REVIEW

Heart involvement in systemic sclerosis: Evolving concept and diagnostic methodologies

Atteinte cardiaque au cours de la sclérodermie systémique : physiopathologie et méthodes diagnostiques

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Summary
Heart involvement, including primary myocardial involvement, is very common in systemic sclerosis. There is strong evidence that primary myocardial involvement is related to repeat focal ischaemic injury causing subsequent irreversible myocardial fibrosis. Clinically evident cardiac involvement is recognized to be a poor prognostic factor; thus preclinical identification is highly encouraged. The severity of heart involvement has been confirmed recently. Echocardiography, including pulsed tissue Doppler echocardiography, is the cornerstone of routine heart assessment. Myocardial perfusion may be assessed by single photon emission computed tomography. If available, cardiac magnetic resonance imaging should be considered as it allows simultaneous measurement of ventricular volumes and function and myocardial perfusion, and assessment of possible inflammation and/or fibrosis. Biological variables, such as B-type natriuretic peptides, are highly relevant, valuable markers of global heart involvement in systemic sclerosis and should be considered for screening of patients and/or research purposes.

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MOTS CLÉS
Myocarde ;

Résumé Les complications cardiaques sont fréquentes chez les patients atteints de sclérodermie systémique, y compris l’atteinte myocardique primitive. Il existe de solides arguments pour affirmer que cette atteinte myocardique primitive est la conséquence d’épisode répétés...
d’ischémie focale génératrice de fibrose myocardique. L’atteinte cardiaque, lorsqu’elle est décelable cliniquement est de très mauvais pronostic ; son identification a un stade plus précoce, préclinique, est recommandée. La sévérité de l’atteinte cardiaque a été confirmée dans des études récentes. L’échocardiographie conventionnelle, incluant la mesure des vitesses annulaires par doppler pulsé tissulaire, est considérée comme la pierre angulaire de l’évaluation chez ces patients. La perfusion myocardique peut être étudiée par tomodensitométrie myocardique. Lorsqu’elle est réalisable, l’IRM s’avère être un outil de choix car elle permet de mesurer les volumes ventriculaires, la fonction ventriculaire gauche et droite, la perfusion myocardique et la recherche d’une possible atteinte myocardique inflammatoire et/ou la fibrose myocardique. Certains paramètres biologiques, les peptides natriurétiques de type B, sont des marqueurs puissants d’atteinte cardiaque et pourraient être utiles pour la détection des patients devant bénéficier d’autres explorations cardiaques ou comme critère d’évaluation pour la recherche.

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Abbreviations

- CCB: calcium channel blocker
- CI: confidence interval
- LVEF: left ventricular ejection fraction
- NT-pro-BNP: N-terminal prohormone brain natriuretic peptide
- SSc: systemic sclerosis
- TDE: tissue doppler echocardiography

Introduction

SSc is a connective tissue disease characterized by widespread vascular lesions and fibrosis of the skin and internal organs. Cardiac involvement is often clinically occult, but is recognized as a poor prognostic factor and is one of the leading causes of mortality in patients with SSc [1].

Cardiac involvement may affect the endocardium, myocardium and pericardium, separately or concomitantly. As a consequence, pericardial effusion, auricular and/or ventricular arrhythmias, conduction disease, valvular regurgitation, myocardial ischaemia, myocardial hypertrophy and heart failure have been reported. In addition, pulmonary arterial hypertension and renal and lung involvement can affect cardiac status adversely [1]. In order to narrow the focus on specific involvement, most of the data we present in this review relate to primary myocardial involvement.

Prevalence and prognosis of overall cardiac involvement

The prevalence of overall cardiac disease varies between studies depending on the methods used for its assessment. Most available data are based upon clinical evaluation, electrocardiogram and thoracic X-ray. Several lines of evidence suggest that both cutaneous subtypes could be affected by cardiac involvement [1,2]. However, an Italian epidemiological study suggested that heart involvement might be more prevalent in the diffuse subtype (32%) than in the limited form (23%) [2]. Such an association has been confirmed recently in a study that focused on depressed LVEF and reported on more than 7000 patients [3]. In addition, data from Perera et al. showed that antitopoisomerase I antibody-positive patients, with the limited or diffuse cutaneous subtype, and with rapid or intermediate skin thickness progression rate, are at considerable early risk of the occurrence of SSc-associated cardiac problems [4]. Indeed, 41% of patients classified as being in the "rapid skin thickness progression subgroup" had cardiac involvement. Among those patients with cardiac involvement, 75% developed cardiac involvement within 3 years of the onset of skin thickening [4].

