Review

Primary myocardial involvement in systemic sclerosis: evidence for a microvascular origin

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ABSTRACT

Systemic sclerosis (SSc) is a connective tissue disease characterised by widespread vascular lesions and fibrosis of the skin and internal organs. Cardiac involvement is recognised as a poor prognostic factor when clinically evident. Primary myocardial involvement is common in SSc. Increasing evidence strongly suggests that myocardial involvement is related to repeated focal ischaemia leading to myocardial fibrosis with irreversible lesions. Reproducible data have shown that this relates to microcirculation impairment with abnormal vasoreactivity, with or without associated structural vascular abnormalities. Consistently, atherosclerosis and macrovascular coronary lesions do not seem to be increased in SSc. Myocardial involvement leads to abnormal systolic and diastolic left ventricular dysfunction and right ventricular dysfunction. Sensitive and quantitative methods have demonstrated the ability of vasodilators, including calcium channel blockers and angiotensin converting enzyme inhibitors, to improve both perfusion and function abnormalities further emphasising the critical role of microcirculation impairment. Recent quantitative methods such as tissue Doppler echocardiography and magnetic resonance imaging have underlined these results.

Systemic sclerosis (SSc) is a connective tissue disease characterised by widespread vascular lesions and fibrosis of the skin and internal organs. Although cardiac involvement is often clinically occult, 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, 2). Once cardiac involvement is clinically evident, it is recognised as a poor prognostic factor (1, 2). All cardiac tunics, endocardium, myocardium and pericardium, may be involved. This may result in pericardial effusion, auricular and ventricular arrhythmias, conduction system defects, valvular impairment, myocardial ischaemia, myocardial hypertrophy and myocardial dysfunction with/without heart failure. Renal and pulmonary involvement can also adversely affect cardiac status. However, this report will focus on primary myocardial involvement, specific to SSc and reflecting the hallmark vascular lesion of this disease. The purpose of this review is to present evidences highlighting the critical role of microvascular abnormalities in SSc contrasting with the weak data suggesting heart macrovascular disease.

Prognostic implication of cardiac involvement

The prevalence of cardiac disease varies depending on its definition. Most of the available data are based on clinical symptoms or common investigations such as EKG, thoracic x-ray or echocardiography (3, 4). EKG left axis deviation or large pericardial effusion were found to be variables independently predicting mortality (5, 6). In the 10-year follow-up of 953 patients having diffuse coetaneous form, Medsger and Steen found that cardiac involvement explained 20% of disease attributed death (7). More recently, in a cohort of 1012 Italian patients, 35% had cardiac symptoms (at least 1 of the following: pericarditis, congestive heart failure, severe arrhythmias, and/or atrioventricular conduction abnormalities) 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 the 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). With the improvement in renal outcome, cardiac involvement has become a major factor in the severity of this disease, although pulmonary arterial hypertension and lung fibrosis are the primary causes of death (11).

Coronary reserve and microcirculation impairment

Overall SSc vascular lesions result in general impairment of the microcirculation. Myocardial fibrosis is thought to follow repeated focal ischaemia. This seems to result from abnormal vasoreactivity, with or without associated structural vascular disease targeting the small vessels. Indeed, evidence comes from histological examinations which have revealed diffuse patchy fibrosis, with contraction band necrosis unrelated to epicardial coronary artery stenosis (12), whereas other studies have revealed concentric intimal hypertrophy associated with fibrinoid necrosis of intramural coronary arteries (13). Moreover, angina pectoris and myocardial infarction have been observed in SSc patients whose epicardial coronary arteries were normal. Indeed, Follansbee *et al*. (14-15) demonstrated normal coronary angiograms in patients with exercise-induced perfusion defects suggesting that abnormal resistance to flow at the level of the microcirculation or myocardial interstitium may account for the observed abnormal perfusion. Typical pathological findings include disseminated plaques of myocardial fibrosis, normal epicardial coronary arteries but arteriolar concentric intimal hypertrophy, which leads to impaired coronary reserve.

