RHEUMATOLOGY

Review

Cardiac arrhythmias and conduction defects in systemic sclerosis

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Abstract

Signs and symptoms of arrhythmias or conduction defects are frequently reported in patients with SSc. These rhythm disorders may have several origins (i.e. related to primary heart involvement, pericardial disease, valvular regurgitation or pulmonary arterial hypertension) and may negatively affect the overall prognosis of these patients. It is therefore important to identify patients at high risk for cardiac arrhythmias with a complete cardiological evaluation and to identify the underlying heart disease, including SSc-related myocardial involvement. In addition, some therapeutic options in SSc patients may differ from those recommended in other populations.

Key words: systemic sclerosis, arrhythmias, conduction defects, cardiac involvement, mortality.

Introduction

SSc is a systemic disease with multiple organ involvement. Although only relatively recently recognized, the heart is frequently affected and the presence of cardiac involvement portends a poor outcome for the patient [1, 2]. Cardiac manifestations of SSc can affect all structures of the heart and may result in pericardial disease,

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arrhythmias, conduction system abnormalities, direct myocardial disease such as myositis, cardiac failure, cardiac fibrosis, coronary artery diseases and, rarely, primary valvular involvement. Primary myocardial manifestations (without systemic or pulmonary hypertension and without significant pulmonary or renal disease) result from the underlying vascular lesions and fibrosis that impair microcirculation and myocardial function, respectively [3].

Several reports have described electrocardiographic abnormalities in SSc. Whether electrocardiographic abnormalities are a consequence of myocardial involvement in SSc, transient oxygen-supply imbalance or other mechanisms remains uncertain [4–6].

An abnormal ECG is present in 25–75% of patients with SSc and is considered an independent predictor of mortality [7, 8]. Arrhythmias may be associated with poor outcome and represent 6% of the overall causes of death in the large European League Against Rheumatism (EULAR) Scleroderma Trials and Research (EUSTAR) database [9]. Out of 128 SSc-related deaths, 33 (26%) were of cardiac origin, with about half of them due to malignant arrhythmias [9]. One report from the Genetics Versus Environment In Scleroderma Outcome Study (GENISOS) cohort, which included 250 patients with 3 years of disease duration, showed a total of 52 deaths, with 29 deaths (55.8%) related to SSc. In the final multivariable Cox model that included non-genetic candidate risk factors

simultaneously in the analysis, only seven variables were independent predictors of mortality: BMI, age, forced vital capacity, blood pressure, pulmonary fibrosis, anti-centromere antibody and cardiac arrhythmias [hazard ratio (HR) 2.18 (95% CI 1.05, 4.50); $P = 0.035$ for cardiac arrhythmias] [10].

Arrhythmias

In a study by Ferri *et al.* [11], resting ECG showed one or more abnormal features in 22/53 (42%) SSc patients. Rhythm disturbances were demonstrated in 30% of patients, but when 24-h Holter ECG monitoring was performed, supraventricular arrhythmias were documented in 66% of SSc patients and ventricular arrhythmias were found in 90%, with multiform ventricular premature beats in 40%, pairs of runs of ventricular tachycardia in 28%, and one or more runs of ventricular tachycardia in 13%. The prevalence and severity of ventricular arrhythmias did not correlate with clinical variants or with other clinical symptoms and signs of the disease. Abnormal ventricular arrhythmias were more likely in patients with echocardiographic abnormalities, although ECG results were normal in about half of the patients who had ventricular arrhythmias. It is generally acknowledged that ventricular arrhythmias, particularly multiform and/or repetitive ventricular premature beats, have a poor prognosis when associated with impaired myocardial function. The high incidence of arrhythmias in this study may be explained by both the high sensitivity and lower specificity of Holter ECG [11].

A multicentre ambulatory ECG study in 183 SSc patients showed ventricular ectopy in 67% of patients, and this abnormality correlated with total mortality and sudden death. Episodes of ventricular tachycardia and supraventricular tachycardia were also observed in 7% and 21% of patients, respectively [8]. Despite the very frequent occurrence of ventricular arrhythmias, sudden cardiac death is not very common in SSc. A large observational study reported sudden cardiac death in 18 (5%) of 391 deaths occurring in 1258 SSc patients, and severe cardiac arrhythmias with a poor prognosis were significantly more frequent in patients with concomitant skeletal and cardiac muscle involvement [12]. In a meta-analysis evaluating 436 consecutive cases, Follansbee *et al.* [6] reported the presence of an abnormal ECG in 46% of patients. Focusing the analysis on 100 selected SSc subjects presenting with evident cardiac abnormalities as assessed by a detailed cardiopulmonary evaluation or who died of more advanced disease, an abnormal ECG was found in 95% of cases.