In an international meta-analysis, among 1645 cases, 578 deaths occurred over 11,521 person-years of follow-up. In multivariable analyses adjusted for age and sex, cardiac involvement (defined by major conduction disturbances, ventricular arrhythmia, heart failure or persistent moderate-to-large pericardial effusion detected by echocardiography) increased the risk of mortality (hazard ratio 2.8; 95% CI 2.1–3.8) as well as renal involvement (hazard ratio 1.9; 95% CI 1.4–2.5), pulmonary involvement (hazard ratio 1.6; 95% CI 1.3–2.2) and antitopoisomerase I antibodies (hazard ratio 1.3; 95% CI 1.0–1.6). Moreover, renal, cardiac and pulmonary involvement tended to occur concomitantly [5]. Such a severity has been confirmed recently in a series of 366 Hungarian patients; 65% of the observed deaths were attributed to cardiopulmonary complications of the disease [6].

Apart from cardiac involvement, pulmonary hypertension may also have a negative effect on the prognosis of patients with SSc. Indeed, two recent studies included patients with mean pulmonary arterial pressure ranging from 40 to 50 mmHg [7,8]. Three-year survival ranged from 28 to 48% in these studies and was reduced significantly compared with primary pulmonary hypertension or systemic lupus erythematosus-associated pulmonary hypertension [7,8]. As pulmonary hypertension is often associated with both right and left ventricular involvement in SSc, one may speculate whether such specific cardiac involvement contributes to the observed high mortality rate [9].

Different manifestations of cardiac involvement in SSc and their prevalence

SSc may be complicated by several distinct cardiac manifestations. Of these, depressed myocardial contractility is supposed to be specific, and the "hallmark" of primary
Pathophysiology of primary myocardial involvement

SSc vascular lesions result in general impairment of the microcirculation. Despite the predominance of vascular abnormalities and documented ischaemia, some studies do not support a higher prevalence of atherosclerotic coronary artery disease in SSc patients than in the general population [13,18]; however, the exact prevalence of atherosclerotic coronary artery disease remains to be determined.

Myocardial fibrosis is thought to occur after repeated focal ischaemia, resulting from abnormal vasoreactivity, with or without associated structural vascular disease. Studies demonstrating the effect of vasodilator agents on perfusion abnormalities further emphasize the potential role of coronary vasospasm. The observations by SPECT of myocardial perfusion defects unrelated to coronary artery distribution and the reversibility of some perfusion defects after vasodilator treatment, which coexist with fixed defects, do suggest the coexistence of ischaemic lesions such as vasospasm and irreversible lesions such as organic vessel disease or myocardial fibrosis [1]. Indeed, some histological examinations have revealed diffuse patchy fibrosis, with contraction band necrosis unrelated to epicardial coronary artery stenosis [19], whereas other studies have revealed concentric intimal hypertrophy associated with fibrinoid necrosis of intramural coronary arteries [20]. Typical pathological findings include disseminated plaques of myocardial fibrosis, normal epicardial coronary arteries but arteriolar concentric intimal hypertrophy, which leads to impaired coronary reserve (Fig. 1).