Coronary sinus blood flow and coronary vasodilator reserve at catheterisation was also investigated in SSc patients (16). At rest, the mean coronary sinus blood flow was not significantly different compared to control subjects. However, after maximal pharmacologic vasodilation using dipyridamole, the vasodilator reserve was greatly reduced. The included patients had the diffuse cutaneous sub-type of the disease, with disease duration of 13±8 years (mean±SD). All the patients had evidence of established myocardial involvement, confirmed using non-invasive procedures that included regional left ventricular hypokinesia. Their coronary arteriograms were normal but endomyocardial biopsies showed fibrotic tissue with a typical SSc vascular lesion with concentric intimal hypertrophy. Altogether, these results demonstrate normal epicardial coronary arteries with remodelled distal lesions, with fixed abnormalities, clinical symptoms and impaired coronary reserve, and are completely consistent with the above hypothesis of predominant microcirculation impairment favouring myocardial involvement. Recent studies using a less validated method based on contrast enhanced transthoracic Doppler before and after adenosine infusion have confirmed these results: 52% of 27 SSc patients (17) and 55% of 44 SSc patients (18), having no clinical evidence of cardiac involvement, had impaired coronary flow reserve, with more pronounced alterations in patients having the diffuse cutaneous sub-type of the disease (18). These results did not allow the assessment of whether a vasospastic or structural process impedes the flow increase. Cardiac magnetic resonance imaging has not been used until now to assess coronary reserve in SSc but may be useful as shown in cardiac syndrome X (19) and allow quantitative measurements with the induction of vasospasm and comparison of pharmacologic procedures.

Heart macrovascular involvement

Atherosclerosis underlying cardiovascular mortality is the leading cause of death in developed countries. Atherosclerosis affects large and medium sized arteries and can result in ischaemia and infarction. It is considered an inflammatory disease, and accumulating data have shown accelerated atherosclerosis in inflammatory rheumatic conditions (20-22). However, despite the predominance of vascular abnormalities and documented ischaemia, the frequency of atherosclerotic coronary artery disease seems to be similar in SSc to that of the general population. Interestingly, it has been noted that fibrosis in cardiac SSc can be distinguished from the fibrosis present in atherosclerotic coronary artery disease: in SSc the fibrosis may involve the immediate subendocardial layer (which is typically spared in atherosclerosis) and hemosiderin deposits (which are commonly observed in atherosclerotic disease) are not seen in SSc (23). One study attempted to characterise the clinical manifestations of patients with SSc who developed a myocardial infarction: from 1,009 SSc hospital admissions, 11 (1.1%) were for an acute myocardial infarction. Three of these patients had normal coronaries, and instead of wall motion abnormalities, left ventricular hypertrophy was the predominant finding on echocardiography. The odds ratio of finding normal coronaries in systemic sclerosis *vs*. the general population who develop an acute myocardial infarction was 33.89 (14.08–81.39). Therefore, normal coronaries are seen more commonly in these patients as compared to the general population (24). Only scarce data are available regarding surrogate markers of macrovascular coronary involvement in SSc. Multidetector computed tomography, a noninvasive procedure, generates a coronary calcium score (CCS) which is a marker for coronary atherosclerosis. A cross-sectional pilot study included 17 patients with SSc and 17 age-, sex-, and race-matched healthy controls. Coronary calcium was found in 12 participants (9 with SSc, 3 controls; p=0.03). The mean±SD CCS in patients with SSc was significantly greater than the controls (126.6±251.0 *versus* 14.7±52.2; p=0.003) (25). A non controlled preliminary study assessed 19 consecutive SSc patients and found that 6/19(31.6%) patients had coronary artery calcification. All patients were asymptomatic. Patients with abnormal coronary calcium score findings were more likely to be older (26). The "gold standard" that is coronary angiography has been used in one study and lesions observed were compared to the expected ones according to probability analysis to provide a reference population. A total of 174 SSc patients were

