Cardiac complications of systemic sclerosis

A. Kahan¹, G. Coghn³ and V. McLaughlin³

The majority of patients with SSc are believed to have subclinical primary cardiac involvement. Overt cardiac manifestations of SSc are associated with poor prognosis and can be difficult to manage. Primary myocardial disease, i.e. without systemic or pulmonary hypertension and without significant pulmonary or renal disease, is postulated to be due to microvascular ischaemia. Undetected early cardiac manifestations can progress silently to myocardial fibrosis. Symptoms may manifest without warning and can rapidly lead to arrhythmia and left and right heart dysfunction and failure. Of the currently practical screening methods, annual echocardiography and/or evaluation of N-terminal portion of pro-B-type natriuretic peptide concentrations should therefore be employed in SSc patients, in order to anticipate the development of cardiac symptoms. Although there is limited evidence in respect of specific therapeutic options, treatment of early abnormalities with calcium channel blockers and angiotensin-converting enzyme inhibitors may improve myocardial perfusion and function, while standard management of overt cardiac disease is equally appropriate in the SSc population. However, it remains to be seen if early intervention can limit the progression of these life-threatening complications.

**KEY WORDS:** Cardiomyopathy, Small coronary artery disease, Myocardial fibrosis, Pericarditis, Arrhythmias, Systemic sclerosis, Vasodilators.

**Introduction**

SSc is a CTD that is characterized by vascular dysfunction and excessive fibrosis. Manifestations of SSc may occur in numerous tissues and organs, and can be particularly problematic when present in the lungs, kidneys or heart. Cardiac manifestations are common in SSc, with an estimated clinical prevalence of 15–35% [1, 2]. In the majority of SSc patients, however, cardiac manifestations may remain subclinical [3–5]. Individuals who develop clinically apparent myocardial manifestations are recognized to be at greater risk of clinical deterioration [6], and monitoring of myocardial involvement represents an important aspect of their disease management [7]. In this review, the primary cardiac manifestations of SSc will be explored, and a case study is used to illustrate some problems associated with diagnosis and management.

**The burden of cardiac manifestations**

Cardiac manifestations may affect patients with either lcSSc or dcSSc and, when clinically evident, are often associated with mortality [1, 2, 8, 9]. Vlachoyiannopoulos et al. [10] retrospectively analysed the clinical files of 254 patients over 4 years. They estimated the mortality rate to be 2% per year, and the incidence of cardiac disease to be between 7% in lcSSc and 21% in dcSSc patients [10]. Similarly, a review of 1095 SSc patients between 1959 and 1988 estimated the overall mortality of SSc to be 33%, with deaths of 42 patients (4.5%) resulting from cardiac manifestations [11]. Another review of 405 SSc patients followed for 5 years between 1990 and 2000, determined that 21 out of a total of 145 (14%) patient deaths were due to cardiac manifestations, at a rate of 1% per year.

**Abnormalities in cardiac function**

Cardiac manifestations of SSc can affect all structures of the heart, and may result in pericardial effusion, arrhythmias, conduction system defects, valvular impairment (in rare cases), myocardial ischaemia, myocardial hypertrophy and heart failure [7]. These primary myocardial manifestations—those without systemic or pulmonary hypertension and without significant pulmonary or renal disease—likely result from the underlying vascular pathology of SSc, i.e. the characteristic vascular lesions and fibrosis that impair microcirculation and myocardial function, respectively [7]. The early myocardial manifestations of SSc are often non-specific, making evaluation of susceptible patients problematic. Patients with cardiac manifestations may therefore remain undiagnosed, potentially enabling the disease to progress silently. Early diagnosis is therefore very important. For patients with SSc undergoing autologous haematopoietic stem cell transplantation, a full cardiological assessment before and during the transplant is recommended, as patients with cardiac abnormalities are known to be at increased risk of mortality [12].

Early and widespread subclinical cardiac dysfunction is understood to occur in many SSc patients. Several in vivo studies, using SPECT, echocardiography and MRI, have shown a higher incidence of abnormalities compared with post-mortem findings [3, 4, 7, 13, 14]. These results suggest the existence of reversible functional and vasospastic abnormalities (demonstrated by SPECT, echocardiography and MRI) as well as fixed abnormalities due to fibrosis or organic abnormalities of small coronary vessels (demonstrated by post-mortem studies and the methods used in vivo) [3, 4, 7, 14]. In a study of 52 consecutive patients with SSc (mean disease duration since first non-RP 6.6±6.1 years) cardiac abnormalities were observed in 75%. Abnormal findings were as common in limited (n=32) as in diffuse (n=20) disease. Thinning of the left ventricular myocardium was found in 29% of the patients and pericardial effusion and systolic and diastolic ventricular dysfunction were also common. Right ventricular dilation was noted in seven patients in whom pulmonary hypertension was excluded by catheterization. Myocardial fibrosis in a non-coronary distribution was found in 21% of the patients [14].