Risk factors for primary myocardial involvement

To investigate the potentially relevant risk factors for myocardial involvement, we first studied the EUSTAR database [3]. By multiple regression analysis, age, sex, diffuse cutaneous disease, disease duration, digital ulcerations, renal and muscle involvement, disease activity score, pulmonary fibrosis and pulmonary arterial hypertension were associated with left ventricular dysfunction [3]. In a second phase, we performed a case-control study of a patient subset of the EUSTAR database, to further identify independent factors associated with left ventricular dysfunction by simple and multiple regression, including variables not registered in the EUSTAR database, and matched for disease duration. Overall, 129 SSc patients with LVEF <55% were compared with 256 SSc patients with normal LVEF, and we demonstrated that male sex (odds ratio 3.48; 95% CI 1.74—6.98), age (odds ratio 1.03; 95% CI 1.01—1.06), digital ulcerations (odds ratio 1.91; 95% CI 1.05—3.50), myositis (odds ratio 2.88; 95% CI 1.15—7.19) and no use of CCBs (odds ratio 0.41; 95% CI 0.22—0.74) were independent factors associated with left ventricular dysfunction [3]. Interestingly, typical cardiovascular risk factors were not associated with a reduced LVEF. Overall, these findings may suggest that markers of severity of SSc, as well as markers of microvascular lesions (i.e., digital ulcerations), are associated with reduced LVEF.
Another important finding of the nested study was the markedly lower proportion of patients with reduced LVEF who had been treated previously with CCBs, especially for >12 months [3]. In addition, this study suggests that immunosuppressive therapies are not associated with reduced cardiac involvement [3]. However, our registry does not allow the efficacy of immunosuppressors to be ruled out in the specific context of myocarditis associated with SSc.

From a different perspective, our study suggests strongly that CCBs have protective effects against the development of left ventricular dysfunction. Our result is concordant with previous short-term studies, which showed beneficial effects conferred by CCBs on myocardial perfusion and function, using various methods of assessment [1,21,22]. In patients presenting with the limited cutaneous SSc subtype, Steen and Medsger found that patients presenting with pulmonary arterial hypertension were treated with CCBs significantly less often than patients without pulmonary arterial hypertension [23].

In another study, the development of digital ulcers was also delayed by vasodilator therapy [24]. Altogether, these observations suggest that CCBs protect against microvascular complications, including in the heart. Therefore, pending the results of long-term prospective study, we recommend the broad use of CCBs in patients with SSc, unless contraindicated.

**Assessment of heart involvement**

A few decades ago, radionuclide ventriculography was recommended for heart function assessment. While it has been supplanted progressively by echocardiography, it should be still considered in some patients with poor echogenicity (<5%) and for research purposes. Doppler echocardiography together with clinical evaluation has been proposed as the candidate method for routine cardiac assessment, as it should detect all types of SSc cardiac complications [25]. Recent studies suggest, however, that these indexes may lack sensitivity and do not allow a prompt diagnosis at a preclinical stage, when therapeutics are supposed to be more effective. Indeed, new methods such as magnetic resonance imaging and strain rate imaging have been shown to be more sensitive methods than conventional echocardiography [9,15,16,26]. While these methods should be encouraged for research purposes, we acknowledge that they may not be recommended for standard evaluation. Pulsed TDE has emerged in recent years as a robust indicator of both left and right ventricular contractility, as well as left ventricular filling patterns. In the specific context of SSc, we and others have demonstrated that the implementation of conventional echocardiography with mitral and tricuspid annular velocities measurements resulted in greater detection of cardiac complications [9]. Considering the availability of pulsed TDE, it has been suggested that it should be considered for routine evaluation of patients with SSc [9].

The investigation of myocardial perfusion and microcirculation may also be considered for some SSc patients. Single photon emission computed tomography was proposed a few years ago for the assessment of myocardial perfusion abnormalities and possibly for distinguishing reversible ischaemia from irreversible lesions. However, this procedure is limited in quantitative studies [1] and has been supplanted progressively by cardiac magnetic resonance imaging, as it allows the identification of small subendocardial perfusion defects, but also coronary flow reserve determination, the identification of myocarditis (especially in patients with myositis) and the morphological evaluation of fibrotic myocardium compared with viable tissue [27] (Figs. 2 and 3). In addition, cardiac magnetic resonance imaging also appears to be a rapid and non-invasive means of determining subclinical right myocardial involvement [28] and is under development for the assessment of the right ventricle in secondary heart involvement related to pulmonary arterial hypertension [29].

With respect to the various possible cardiac complications of SSc, and considering the impact of repeated (at least twice a year) echocardiography coupled with pulsed TDE, screening methods may be advocated.