assessed for cardiovascular lesion because of various clinical reasons. The prevalence of coronary artery disease was 22% (37/172) with a prevalence of 17% in males and 24% in females. Comparisons with referent population revealed no deviation and no inflation of the risk of coronary artery disease in SSc patients. Only age and typical chest pain were associated with higher risk and interestingly esophageal involvement and pulmonary hypertension had a protective effect (27). These latter conditions may have mimicked coronary artery disease by the generation of angina-like symptoms. Prostanoid therapy has been suspected to induce ischemic complications in rare cases. A controlled study has reported a higher number of events (myocardial infarction or stroke) in patients receiving prostanoids just reaching statistical significance (7/50 *vs*. 1/42; p=0.04). However, it must be underlined that overall, these events occurred in patients having classical cardiovascular risk factors, and thus patients may have developed atherosclerosis unrelated to SSc (28).

Overall, there is no evidence of increased risk of coronary artery disease in SSc and the available data regarding non-invasive methods are too limited to draw any firm conclusion. Therefore, even if some evidence has suggested some macrovascular involvement of peripheral arteries (29), these data strongly suggest that the main vascular lesions of the heart in SSc are driven by small vessel involvement and that microvascular impairment is the leading mechanism of myocardiopathy in SSc. This raises the paradigm of micro *vs*. macrovascular impairment in SSc and enlightens another specificity of SSc in comparison with other connective tissue disorders and inflammatory rheumatic conditions in which accelerated atherosclerosis is now considered as demonstrated and has emerged as a major issue.

Recent development in cardiac biomarkers may suggest that clinicians will soon have the opportunity to detect both cardiac fibrosis (and remodelling) and predictive markers of atherosclerotic involvement; their integration in our algorithm needs to be evaluated but is very challenging.

Myocardial perfusion

Single photon emission computed tomography (SPECT), allowing the assessment of myocardial perfusion, has demonstrated evidence of reversible ischaemia together with irreversible lesions and demonstrated by the induction of coronary vasospasm by cold pressor provocation (30, 31). A study evaluating patients with SSc and other connective tissue disorders showed reversible perfusion abnormalities suggesting cold-induced ischaemia in four of ten patients with SSc, but in none of the patients with other rheumatic diseases (32). This suggested a functional "Raynaud's phenomenon of the heart" in SSc. Although the clinical and prognostic significance of the abnormalities induced by cold-challenge are not completely defined, Steen *et al*. demonstrated that exercise-induced perfusion defects seen by scintigraphy was predictive of developing subsequent cardiac disease or death (33). More recently, Mizumo *et al*. investigated 51 SSc patients using myocardial contrast echocardiography (34). Indeed, all patients had normal myocardial blood flow at rest; using cold provocation test, they also observed a so called "cardiac Raynaud's phenomenon", but more interestingly, demonstrated that it was a strong predictor of future LV dysfunction according to multivariate analysis. Studies demonstrating the effect of vasodilator agents on perfusion abnormalities further emphasise the key role of coronary small vessel vasospasm. Indeed, treatments with nifedipine, dipyridamole, nicardipine or captopril have evidenced improved perfusion using thallium-201 myocardial SPECT (35-39). SPECT is a nuclear medicine tomographic imaging technique using gamma rays. The basic technique requires injection of a gamma-emitting radioisotope into the bloodstream of the patient. Myocardial perfusion imaging is a functional cardiac imaging, used for the diagnosis of ischemic heart disease. SPECT imaging performed at baseline or after stress reveals the distribution of the radionuclide, and therefore the relative blood flow to the different regions of the myocardium. Diagnosis is made by comparing stress images to a further set of images obtained at rest. This technique allows to distinguish diffuse patchy defects evocative of microcirculatory impairment to homogeneous large fixation defect related to coronary distribution suggestive of epicardial stenosis (Fig. 1). In all these studies, some perfusion defects observed in SSc patients were reversible, whereas others remained fixed; the hypothesis is the co-existence of ischaemic lesions accessible to reperfusion after vasospasm and irreversible lesions such as organic vessel disease or myocardial fibrosis. Ishida *et al*. found, using stress SPECT, decreased heart perfusion in 82% of SSc

