Review Article

Systemic Sclerosis: The Heart of the Matter

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Systemic sclerosis (SSc) is a chronic multi-system disease of unknown aetiology that is characterised by the involvement of small vessels, resulting in fibrosis and obliteration of vessels and fibrosis of various organs, including the heart.[1] Cardiac dysfunction is a significant cause of the high morbidity and mortality in SSc.[2,3] While the proportion of deaths related to renal crisis and to pulmonary causes has substantially altered, cardiac-related deaths have remained essentially unchanged over the last three decades, at approximately 15% of all scleroderma deaths.[2] The heart involvement in SSc is either primary, related to myocardial fibrosis, or secondary, as may occur in cases complicated by pulmonary arterial hypertension (PHT) or systemic hypertension in those with renal crisis.[4-7] The above data for estimated cardiac mortality in most studies reflect deaths attributed to primary cardiac causes (fibrosis) and not to secondary causes. In this review, we will focus on the clinical aspects of primary cardiac dysfunction, highlighting newer diagnostic modalities for detecting myocardial fibrosis.

Prevalence of cardiac dysfunction in SSc - morbidity and mortality

The epidemiology of cardiac involvement in SSc has been the subject of several recent studies.[1,8-10] Most importantly, the prevalence of overt left ventricular (LV) systolic dysfunction and its associated risk factors has been defined, and patients with diffuse cutaneous SSc appear to be most susceptible to direct cardiac involvement.[11] In our recent study, using cardiac MRI in a mixed SSc patient population, disease subtype analysis showed no differences in the degree of fibrosis between diffuse cutaneous SSc and those with limited SSc.[12] In this study,[12] in contrast with previous reported prevalence of heart involvement in SSc (~20%), approximately 60% of patients with SSc had evidence of late enhancement on delayed enhanced cardiac MRI, which was consistent with fibrosis. It is likely that these disparate findings are in part due to methodological differences among studies and to heterogeneity in patient populations.

In one study, only two variables independently predicted mortality: left axis deviation and large pericardial effusion.[13] Clinical heart symptoms were observed in 15% of 953 patients with the diffuse cutaneous form of the disease: in the 10-year follow up, cardiac involvement explained 20% of disease-attributed deaths, with the greatest impact occurring in the first 5 years, when 44% of deaths were cardiac or renal.[8] 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.[10] In 309 French-Canadian patients, 11.4% of deaths involved the heart.[14] An international meta-analysis of pooled cohorts of 11,526 person-years[2] found that heart involvement was present at some time in 10% of patients (8-28% according to series). Standardised mortality ratios varied by cohort (1.5 to 7.2). In multivariate analyses that adjusted for age and sex, renal (hazard ratio, HR=1.9; 95% confidence interval, CI: 1.4-2.5), cardiac (HR=2.8; 95% CI: 2.1-3.8), and pulmonary (HR=1.6; 95% CI: 1.3-2.2) involvement, and anti-topoisomerase I antibodies (HR=1.3; 95% CI: 1.0-1.6) increased mortality risk. Renal, cardiac, and pulmonary involvement tended to occur together ($p<0.001$). For patients without adverse predictors for 3 years after enrolment, the subsequent risk of death was not significantly different from that for the general population in three cohorts, but was significantly increased in three cohorts that were comprised mostly of referred patients. Despite the above discrepancies, the majority of these studies create the impression that the morbidity and mortality are mainly related to the extent and severity of internal organ involvement, particularly the kidney, the heart and the lung.

Myocardial fibrosis

Pathology

Myocardial fibrosis was first identified over two centuries ago, when autopsy studies reported the presence of fibrotic tissue within the myocardium. It is estimated that fibrosis is found in over fifty percent of patients with scleroderma in necropsy studies.[11,15,16]

Until 1969, most autopsy studies of scleroderma were based on small numbers of cases; therefore, the patchy distribution of myocardial fibrosis could have resulted in a lower reported prevalence.[15,16] With the newest imaging modalities, however, such as delayed enhanced cardiac MRI, a prevalence of up to 66% has been reported in patients with both limited and diffuse scleroderma.[12]

The first controlled autopsy study in a large number of well-defined scleroderma subjects was reported in 1969 by D'Angelo et al.[16] Those authors observed some degree of myocardial fibrosis in 81% of scleroderma patients, compared to 55% of controls. Autopsy lesions of the pericardium were found significantly more frequently in scleroderma patients than in their matched controls, while no differences were observed in the prevalence of valvular heart lesions. In the study of Murata et al,[17] autopsies were performed on six patients who died during the follow-up period: one with *cor pulmonale*, two with LV wall motion abnormalities and three with septal hypertrophy. The autopsy findings in this study were different from those in the study of D'Angelo et al.[16] Specifically, the main finding described by Murata et al[17] was LV hypertrophy due to endomyocardial, patchy fibrosis of the median papillary muscle or the atrioventricular node and left bundle branches. Bulkley et al,[15] in their study of 52 autopsied subjects, reported that myocardial involvement was morphologically characterised by contraction band necrosis and replacement fibrosis, probably due to intermittent spasm of small coronary arteries, which the authors termed myocardial Raynaud's phenomenon.