Screening for biological markers of possible cardiac dysfunction can be beneficial. One increasingly common example of these surrogate measures is B-type natriuretic peptide (BNP), which is secreted from cardiomyocytes in response to atrial or ventricular wall stretch. Plasma concentrations of BNP correlate with the risk of death and cardiovascular events [15] and N-terminal portion of pro-BNP (NT-pro-BNP) can be measured in clinical practice. Normal values for the concentration of NT-pro-BNP vary according to gender and age; however, the upper normal limit for its serum concentration is generally regarded to be 125 pg/ml [16]. Annual evaluation of NT-pro-BNP can be a useful addition to
standard screening practice for patients with SSC, as myocardial involvement may be primary, due to pulmonary or systemic hypertension or resulting from conventional cardiac diseases that are typically more common among a middle-aged patient population.

Abnormalities in cardiac microcirculation

Numerous abnormalities in the cardiac microcirculation may affect patients with SSC. Vasospasm of the small coronary arteries and arterioles is a major, important and early cardiac manifestation that can be observed at rest or induced in both symptomatic and asymptomatic SSC patients following cold pressor testing [17]. Interestingly, this type of microvascular ischaemia has been investigated in other rheumatic diseases associated with RP, but has not been detected in those cases [18].

One abnormality of the myocardial microcirculation that is typically exhibited late in patients with SSC is reduced coronary flow reserve, which is believed to result from fixed, structural abnormalities of the small coronary arteries and arterioles. This has been investigated in patients with dcSSc with established myocardial involvement and normal coronary arteriograms [19]. These patients were no different to controls at baseline, but exhibited strikingly reduced vasodilator reserve following maximal coronary vasodilation with intravenous dipyridamole [19].

Thallium-201 SPECT and MRI enable abnormalities in cardiac perfusion to be investigated in greater detail [20]. Studies using these techniques have demonstrated that SSC patients may benefit from the administration of the calcium channel blockers nifedipine (Fig. 1) [7, 21–23], the angiotensin-converting enzyme (ACE) inhibitor captopril, as well as intravenous dipyridamole used as a pharmacodynamic test inducing maximal coronary artery vasodilatation [21]. Treatment of SSC patients with these agents has been observed to improve myocardial perfusion; however, not all abnormalities in myocardial perfusion may be reversible. It is possible that ischaemic lesions amenable to vasodilator therapy may co-exist with irreversible lesions, such as those vessels with organic abnormalities or associated with fibrosis [7].

Abnormalities in myocardial tissue

Myocardial fibrosis is a hallmark cardiac manifestation of SSC that can remain subclinical for a considerable period of time [7]. Myocardial fibrosis occurs later in SSC and can lead to systolic and diastolic dysfunction, including exercise-induced dysfunction, segmental dysfunction, decreased peak filling rate and reduced global left and right ventricular ejection fractions [11].

Myocardial fibrosis in SSC can affect both ventricles, leading to increased ventricular mass, decreased movement of the ventricular walls and impaired relaxation of myocardial tissue during diastole [8, 24]. The results of a recent assessment of left ventricular functional impairment in patients with CTD, conducted at the Royal Free Hospital in London, are shown in Table 1.

The combined effects of myocardial fibrosis and reduced perfusion can be investigated using tissue Doppler echocardiography (TDE), which enables sensitive and non-invasive measurement of myocardial contractility. Using this technique, myocardial contractile velocities and strain rates in SSC patients have been determined to be reduced, although the exact pathological mechanism underlying such reductions unclear [7]. Vignaux et al. [22] investigated the effects of nifedipine in 18 SSC patients with reduced systolic and diastolic contractile strain rates. In these patients, nifedipine significantly improved MRI perfusion index, and the systolic and diastolic TDE strain rates [22]. Further investigations to evaluate the effects of nifedipine in a greater number of patients with cardiac manifestations of SSC are, however, necessary. Short-term treatment with the dual endothelin receptor antagonist bosantan has been evaluated in 18 SSC patients without clinical heart failure and with normal pulmonary arterial pressure [25].

Short-term treatment with bosantan simultaneously improved myocardial perfusion and function. It remains to be seen if long-term treatment might result in additional remodelling effects.

Managing symptomatic cardiac disease in SSC

Other than the mechanistic studies listed above, we have no specific information on effective treatments for myocardial involvement in SSC. Ameliorating damage through tight control of systemic hypertension and early aggressive management of pulmonary hypertension are obviously important to prevent secondary cardiac damage. When left ventricular function is impaired, it is safe to assume that standard techniques should be used aggressively; ACE inhibition, vasodilating β-adrenoceptor blockade (if tolerated) implantable cardioverter defibrillators (ICDs) and cardiac resynchronization therapy (CRT), for example, all have their place. As with other causes of severe diastolic heart failure, diuretics remain the only proven therapy. Finally, in patients presenting with acutely deteriorating cardiac failure and persistent troponin leakage, indicative of active myocarditis, most experts would recommend aggressive cytotoxic therapy until troponin negativity is achieved.

Case study

A 22-year-old male student first presented in March 2005 with an abrupt onset of diphasic RP that primarily affected the fingers. The patient had an unremarkable medical history, with no incidence of skin thickening, pigment abnormalities or rash, leading to a differential diagnosis of MCTD.