One would think that the 6-minute walk test might be adequate, as it is a simple, safe and reproducible test that is used largely in the evaluation of several moderate-to-severe heart or lung diseases. However, conflicting results have been reported regarding its use in SSc. In a recent study, we investigated 87 patients with SSc and demonstrated that the
Figure 2. Cardiac magnetic resonance imaging. Left ventricular short-axis acquisition immediately after the injection of gadolinium (a: first-pass myocardial perfusion) and 10 min after injection (b: delayed enhancement). Early subendocardial hypoenhancement of the left ventricular lateral wall shown on first-pass perfusion is related to impaired microcirculation (coronary computed tomography angiography was normal). Delayed enhancement exhibits linear subendocardial hyperenhancement in the lateral wall and focal intramyocardial hyperenhancement in the septal wall, highly suggestive of myocardial fibrosis.

6-minute walk test relates to broad factors; our results question highly the specificity of the 6-minute walk test in this systemic disease and its relevance for monitoring therapy in the context of SSc [30].

A more attractive solution is the use of natriuretic peptides. Indeed, we have demonstrated that elevated serum NT-pro-BNP is a sensitive and specific diagnostic marker of early elevated systolic pulmonary artery pressure in SSc [31]. In another study, NT-pro-BNP levels correlated with haemodynamics and prognosis in patients with established pulmonary arterial hypertension [32]. Recently, we suggested that both lung diffusion carbon monoxide capacity and NT-pro-BNP levels can be used to identify SSc patients at high risk of the development of pulmonary arterial hypertension [33]. Apart from their role in the detection/management of pulmonary arterial hypertension, natriuretic peptides are candidate markers for the detection of left/right ventricular dysfunction. In a recent article, we reported a study of 69 consecutive patients with SSc (mean age 56 ± 13 years, 56 women) using echocardiography enhanced by pulsed TDE measurements, and plasma NT-pro-

Figure 3. Cardiac magnetic resonance imaging. Left ventricular short-axis acquisition immediately after the injection of gadolinium. Early hyperenhancement of the left ventricular inferior wall related to myocardial inflammation.

BNP [34]. Overall, 18 patients had manifestations of cardiac involvement, of whom seven had depressed left ventricular myocardial contractility, eight had depressed right ventricular myocardial contractility and eight had elevated systolic pulmonary arterial pressure. In this study, we confirmed that NT-pro-BNP correlated with pulmonary arterial pressure and correlated inversely with left ventricular contractility. Moreover, we demonstrated that NT-pro-BNP detected accurately patients with depressed myocardial contractility and overall cardiac involvement (area under the curve 0.905 [0.814–0.996] and 0.935 [0.871–0.996], respectively) (Fig. 4) [34]. Considering SSc patients with normal echo-

Figure 4. Receiver operating characteristic (ROC) curve for the detection of overall cardiac involvement by N-terminal prohormone brain natriuretic peptide.
diography and TDE as controls, and using a 125 pg/mL cut-off concentration as recommended by the manufacturer for ambulatory patients, sensitivity and specificity were 92% and 71% in the detection of depressed myocardial contractility and 94% and 78% for overall cardiac involvement, respectively [34].

**Recommendations for assessing heart involvement in routine practice**

Doppler-echocardiography together with clinical evaluation should be considered for routine cardiac assessment [25]. Given the broad availability and sensitivity of pulsed TDE, we believe that it should be included in all cardiac evaluations in routine practice [9].

B-type natriuretic peptides have emerged in recent years as candidate markers for the diagnosis of both pulmonary hypertension and primary myocardial involvement in the specific context of SSc [34]. Given the simplicity, robustness and wide availability of brain natriuretic peptide and NT-pro-BNP assays, we recommend its use for the detection of any cardiac involvement in SSc patients, and believe that it might become the test of first choice for risk stratification and for following the cardiac status of patients with SSc.

Magnetic resonance imaging should be considered in some selected SSc patients to investigate myocardial perfusion and microcirculation or in the context of suspected myocarditis.

**Conclusion**

Cardiac involvement occurs frequently in SSc and clinicians should not focus solely on pulmonary arterial hypertension. Thanks to recent innovations, clinicians have a large panel of methods, some of which should possibly be reserved for research, and others that seem to be widely available and suitable for routine clinical practice. Indeed, conventional echocardiography, pulsed TDE and natriuretic peptides may be used for routine assessment. Magnetic resonance imaging and strain rate imaging are unavailable for routine use as yet, and may only be considered in specific patients or for research purposes.

**Conflicts of interest**

None.

**References**