Pathogenesis of myocardial fibrosis - vasospasm of the small coronary arteries - the role of vasodilators in myocardial dysfunction

The exact pathogenesis of myocardial fibrosis is unknown.[18] It is believed that the mechanisms responsible for collagen deposition in the skin are very likely also operative in the myocardium. In this regard, microvascular injury, with its related endothelial activation, is probably an early and important event that precedes all pathological changes. It is likely that parenchymal cells are destroyed by ischaemia of the intra-myocardial microvasculature.[19] Inflammation and autoimmunity, which may result from cell damage, may lead to fibroblast activation and recruitment as well as differentiation into myofibroblasts. The resultant production of collagen will ultimately lead to organ fibrosis.[20]

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, has a beneficial effect on myocardial perfusion and function and thus might limit the progression of the disease.

Characteristic SSc vascular lesions result in major impairment of the microcirculation. Coronary vasodilator reserve on catheterisation was investigated in diffuse cutaneous SSc patients:[21] 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[22] and 55% of 44 SSc patients,[23] 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 plays a major role in the early myocardial abnormalities in SSc. Thallium-201 SPECT, allowing the assessment of myocardial perfusion, has provided evidence of associated reversible ischaemia. Some studies demonstrated the induction of coronary vasospasm by cold pressor tests.[24,25] Several studies demonstrating the beneficial effect of vasodilator agents on myocardial perfusion abnormalities further emphasise the potential role of coronary vasospasm. After intravenous administration of dipyridamole,[26] as well as after treatment with nifedipine,[27] nicardipine[28] or captopril,[29] improved myocardial perfusion was seen on 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 myocardial fibrosis.

Using stress thallium-201 myocardial SPECT, decreased heart perfusion was observed in 82% of SSc patients studied;[30] the incidence of fixed or reversible defects and reverse redistribution, was 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;[31] nifedipine (20 mg, 3 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. The beneficial effects of vasodilators, such as calcium channel blockers, mostly of dihydropyridine type, and angiotensin-converting enzyme inhibitors, were clearly demonstrated due to a striking improvement in the vasospastic component of the "primary" myocardial disease. The beneficial effect of vasodilators on myocardial dysfunction has also been demonstrated. Nicardipine was shown to acutely improve global left ventricular ejection fraction (EF) and segmental abnormalities.[26] Improvements in both LVEF and right ventricular (RV) EF after oral treatment with nicardipine (40 mg) and a correlation between improvement in LVEF and RVEF have been demonstrated. These results provided further evidence for the same pathogenic pathway, with reversible vasospastic small coronary artery disease inducing segmental and global heart dysfunction.

Tissue-Doppler echocardiography (TDE) is a recently developed ultrasound technique that allows direct measurement of myocardial velocities and strain rate (SR). A recent study investigated consecutive SSc patients with normal cardiac examination, pulmonary artery pressure and radionuclide LVEF and matched controls;[32] SSc patients had lower systolic SRs and lower diastolic SRs than controls. A study using this sensitive method demonstrated that nifedipine (60 mg/day for 14 days) significantly increased segmental (posterior wall) systolic SR and diastolic SR.[33] As peak systolic and early diastolic SR are respective markers of regional contractility and diastolic function, this study strongly suggested that nifedipine improved intrinsic myocardial properties.

The role of microvascular remodelling in the pathogenesis of myocardial fibrosis is further supported by autopsy findings of concentric intimal hypertrophy in the small arteries and a characteristic absence of coronary arteriosclerosis in these patients.[17,34] The early pathological studies highlighted a discrepancy between the amounts of collagen deposition in the heart that could not be explained by the wall thickness abnormalities of the small arteries. Based on these observations, other authors showed that the collagen deposition is not entirely accounted for by ischaemia of the microvasculature.[15]

Pattern and distribution of myocardial fibrosis

The first autopsy study to suggest that myocardial fibrosis in SSc patients was patchy and linear, involv-

ing both ventricles, was reported by Fernandes et al.[35] As only a small number of patients were studied, the conclusions derived from these data are limited.[35] A detailed description of both the pattern and distribution of the myocardial fibrosis was provided by a recent cardiac delayed-enhanced MRI study in 36 patients with SSc.[12] The predominant pattern was a linear one, involving the mid-wall region of the LV and non-vascular regions. In addition to the linear pattern, a few patients had late enhancement at the upper and lower RV insertion points, which was not necessarily associated with pulmonary hypertension (Figure 1).

Myocardial fibrosis and disease subtypes

It has been believed that myocardial involvement is greater in the diffuse than in the limited disease subtype.[11,17,36-38] However, this notion is not supported by histological studies or by data derived from non-invasive studies that show comparable dysfunction in patients with the two disease subtypes. Studying SSc patients with endomyocardial biopsies, Fernandes et al[35] reported similar amounts of interstitial fibrosis in both forms of the disease. Follansbee et al[39] found no differences between the disease subtype in the degree of fibrosis identified in an autopsy study. The extent