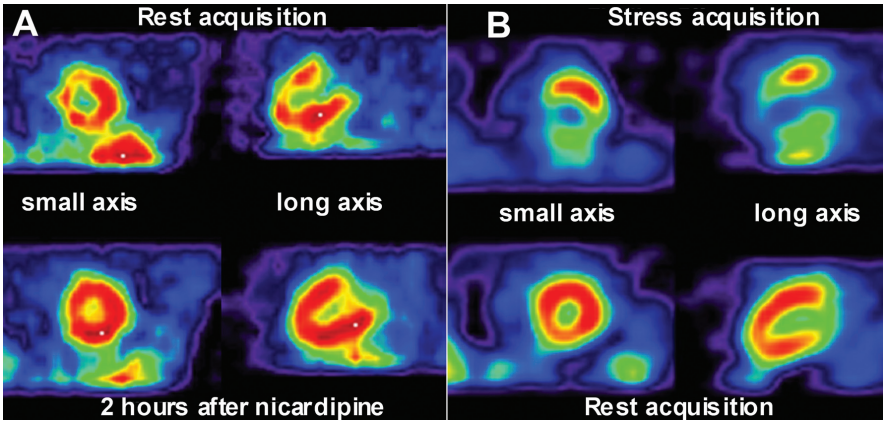

Fig. 1. Thallium scintigraphy showing in microvascular *versus* macrovascular disease.
A. heterogeous myocardial fixation with diffuse patchy defects, partially regressive after nicardipine intake (2 hours), suggestive of microcirculatory impairment in a patient with systemic sclerosis.
B. homogeneous myocardial fixation with large septal, inferior and lateral defects at stress, and complete recovery at rest, suggestive of multivessel epicardial stenosis.

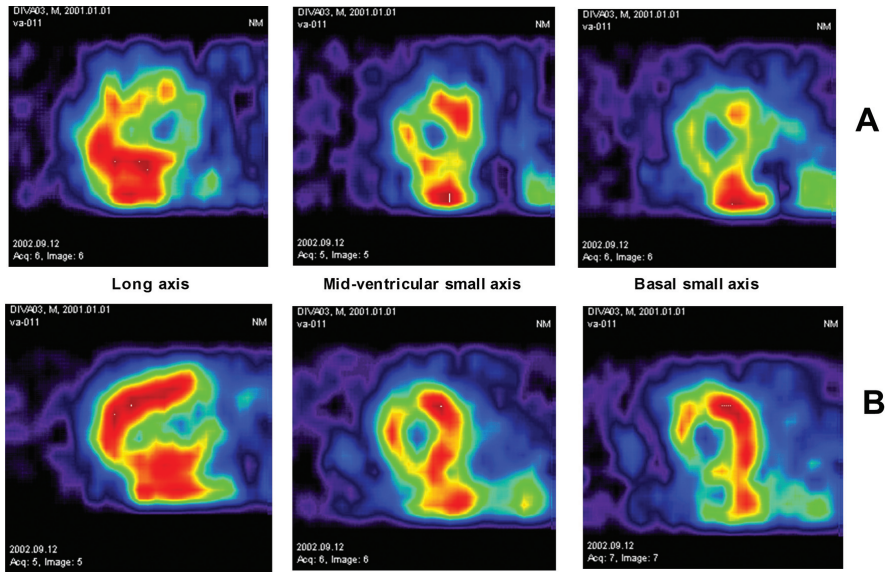

Fig. 2. Severe microvascular impairment in a patient with systemic sclerosis.
Severe heterogenous myocardial fixation with diffuse patchy defect (**A**) and slight improvement after nicardipine intake (**B**), suggestive of very severe microcirculatory impairment.