Many electrophysiological abnormalities can be revealed only after careful and specific cardiac workup. Rokas *et al.* [13] assessed SSc patients without evidence of myocardial involvement and arrhythmias by rest and 24-h Holter ECG, echocardiography and radionuclide ventriculography. They found one or more of significant supraventricular or ventricular tachyarrhythmia, sinus node dysfunction and atrioventricular conduction delay in 57% of the patients. The marked atrial conduction delay probably occurs because of depression of the conduction velocity of abnormal atrial fibres, changes in the resting membrane potential, the action potential amplitude or the maximal velocity of the action potential upstroke, which are all associated with depressed conduction velocity and abnormal excitability. This high prevalence in the absence of any clinical symptoms or signs on standard ECG highlights the need for complete investigation, even at an early stage of the disease, long before the clinical manifestations of scleroderma heart disease (SHD) have appeared.

Other parameters that can be evaluated in SSc patients during 24-h Holter ECG monitoring are heart rate variability (HRV) and heart rate turbulence (HRT). HRV is a measure of cardiovascular autonomic activity and its decrease after myocardial infarction is thought to be associated with increased cardiovascular risk. HRT describes a fluctuation during sinus cycle length that occurs after a ventricular premature beat. It is controlled by the autonomic nervous system and reflects baroreflex sensitivity. As observed in post-infarction studies, HRT impairment is an independent risk factor for malignant ventricular arrhythmia and sudden cardiac death. Bielous-Wilk *et al.* [14] analysed 27 SSc patients without clinically evident heart disease and observed a significantly greater number of premature contractions (supraventricular and ventricular), indicating a possible arrhythmogenic substrate within myocardium. Four patients also manifested supraventricular tachycardia. Several studies demonstrated impairment of HRV in time and frequency domains as well as HRT, confirming that patients with SSc develop cardiac autonomic nervous system dysfunction [14, 15]. Moreover, HRT seems to be a potential useful tool for the identification of patients at risk for ventricular arrhythmia, and might be considered an independent risk factor for mortality in SSc, although further studies are warranted before recommending routine HRT measurement in all SSc patients [15].

Conduction and other frequent ECG abnormalities

An interesting autopsy study in 35 SSc patients showed focal fibrotic changes in the specialized conduction tissue of the heart, but they were not unequivocally related to the presence of SSc-type myocardial fibrosis. In fact, they were generally present with equal frequency in the group of patients with and without SHD. Moreover, they are infrequently of clinical significance. Although conduction abnormalities were more common in SSc patients with myocardial disease, specific conduction system disease was not the cause of death in most patients. In fact, the conduction system appeared to be relatively spared from the myocardial changes of SSc, and the high incidence of conduction disturbances may be a consequence of, rather than caused by, specific damage to the proximal portion of the specialized conduction tissue [16]. In a prospective study, 16 of 50 SSc patients (32%) had resting ECG conduction abnormalities. The most common alteration was left bundle branch block (16%), followed by first-degree atrioventricular block (8%), while second- and

third-degree atrioventricular block were infrequent (<2%) [7]. In a large study by Ferri *et al*. [11], resting ECG demonstrated conduction defects in 19% and ST-T changes in 5%. Moreover, this prevalence increased to 34% for ST-T changes and to 33% for A-V block (mostly first- or second-degree atrioventricular block) when 24-h Holter monitoring was performed. Other authors showed a similar prevalence of conduction disturbances. In addition, QTc prolongation, which can lead to life-threatening tachyarrhythmias, has also been reported [17].

An electrocardiographic study performed in 102 SSc patients investigated the functional correlates of the abnormalities found in 48 patients in whom detailed cardiac physiological data were available. About 50% had normal findings on ECG; the most common ECG abnormality was isolated nonspecific ST-T wave changes (14%), and conduction abnormalities were common (17%). Functional correlations showed that 5/48 (10%) had septal infarction pattern and 10/48 (21%) had ventricular conduction defects. Four of the five (80%) patients with septal infarction pattern had septal or anteroseptal thallium perfusion defects; the fifth had an inferoapical perfusion defect. In four of the five cases, the perfusion defects were fixed, suggesting underlying myocardial fibrosis. Six of the 10 (60%) patients with ventricular conduction abnormalities also had septal or anteroseptal thallium perfusion abnormalities. All six had fixed perfusion defects, and four of the six also had redistribution defects. Therefore 10/15 (67%) SSc patients with one of these ECG abnormalities had a septal or anteroseptal thallium perfusion defect compared with 6/33 (18%) of the remainder ($P < 0.005$). Three patients with septal infarction pattern and three with ventricular conduction defects underwent coronary angiography. All had septal thallium perfusion abnormalities, but all six had normal coronary angiography results. Septal infarction pattern seemed to be an unrecognized ECG abnormality associated with SSc, related to abnormal perfusion in the septum and anteroseptal wall in the absence of extramural coronary artery disease. These fixed defects suggested underlying myocardial fibrosis, consistent with the hypothesis that septal infarction pattern or ventricular conduction abnormalities identify more advanced myocardial involvement in patients with SSc [6].