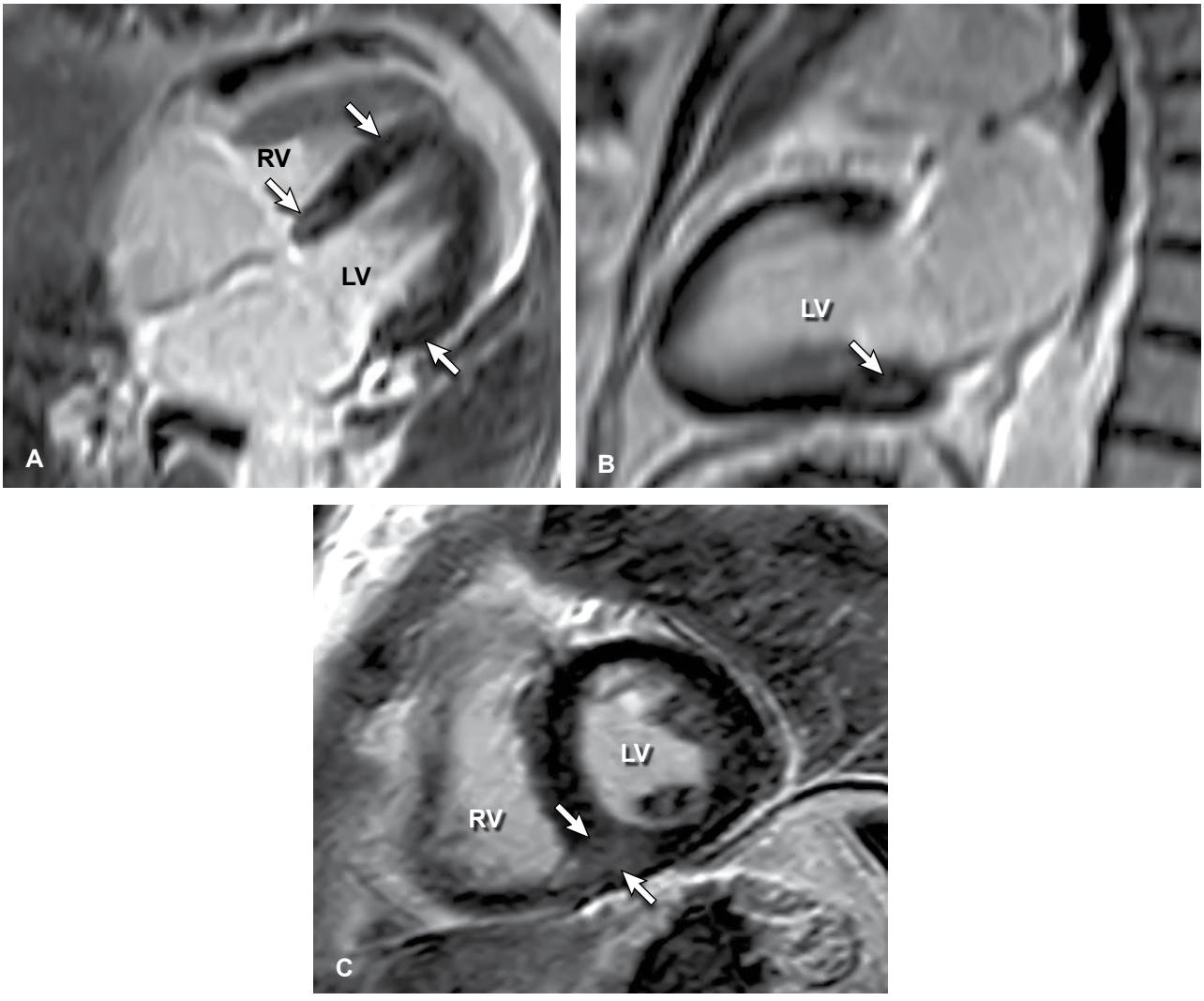

Figure 1. Representative delayed-enhanced magnetic resonance images in a patient with systemic sclerosis. A: Four-chamber view, showing relatively intense linear mid-wall enhancement (arrows) in the basal segments of the interventricular septum and free wall, as well as a focus of more subtle enhancement at the apical segment of the interventricular septum. B: Vertical long-axis view, showing linear mid-wall enhancement (arrow) in the basal segment of the inferior wall. C: Short-axis view, showing globular patchy enhancement with indistinct borders (arrows) at the lower RV insertion point. RV – right ventricle; LV – left ventricle. From reference 12. This material is reproduced with permission of John Wiley & Sons, Inc. © 2007 American College of Rheumatology.

of functional abnormalities does not appear to differ significantly between the limited and diffuse forms of the disease. Assumed to be caused by myocardial fibrosis, LV diastolic dysfunction detected by Doppler echocardiography has been equally reported in patients with limited and diffuse scleroderma.[40] Likewise, nuclear studies, such as thallium perfusion, have reported no differences in the number of fixed perfusion defects between the two disease subtypes.[32,41] In our recent study using cardiac MRI in a mixed SSc patient population, disease subtype analysis showed no differences in the degree of fibrosis between diffuse cutaneous SSc and limited SSc.[12] In addition, patients with a long-duration Raynaud's phenomenon had a larger number of enhancing segments on MRI, representing areas of myocardial fibrosis, than did those whose Raynaud's phenomenon duration was <15 years.