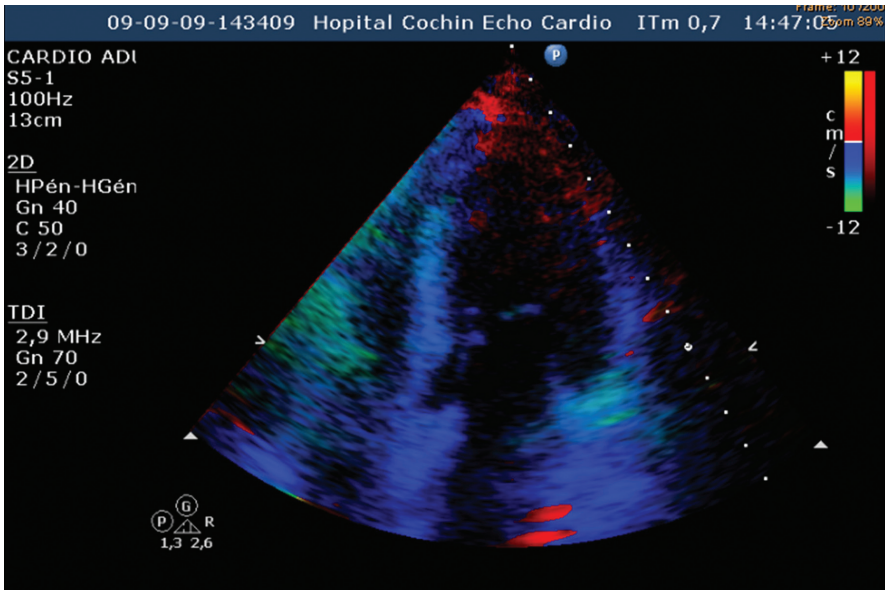

Fig. 3. Echocardiography, strain imaging of the left ventricle, 4 chamber apical view. Colours are related to myocardial velocities.

patients studied. The incidence of fixed or reversible defects, and reverse redistribution, were significantly higher in symptomatic patients, emphasising the value of thallium-201 defects (39). SPECT is however limited as it allows only qualitative/semi-quantitative evaluation of myocardial perfusion and is responsible of patients' radiation. Cardiovascular magnetic resonance imaging (MRI) is an accurate quantitative method developed for the non-invasive assessment of myocardial perfusion (40). MRI is also very sensitive and can detect subendocardial perfusion abnormalities in patients with cardiac syndrome X, with a much higher sensitivity than conventional perfusion techniques (19). Therefore, using MRI, myocardial perfusion was investigated in SSc patients before and after 14 days of treatment with nifedipine (60mg/day) (41) or before and after treatment by bosentan in patients free of pulmonary arterial hypertension (42). The results confirmed improvement, with a mean increase of the global perfusion index of about 40% and a decrease in the number of patients with more than one segmental perfusion defect. The MRI parameters analysed for myocardial perfusion evaluation are usually determined by analysing the first pass of a contrast agent bolus through the myocardium. 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 the evaluation of fibrotic myocardium compared to viable tissue (43-45). Few studies have used this technique, but the few studies that have used this technique have demonstrated that delayed hyper-enhancement can identify myocardial fibrosis in a significant percentage of patients with SSc and may be a useful noninvasive tool for determining cardiac involvement. Using qualitative and quantitative methods, these data show the beneficial effects of vasodilators, *i.e.*, calcium channels blockers mostly of dihydropyridine type, and angiotensin converting enzyme inhibitors, that induce a striking improvement in the small vessel vasospastic reversible component of the "primary" myocardial disease (Fig. 2). Long-term effects of vasodilators remain to be determined.