During the following 18 months, this patient began to exhibit pitting of the fingertips and significant changes in the extent and severity of skin thickening over the fingers, the dorsum of the hands and the cheeks. Increasingly severe episodes of RP, recurrent digital swelling and gastro-oesophageal reflux were also reported. Clear facial manifestations of SSC had become identifiable; however, the patient did not experience any digital ulceration or any clinical evidence of cardiac, pulmonary or renal dysfunction. In September 2006, a diagnosis of dcSSc was confirmed.

At this time, the patient had begun to exhibit dyspnoea on exertion and was increasingly aware of intermittent pounding palpitations during exertion and rest, leading to suspicion of cardiac dysfunction. Cardiac examination revealed mild tachycardia with a clear summation gallop at the apex, but no evidence of increased P2 or murmur. Examination by a cardiologist revealed regular rate and rhythm, tachycardia, with normal S1 and loud P2.
There was a right- and left-sided S3 and slight parasternal lift, and point of maximum impulse was laterally displaced. The patient’s serum concentration of NT-pro-BNP had increased from an earlier measurement of 67 ng/l in March 2006 to 560 ng/l. Echocardiography demonstrated severe global left ventricular systolic dysfunction with a left ventricular ejection fraction of 25%, biastral enlargement and right ventricular enlargement. The estimated right ventricular systolic pressure was 32 mmHg. A diagnosis of SSc-related cardiomyopathy New York Heart Association functional Class III was reached. The ACE inhibitor lisinopril was prescribed, supplemented with carvedilol (6.25 mg b.i.d.).

By November 2006—just 2 months later—cardiac symptoms in the patient had progressed significantly. The patient had developed fluid retention that necessitated hospital admission for intravenous diuresis. The patient’s serum concentration of NT-pro-BNP had elevated further to 2630 ng/l—approximately 40-fold higher than when first evaluated. Cardiac angiography found a left main artery with a normal calibre, a left anterior descending artery of moderate size, a non-dominant and moderately sized left circumflex artery and a dominant right coronary artery of moderate size. No vessels exhibited angiographic signs of stenosis.

Medical therapy for congestive heart failure, including diuretics, lisinopril and carvedilol, was optimized during hospitalization. Computed tomography did not show any evidence of interstitial lung disease. The patient was discharged from the hospital, but unfortunately died at home 2 weeks later.

This example demonstrates that cardiac manifestations, when present in patients with SSc, can and should be monitored closely. Once cardiac dysfunction becomes apparent in patients with SSc, it can severely increase morbidity and rapidly lead to death.

Future directions

The overall mortality in SSc resulting from cardiac complications is relatively low in comparison with manifestations such as interstitial lung disease and pulmonary arterial hypertension [10, 11]. The especially poor prognosis associated with clinically apparent cardiac manifestations does, however, necessitate consideration of future research. The most pressing issues are the current paucity of detailed information in respect of the natural history of cardiac involvement and the lack of high-quality observational data, which are required to plan appropriate trials. Large-scale prospective observational registries linking the known abnormalities on echocardiography, serum markers and functional testing to the subsequent development of overt cardiac disease are urgently required. In respect of future trials, it is unclear at present whether we can identify subgroups with a sufficiently aggressive course. The choice of end points and therapeutic agent(s) to be evaluated also requires careful consideration.

Conclusions

Patients with SSc may experience cardiac manifestations, although for the majority cardiac abnormalities, where present, will remain subclinical. For patients who develop overt cardiac complications, the prognosis is typically very poor.

When cardiac failure is observed, standard heart failure therapies should be used as for any other patient group with impaired cardiac function. At present, no treatments have been demonstrated to alter the natural history of primary cardiac involvement in patients with SSc. However, plausible treatment options exist; the ACE inhibitor captopril and the calcium channel blockers nifedipine and nicardipine have been shown to improve cardiac microcirculation for some patients. Nifedipine and bosentan may simultaneously increase myocardial perfusion and function, which are commonly impaired in patients with SSc. It remains to be shown whether early intervention with these agents can limit the progression of these life-threatening complications. Ultimately, randomized clinical trials are required.

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Table 1. The frequency of selected complications in a cohort of patients with SSc undergoing catheterization for presumed PAH, compared with other CTDs, at the Royal Free Hospital, London

<table>
<thead>
<tr>
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<th>Pulmonary fibrosis, n (%)</th>
<th>Left ventricular problem, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM and PM</td>
<td>16 (88)</td>
<td>9 (56)</td>
</tr>
<tr>
<td>SLE</td>
<td>25 (76)</td>
<td>4 (16)</td>
</tr>
<tr>
<td>SS</td>
<td>7 (57)</td>
<td>2 (28)</td>
</tr>
<tr>
<td>RA</td>
<td>7 (57)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>MCTD</td>
<td>19 (68)</td>
<td>7 (37)</td>
</tr>
<tr>
<td>SSc</td>
<td>446 (70)</td>
<td>97 (22)</td>
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References