Clinical manifestations of myocardial fibrosis

The most common manifestations of myocardial fibrosis are listed in Table 1. The notion that myocardial fibrosis takes time to develop, thus cardiac complications are only found in patients with long-standing skin involvement, is not applicable to all cardiac manifestations. Whereas this may be true for LV systolic dysfunction, other cardiac manifestations, such as sudden death or cardiac arrhythmias, may occur during the early stage of the disease. Autopsy studies of patients with cardiac causes of death showed extensive fibrosis during the first few years from the onset of Raunaud's phenomenon or other skin manifestations.[15] In the MRI imaging study, extensive fibrosis and arrhythmias were detected in patients with a relatively long duration of skin manifestations.[12]

LV dysfunction

Systolic dysfunction

Congestive heart failure related to myocardial fibrosis may complicate the clinical course of SSc patients.[42,43] However, its prevalence appears to be relatively low. Using Doppler echocardiography, a large French multi-centric study reported systolic dysfunction in less than 2% of the SSc cohort.[44] At an early stage, the impaired systolic function may not be suspected, or may be masked by respiratory causes of dyspnoea or by patients' limited engagement in activities demanding increased cardiac work. As shown by MRI measurements, despite excessive fibrosis, the systolic function of the LV is well preserved in these patients.[12] Coronary artery disease, arterial hypertension and acute myocarditis are the most common causes of LV systolic function impairment.[32,45,46] In particular, myocarditis has been described early in the disease course of SSc patients with active peripheral myopathy who were treated with steroids and immunosuppressive agents.[47-50] Cardiac MRI appears to be a useful diagnostic tool in the differential diagnosis between myocarditis and fibrotic cardiomyopathy in SSc patients (Figure 2).[51] The absence of enhancement of the T2-weighted magnetic resonance signals argues against myocarditis in these patients.[51]

Table 1. Clinical manifestations of heart involvement in systemic sclerosis.

Cardiac involvement	Pathophysiology	Frequency	Clinical manifestations	Diagnostic tools	Treatment
Arrhythmias	Re-entry mechanism or inflammation	Uncertain	Palpitation, syncope	ECG, especially Holter with symptom diary; stress test	Treat only if haemodynamically significant
Conduction defects	Local fibrosis	10% on ECG	Syncope	ECG	May require pacemaker
Pericardial disease	Inflammation or effusion	10% clinically, 30% at autopsy	Chest pain, dyspnoea	ECG, echocardiogram	NSAID, corticosteroids, drainage, fenestration
Myocardial involvement	Myocarditis	Rare	Congestive cardiac failure, arrhythmias	ECG, echocardiogram, MUGA, gated cardiac MRI	Management of heart failure; immunosuppression/ corticosteroids if myocarditis
	Myocardial fibrosis	30-50% dcSSc			Unknown

NSAID – non-steroidal anti-inflammatory drugs; MUGA – multiple gated acquisition scan; dcSSc – diffuse cutaneous systemic sclerosis.