Myocardial function

Myocardial fibrosis is the hallmark of established myocardial involvement in SSc; fibrotic lesions are patchy, distributed in both ventricles and are not consistent with coronary artery distribution (12, 13). Although advanced myocardial fibrosis may lead to congestive heart failure, systolic or diastolic dysfunction can occur many years before becoming clinically evident. Several studies, using radionuclide ventriculography, found mild global dysfunction in the heart with a few patients having decreased left ventricular ejection fraction (LVEF), although segmental dysfunction or exercise-induced dysfunction was more prevalent (46-49). Follansbee *et al*. reported that 15%

of 26 patients had abnormal LVEF at rest, with 46% having dysfunction after exercise (15). Left ventricular wall motion was investigated in 80 SSc patients, revealing that 29% of them had hypokinesia (50). Another study focused on cardiac function in 42 consecutive SSc patients with normal pulmonary arterial pressure and less than five years of disease duration compared to 20 matched controls (51). Radionuclide ventriculography showed that 16 SSc patients had reduced RVEF (<35%), three had reduced LVEF (<55%) and ten had reduced peak filling rate (PFR), evocative of LV diastolic dysfunction. Moreover, RVEF was correlated with both LVEF and PFR (r=0.64 and r=0.36, respectively), whereas no correlation was found with either pulmonary function impairment or pulmonary arterial pressure, strongly suggesting intrinsic myocardial involvement in these patients (51). These results are consistent with those of Follansbee *et al*. (15) who studied 26 SSc patients with diffuse coetaneous disease. They found that four had reduced LVEF and seven had reduced RVEF, which included the four patients with reduced LVEF. The patients with reduced RVEF had an abnormal LV response to exercise (p<0.002), and RVEF was lower in those patients having high thallium-perfusion score defects (36±12 versus 47±7, p<0.025). The link between perfusion abnormalities and dysfunction suggests a similar mechanism for myocardial involvement, which is also supported by the results from another study (15): the group with thallium defects scores above the median had a significantly lower mean LVEF than the other group and all patients with abnormal resting LVEF had thallium scores above the median.

With improved echocardiographic techniques including the use of Doppler tissue indexes (Fig. 3), increased awareness of diastolic dysfunction and primary right ventricle involvement in SSc have been reported (52-55). Such abnormalities need now to be evaluated in the long-term to determine their predictive value.

The effect of vasodilators on function parameters also supports global myocardial involvement and a link between perfusion defects with impaired function. Nicardipine has been shown to acutely improve global LVEF global, segmental abnormalities and RVEF after oral treatment (40mg). A correlation between improvement in LVEF and RVEF (r=0.48, p=0.0013) has been demonstrated (51). This provides further evidence for the same pathogenic pathway with global heart involvement. Tissue-Doppler echocardiography (TDE) is an ultrasound technique that allows direct measurement of myocardial velocities and strain rate (SR). Previous studies have demonstrated that SR is a powerful indicator of myocardial contraction, independent of myocardial translational motion, less dependent on loading conditions, and is far more sensitive than conventional echocardiography. A study using this sensitive method demonstrated that nifedipine (60mg/day for 14 days) significantly increased segmental (posterior wall) systolic SR, from 1.50.4s-1 at baseline to 2.30.6 (p=0.0002), and diastolic SR, from 3.01.2s-1 at baseline to 4.21.6 (p=0.0003) (41). As peak systolic and early diastolic SR are respective markers of regional contractility and diastolic function, our study strongly suggests that nifedipine improves intrinsic myocardial properties (41). With these results, together with the increased perfusion shown by MRI, we assume that an increase in myocardial perfusion may be the main determinant in the observed increased contractility, highlighting the beneficial effects of nifedipine on global intrinsic heart function.

Conclusion

These studies demonstrate a high prevalence of "primary" myocardial involvement in SSc patients. Primary myocardial involvement is likely to result from the general microvascular vasospastic mechanism that is thought to play a key role in this disease. There is little evidence to suggest a role for macrovascular involvement in SSc; assessments of coronary circulation support the key role played by myocardial microcirculation. Vasospasm could initially impair perfusion and function but with reversible involvement. This could be followed by structural arteriolar lesions leading to irreversible lesions. This hypothesis suggests that early treatment with vasodilators, such as calcium channel blockers and angiotensin converting enzyme inhibitors, may limit the progression of this major life-threatening complication of the disease. Indirect evidences support this hypothesis (56), but controlled studies are warranted before drawing firm conclusions.

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