. 1) and a decrease in the number of patients with more than one segmental perfusion defect, from 7 out of 26 (26%) to 0 out of 26 (P < 0.05). High-resolution perfusion MRI techniques can be used to identify small subendocardial defects. These defects do not correspond to any epicardial coronary artery distribution, and are therefore highly suggestive of microvascular alteration confirming previous hypotheses. MRI may also allow non-invasive coronary reserve determination and the evaluation of fibrotic myocardium compared with viable tissue.

Thus, the beneficial effects of vasodilators, such as calcium channel blockers mostly of dihydropyridine type and angiotensin converting enzyme inhibitors, were clearly demonstrated in SSc patients, inducing a striking improvement in the early vasospastic reversible component of the ‘primary’ myocardial disease.

Abnormalities of myocardial function

Myocardial fibrosis is characteristic of established, late, myocardial involvement in SSc; fibrotic lesions are patchy, distributed in both ventricles and are not consistent with large coronary artery distribution [11, 29]. Left ventricular mass has been shown by echocardiography to be increased in SSc [30]. Although advanced myocardial fibrosis may lead to congestive heart failure, systolic or diastolic dysfunction can occur early in the disease, many years before becoming clinically evident.

Several studies, using radionuclide ventriculography, found a decreased global left ventricular ejection fraction (LVEF) in a minority of patients, although segmental dysfunction [31] or exercise-induced dysfunction was more prevalent [32]. Left ventricular wall motion was investigated in 80 SSc patients, revealing that 29% of them had hypokinesia [33]. With improved echocardiographic techniques, diastolic dysfunction in SSc has been reported [34–36]. Such abnormalities were correlated with disease duration [34], suggesting impaired diastolic relaxation of the left ventricle together with a defective cardiac functional reserve [35]. There was some controversy concerning left ventricular diastolic dysfunction in SSc, as a primary event or secondary to other cardiac abnormalities [37, 38]. A recent study focussed on cardiac function in 42 consecutive SSc patients with normal pulmonary arterial pressure and less than 5 years of disease duration compared with 20 matched controls [39]; radionuclide ventriculography showed that 16 patients had reduced right ventricular ejection fraction (RVEF), 3 had reduced LVEF and 10 had reduced peak filling rate (PFR), highlighting early right systolic and left diastolic dysfunction (Fig. 2); moreover, RVEF was correlated with both LVEF and PFR, whereas no correlation was found with either pulmonary function impairment or pulmonary arterial pressure, strongly suggesting intrinsic myocardial involvement in these patients. In 26 SSc patients with diffuse cutaneous disease, four had reduced LVEF and seven reduced RVEF, including the four patients with reduced LVEF [1]; the group with thallium defect scores above the median had a significantly lower mean LVEF than the other group, and all the patients with abnormal resting LVEF had thallium scores above the median. The link between myocardial perfusion abnormalities and dysfunction suggests a similar mechanism for myocardial involvement.

The beneficial effect of vasodilators on myocardial dysfunction has also been demonstrated. Nicardipine was shown to acutely improve global LVEF and segmental abnormalities [31]. Recently, improvements in both LVEF and RVEF after oral treatment with nicardipine (40 mg) (Fig. 2) and a correlation between improvement in LVEF and RVEF have been demonstrated [39]. These results provided further evidence for the same pathogenic pathway, with reversible vasospastic small coronary artery disease inducing segmental and global heart dysfunction.

![Fig. 1. Individual data showing the significant increase in myocardial perfusion index, as measured by magnetic resonance imaging after 14 days of treatment with nifedipine (60 mg/day) in SSc patients (n = 18).](image-url)
Tissue-Doppler echocardiography (TDE) is a recently developed ultrasound technique that allows direct measurement of myocardial velocities and strain rate (SR) [40–43]. Previous studies have demonstrated that SR is a powerful indicator of myocardial contraction, independent of myocardial translational motion, and is far more sensitive than conventional echocardiography [40–43]. A recent study investigated consecutive SSc patients with normal cardiac examination, pulmonary artery pressure and radionuclide LVEF and matched controls [44]; SSc patients had lower systolic SRs and lower diastolic SRs than controls; 10 of 17 SSc patients had reduced systolic SR and 11 of 17 patients reduced diastolic SR. Another study [45] also reported that early diastolic velocities were significantly lower in SSc patients than in control subjects.

A study using a sensitive method demonstrated that nifedipine (60 mg/day for 14 days) significantly increased segmental (posterior wall) systolic SR and diastolic SR [28]. As peak systolic and early diastatic SR are respective markers of regional contractility and diastolic function, this study strongly suggested that nifedipine improved intrinsic myocardial properties; SR determined by DE is less load-dependant than other methods [41,42], and the afterload estimated by the systolic blood pressure heart rate product did not change significantly after nifedipine [28]. These results, together with the increased perfusion shown by MRI, suggested that an increase in myocardial perfusion might be the main determinant in the observed increased contractility, highlighting the global intrinsic beneficial effects of nifedipine.

Cardiac involvement in the cutaneous subtypes

Although cardiac abnormalities could be more prevalent and severe in the diffuse cutaneous subtype of the disease, which has been the most intensively investigated, there is increasing evidence suggesting that cardiac involvement is also a frequent finding in the limited cutaneous subtype. In the large epidemiological Italian study, although heart symptoms were found more frequently in the diffuse subtype (32%) as compared with the limited form (23%), the difference was not statistically significant [8]. Some data have even suggested a more prevalent involvement in the limited subtype of the disease. Echocardiography has shown 18 of 57 patients with left ventricular abnormalities in the limited cutaneous form compared with 5 of 23 patients in the diffuse form [33].

Conclusion

‘Primary’ myocardial involvement is a frequent and early finding in SSc patients, both in the diffuse and limited cutaneous forms of the disease. Primary myocardial involvement is likely to result from the general vasospastic mechanism that is thought to play a key role in this disease. Vasospasm of the small coronary arteries or arterioles would initially impair perfusion and function, with reversible involvement. This would be followed by structural coronary arteriolar lesion leading to irreversible abnormalities. Early treatment with vasodilators, such as calcium channel blockers and angiotensin converting enzyme inhibitors, was shown to be beneficial on myocardial perfusion and function and thus might limit the progression of this major life-threatening complication of the disease.

The authors have declared no conflicts of interest.

References

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