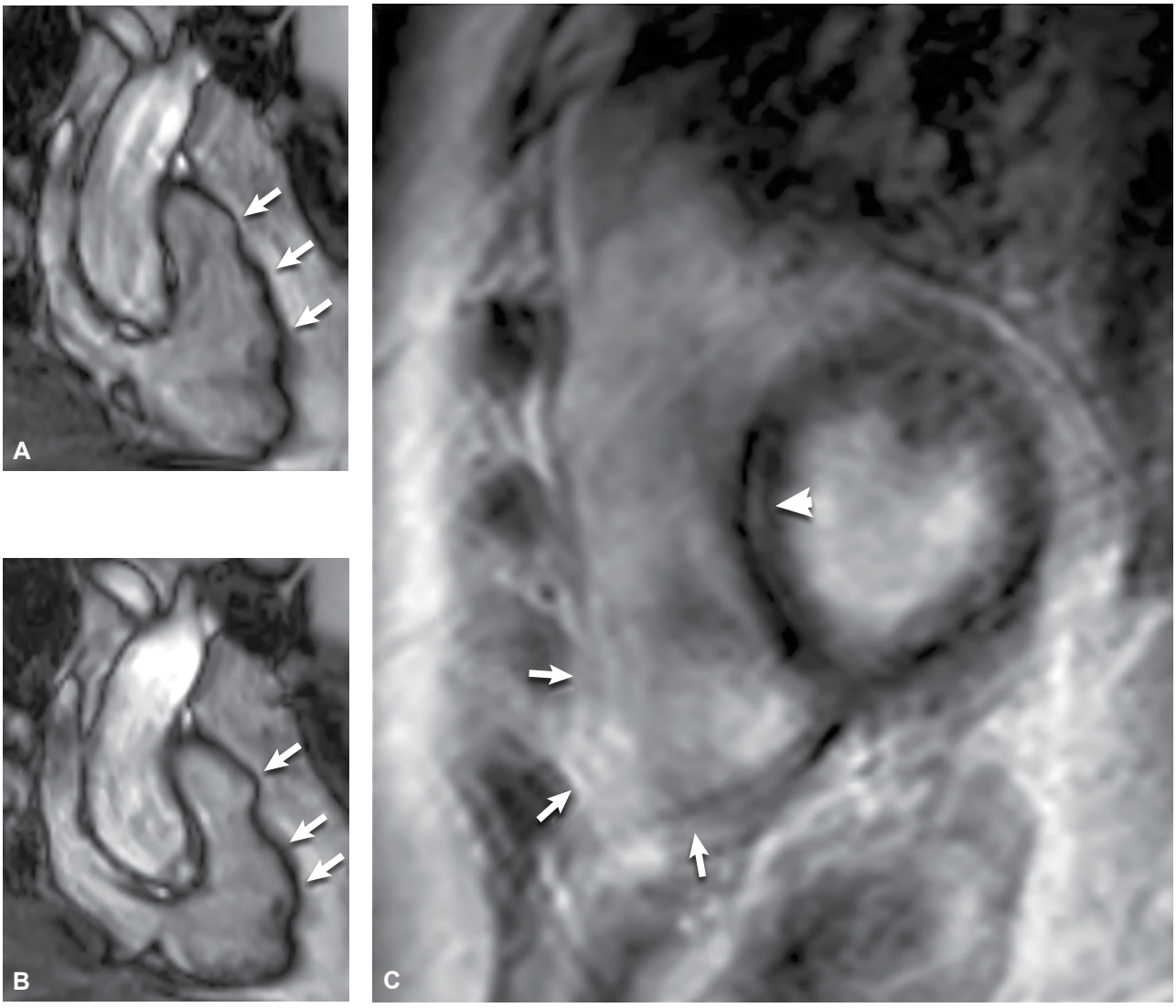

Figure 2. Cine MRI images of the right ventricular (RV) long axis at end-diastole (A) and end-systole (B). Note the irregular shape of the RV free wall (black and dark grey), with aneurysms (arrows) bulging during both diastole and systole. Delayed-enhanced MRI image in the short axis plane shows increased enhancement (white and light grey) of the RV myocardium (arrows) and the interventricular septum (arrowhead) due to myocardial fibrosis (C). From reference 51. © 2006 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Diastolic dysfunction

This is usually the result of primary myocardial involvement in SSc, or involvement secondary to arterial hypertension, PHT and pericardial disease.[52] Diastolic dysfunction is very common in SSc patients. Its prevalence has a wide variation (27-60%), most likely due to differences in diagnostic methodology and heterogeneity in patient populations.[46,53] In previous studies of SSc patients with no history of arterial hypertension, LV diastolic dysfunction due to myocardial fibrosis appeared in 38% of the patients.[40,54] Diastolic dysfunction in these patients correlated well with a longer Raynaud's duration.[55] The absence of diastolic dysfunction does not necessarily exclude the presence of myocardial fibrosis; however, the clinical importance of diastolic dysfunction in SSc patients, assessed using non-invasive methods, has not been studied in detail. It seems that the early diastolic mitral annular velocity (E') ratio (E/E' ratio) assessed by tissue Doppler imaging (TDI) is more sensitive than the E/A ratio assessed by conventional Doppler imaging for identifying LV diastolic dysfunction in SSc patients.[56]

RV dysfunction

The RV dysfunction in patients with SSc can result from pressure overload related to PHT or can occur independently of PHT due to myocardial fibrosis and/or microvascular disease.[57-62] There is a paucity of data regarding the type and exact prevalence of RV dysfunction in these patients, partly because of the lack of sensitive diagnostic tests and the RV's complex geometry.

Systolic dysfunction

RV systolic function impairment in SSc may be secondary to PHT or it may occur independently of PHT and be related to myocardial fibrosis.[57] Bewely et al[63] also described isolated RV systolic dysfunction in SSc, caused by primary myocardial involvement. Myocardial tissue Doppler measurements of the peak systolic velocity of the tricuspid lateral annulus and tricuspid annular plane systolic excursion have been used to assess RV function in previous studies.[42,64] In the study of Hsiao et al,[59] subclinical RV systolic dysfunction was more common than previously thought, even after adjustment for potential contributing factors such as age, sex, heart rate, forced vital capacity and diffusion lung carbon monoxide. RV function in SSc and its correlation with clinical characteristics of the disease remain to be determined with newer diagnostic modalities, such as cardiac MRI and speckle-tracking–derived strain and strain-rate analysis.[65-67] In a recently reported case of an SSc patient, cardiac cine MRI revealed the presence of multiple aneurysms in the free wall of the RV (Figure 2).[51] These aneurysms were distributed in a non-vascular region and corresponded to areas of hyper-enhancement detected by MRI, suggesting a myocardial fibrosis aetiology. In this particular patient group, delayed-enhanced MRI may prove a useful method for screening for myocardial fibrosis, monitoring its progression and possibly intervening therapeutically.

Diastolic dysfunction

RV diastolic dysfunction was associated in the majority of previous studies with the presence of PHT and diastolic dysfunction of the LV.[57,58] With the widespread use of tissue Doppler imaging for regional and global diastolic function, however, RV diastolic dysfunction has been found to be not associated with the systolic and diastolic function of the LV. These data from SSc patients raise a few concerns about the methods of selection and investigation that were used in previous studies.

In a mixed population of diffuse and limited SSc patients, Giunta et al[57] revealed the presence of RV diastolic dysfunction in approximately 40% of these patients, independently of age, disease duration, extent of skin involvement and the presence of pulmonary fibrosis. In a multi-centre prospective study by de Groote et al,[44] RV diastolic dysfunction was found in 17.7% of the patients. These discrepancies between studies were related with the population size and the methods that were used for assessing diastolic function. The general impression from the previous studies that attempted to identify RV diastolic dysfunction is that the addition of tissue Doppler and other sensitive modalities, such as strain-rate imaging, might improve the detection of heart involvement in patients with SSc.[68]

Pericardial disease in systemic sclerosis

The frequency and the characteristics of pericardial involvement have been described in several previous studies and include fibrinous pericarditis, chronic fibrous pericarditis, pericardial adhesions, and pericardial effusions.[5] Necropsy studies report pericardial disease in between 33% and 72% of cases, while symptoms from pericarditis occur in only 7% to 20% of patients. All these studies based their results on macroscopic examination.[15,69,70]

Recently, Byers et al[71] investigated the pericardial involvement histologically, studying the levels of mast-cell infiltration in the pericardium due to fibrosis in 44 SSc patients and 19 age/sex matched controls. Chronic pericarditis was seen in the majority of these patients but in only one of the controls, and myocardial fibrosis was seen in 15 (37.5%) of the SSc cases but in none of the controls. The degree of fibrosis was greater in those with SSc, although the numbers of mast cells (thought to be important in fibrogenesis) were similar in both groups. In addition, even though in most cases the pericardial changes seen are primary, it has been suggested that in some patients they are secondary to uraemia in the context of end-stage SSc. The observations of Byers et al[71] indicate histologically that pericarditis is a primary disease, rather than secondary to uraemia, and confirm the high incidence of pericardial disease as previously reported. The characteristics of the inflamma-

tion were the chronicity and a significant increase in fibrous tissue.

Pericardial tamponade is exceptional in SSc patients and the treatment of choice is usually pericardiocentesis.[72-75] The majority of the reported cases of pericardial tamponade had a poor outcome due to severe pulmonary hypertension, renal or heart failure, with infrequent exceptions.[73] Pericardial tamponade has been reported in two SSc patients during pregnancy, highlighting the tamponade physiology and the therapeutic approach in this particular group of patients (Figure 3).[76-78]

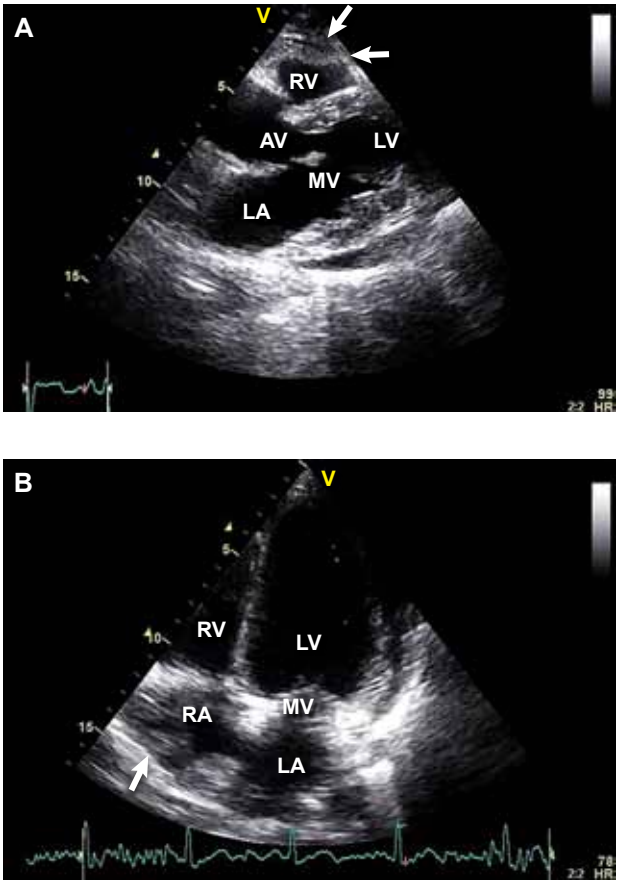

Figure 3. Echocardiographic images (A, parasternal long-axis view and B, 4-chamber view) showing mild to moderate pericardial effusion. Note the diastolic collapse of the free wall of the RV (A, parasternal view, arrows) and the paradoxical movement of the right atrial free wall (B, 4-chamber view, arrow). RV – right ventricle; LV – left ventricle; LA – left atrium; RA – right atrium; MV – mitral valve; AV – aortic valve. From reference 78. © 2010 Clinical and Experimental Rheumatology S.A.S. Reprinted with permission from Clinical and Experimental Rheumatology.

Coronary artery disease

The epicardial coronary arteries in SSc patients have been reported to be free of significant disease, even in the setting of myocardial infarction, congestive heart failure and sudden cardiac death – although these reports included only small numbers of patients.[15,79] Myocardial perfusion defects were investigated in non-invasive studies, but those studies had a low predictive accuracy of around 30%.[80-84] In SSc, the false positive rate is not known, because no large studies have been performed to assess both perfusion defects and coronary anatomy using coronary angiography. Echocardiography and Doppler imaging have shown impaired coronary flow in SSc patients, both with and without cardiac symptoms.[22,23,32,85] The prevalence of angiographically documented coronary artery disease was reported by Akram et al,[86] and was found to be approximately 22%, similar to that in the general population. The most common reported findings in coronary angiography studies are tortuosity (50%), calcification (33%), stenosis (20%), ectasia and slow flow (20%), and spasm (<10%). Myocardial infarction in SSc patients has been reported at a rate of approximately 1.09%.[87] Even though the prevalence of coronary artery disease in SSc is low, subclinical coronary artery atherosclerosis detected by multi-detector computed tomography was found in a majority of SSc patients compared to controls.[88]

Conduction system and arrhythmias

Conduction defects and arrhythmias are seen frequently in SSc patients as a result of focal fibrosis or ischaemia of the conduction system.[15,89-91] Premature ventricular systoles – monomorphic, bigeminy, trigeminy or in pairs – have been reported most commonly (67%) in SSc patients.[90] Atrial fibrillation, atrial flutter and supraventricular paroxysmal tachycardia have been reported in 20-30% of patients. Non-sustained ventricular tachycardia was reported in 7-13% of SSc patients, independently of scleroderma subtype and auto-antibodies.[92] Conduction disturbances due to the presence of fibrosis in the atrioventricular node were found in 25-75% of patients. Sudden death was reported in 5-21%, with the greatest incidence being in patients with myocardial and skeletal muscle involvement.[15,49] In our recent MRI study of 36 SSc patients, the most common arrhythmias were ventricular ectopy and

monomorphic tachycardia, results that were similar to data reported previously.[12,49,90,93] In contrast with previous reports, there was no association between arrhythmias and disease duration, or other clinical parameters such as the extent of skin involvement, the duration of Raynaud's phenomenon or disease subtype. Myocardial fibrosis, autonomic dysfunction early in the disease course,[94,95] and frequent electrophysiological or morphological abnormalities affecting both the atrioventricular node and His bundle,[96-98] seem to play a pivotal role in the pathogenesis of arrhythmic activity in SSc patients. It has been widely reported that these mechanisms are associated with individual groups of scleroderma patients and various stages of the disease course.

Conduction disturbances in SSc are due to fibrosis of the sinoatrial node, presenting as an abnormal ECG with bundle and fascicular blocks, and occur in 25-75% of patients. Second- or third-degree atrioventricular blocks are rare (<2%).[41]

Standard 12-lead ECG and 24-h Holter monitoring are the most widely applied diagnostic modalities for the evaluation of SSc patients with arrhythmias and conduction abnormalities, and should be performed as routine at least once per year. ECG signal averaging can detect a substrate for malignant arrhythmias and identify patients who warrant further investigation.[99] Invasive electrophysiological studies are indicated when a serious sustained arrhythmia is suspected, before proceeding to ablation therapy.[100-102]

The prognostic importance of cardiac arrhythmias in SSc has been identified in previous studies.[90] Mortality rates are higher in patients with cardiac arrhythmias on Holter records compared to patients with normal Holter monitoring findings. In the majority of these patients, a longer duration of the disease course, the diffuse subtype, the presence of anti-topoisomerase I autoantibodies, and other organ involvement (mainly lung and kidneys), dramatically reduce survival.[19]

One thing that should be taken into account in the management of cardiac arrhythmias in these patients is the aetiopathogenesis of the arrhythmias and the comorbidities associated with scleroderma. Antiarrhythmic drugs are the cornerstone of treatment, but drugs should be selected on the basis of their electrophysiological effects, the type of arrhythmia and the other organ involvement. Since no randomised controlled trials have evaluated any of these therapies, they should be tailored to the individual patient. Verapamil-type calcium channel blockers are the preferred option for supraventricular arrhythmias, while digoxin can be used to decrease the ventricular response in atrial fibrillation with respect to renal function. Classic beta-blockers and amiodarone are contraindicated because of the Raynaud's phenomenon and the presence of pulmonary fibrosis, respectively. Life-threatening ventricular tachycardia is an indication for treatment with an implantable cardioverter defibrillator. Radiofrequency ablation is an alternative therapeutic option in patients with drug-intolerant and drug-resistant tachycardia, and has shown great success rates.[101] Pacemaker implantation is the method of choice for the management of serious conduction abnormalities. The early recognition and quantification of myocardial fibrosis with delayed enhanced cardiac MRI could help to identify the group of scleroderma patients at high risk of developing life threatening arrhythmias.[12]

Conclusions and future perspectives

Heart involvement is a major part of the natural history of scleroderma and is associated with increased mortality. Fibrotic changes in the myocardium are the common cause of clinical manifestations of heart involvement in SSc patients. Symptoms of cardiac pathology in SSc usually occur relatively late and are non-specific – thus, they often go unrecognised.[103] This makes early recognition and the initiation of proper treatment difficult.

The concept of cardiac dysfunction in SSc due to myocardial fibrosis has received new interest with the advent of newer non-invasive imaging techniques, as well as the interest in detecting subclinical disease. Nuclear studies and advanced echocardiographic techniques have been applied in recent studies, in order to identify myocardial fibrosis early in the disease course, and to gain a better understanding of its nature and the correlations between the clinical and laboratory characteristics of the disease. Although the various non-invasive methods may reveal functional abnormalities of both ventricles,[12] these measurements are generally not specific for myocardial fibrosis. The renaissance in cardiac imaging would enhance the study of heart involvement in SSc. In particular, cardiac MRI is proving to be an accurate diagnostic tool for myocardial fibrosis early in the disease course.[4,12,51,65,104,105,107] Tissue Doppler imaging and its new application, strain and

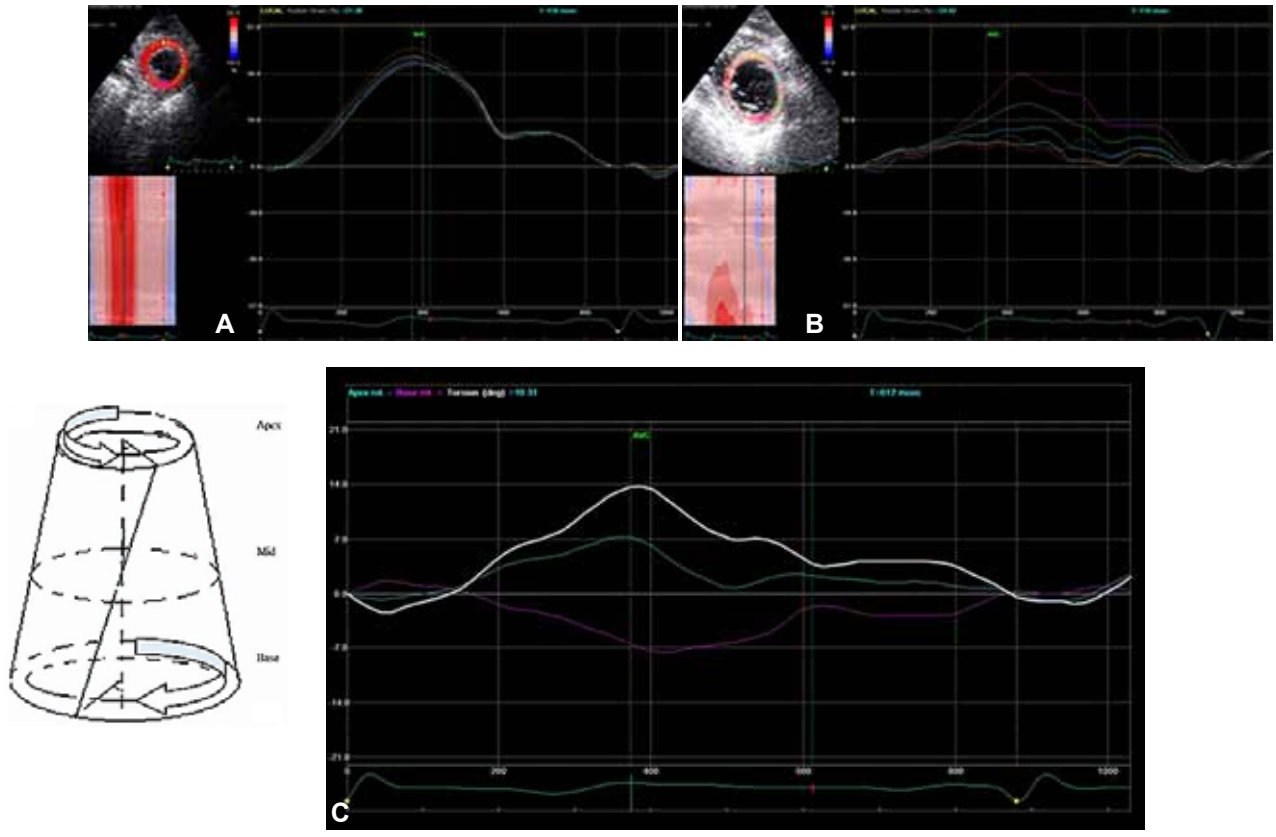

Figure 4. Left ventricular (LV) short axis two-dimensional imaging. The model on the left shows that the LV torsion was defined as the difference between apical and basal rotation. The software segments each plane into 6 parts with different colours (anteroseptal, anterior, lateral, posterior, inferior wall, and interventricular septum). A: Apical rotation curves in one scleroderma case; B: Basal rotation curves in the same case; C: Apical rotation (green line), basal rotation (purple line), LV twist (white line) in the scleroderma patient. This analysis was performed using customised software within the EchoPAC platform (GE Medical Systems). AVC – Aortic valve closure.

strain-rate imaging, could help us to assess regional systolic and diastolic dysfunction of the LV.[33,45,68,106] Speckle-tracking–derived strain and strain-rate is a new method for evaluating LV and RV contractility, through its ability to follow a concrete myocardial region independently of the position or angle of the ultrasound beam.[67] LV torsion and untwisting assessed by speckle-tracking imaging is another modality for the detection of subclinical systolic dysfunction in SSc patients, since it has been postulated that myocardial fibrosis could contribute to myofibre rearrangement and slippage, and might also influence LV torsion (Figure 4).

Newer diagnostic modalities in patients with SSc at various stages of the disease may provide important new insights into cardiac physiology, monitoring its progression and potentially evaluating the effects of therapeutic intervention.

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