Pathophysiological alterations

Cardiac involvement is the result of microvascular alterations, collagen overproduction by altered fibroblasts with extracellular matrix deposition and complex immune system dysregulation. A variable combination of the above mechanisms leads to ischaemic, fibrotic and inflammatory lesions involving all cardiac structures, including the cardiac conduction system. Histology examinations revealed the presence of patchy myocardial fibrosis that could involve the conduction system in SSc [7, 16]. However, it is unclear whether fibrosis is the only underlying pathology responsible for these conduction defects. Ridolfi *et al.* [16] concluded that focal fibrotic changes may be present within the sinoatrial node and

proximal portion of the bundle branch system, but they are unrelated to the presence of SHD, as it was found with equal frequency in the group of patients without SHD. The majority of conduction defects appear to be a consequence of damaged myocardium rather than specific damage to the proximal portion of the specialized conduction tissue. The conduction tissue of the heart was relatively spared from injury by the SSc disease process when compared with the changes seen within the contracting myocardium. Moreover, compared with the contractile myocardium, specialized conduction tissue appears to be less sensitive to ischaemic injury, arguing against the so-called intra-myocardial RP, which suggests that focal contraction band necrosis is caused by intermittent spasm before evolving to focal replacement fibrosis. This may explain the relatively rare involvement of the conduction system of the heart by the SSc process [16].

In contrast, other authors found an association between atrioventricular node fibrosis and first-degree atrioventricular block [7]. Interestingly, a recent cardiac MRI study on SSc patients reported a correlation between the presence of cardiac arrhythmias, conduction disturbances and myocardial fibrosis [18]. Analysis of Holter monitoring data showed that 19/36 patients (53%) had abnormal study results. Among the 19 patients, 12 (63%) had premature ventricular contractions, 2 (10.5%) had supraventricular tachycardia, 3 (16%) had premature atrial contractions, 2 (10.5%) had atrial fibrillation and 2 (10.5%) had non-sustained ventricular tachycardia. Two additional patients (10.5%) had right bundle branch block and one patient (5%) had left bundle branch block. Compared with the 17 patients with normal Holter study results, patients with abnormal results were more likely to have pulmonary hypertension by Doppler echocardiography, a decreased left ventricular (LV) ejection fraction, an increased right ventricular (RV) diameter and a greater number of enhancing myocardial segments at delayed enhanced cardiac MRI study [18].

Studies that correlate autoptic findings with cardiac MRI abnormalities are not presently available, but we can make some indirect correlations. Cardiac MRI enables analysis of the different patterns of heart involvement in SSc by differentiating morphological, functional, perfusion and delayed contrast enhancement abnormalities. The high frequency of heart abnormalities observed on cardiac MRI is consistent with necropsy studies, which have shown that approximately 80% of patients with SSc have histological lesions of heart involvement [19].

In the large EUSTAR database, the prevalence of LV dysfunction is 5.4%, and conduction abnormalities on ECG have been observed in 33% of patients with depressed LV ejection fraction [20].

The frequent ECG abnormalities observed in these studies indicate the presence of alterations in the cardiac centres of impulse formation and conduction, and suggest that electrical instability of the heart is an integral clinical feature of SHD [7].

A recent study evaluated myocardial dysfunction using novel speckle-tracking strain. Of a total of 104 patients

with SSc [53 dcSSc; mean age (S.D.) 54 (12) years, 77% female], 28 patients had abnormal findings (ventricular tachycardia or ventricular ectopics > 100/day) on ECG Holter monitoring. Compared with SSc patients with normal results on ECG Holter monitoring, SSc patients with abnormal results showed impaired global longitudinal strains [mean −18.5% (S.D. 1.5) vs −17.1% (2.1); $P < 0.01$] and circumferential strains [mean −18.7% (S.D. 2.0) vs −17.3% (2.5); $P = 0.01$], and each strain measure was independently associated with abnormal Holter findings.

The predictive value of such findings remains to be established but it strengthens the proposed relationship between myocardial impairment and rhythm disturbances [21].

In conclusion, fibrosis, dynamic vasospasm and inflammation of the heart and small heart nerves are possible causal factors. Sympathetic autonomic nervous system activation resulting from even subclinical heart failure, and a subsequent recruitment of baroreceptors, may also be important causal factors and may contribute to the severity of SHD [12].

Diagnostic workup

The cardiac workup in patients with SSc includes routine and second-level investigations, both for electrical assessment and heart evaluation, as summarized in Table 1. Standard 12-lead ECG as well as Doppler echocardiography should be performed routinely in all SSc patients, even if the patient is asymptomatic. If the patient complains of palpitations, syncope or dizziness, the next steps must include exercise testing, upright tilt-table testing and 24-h Holter monitoring.

When significant changes are detected in the conduction and rhythm systems, careful investigations for heart disease must be performed. First, classic cardiovascular risk factors should be assessed together with any potential signs or symptoms of ischaemic heart disease. If SHD is suspected, echocardiography should be performed, when possible, by pulsed Doppler. In addition, cardiac MRI to evaluate tissue damage may be considered, particularly if there are any signs of myositis, in order to rule out myocarditis, which demands specific management [22].

Although not yet endorsed by any guideline, given the high prevalence and the prognostic significance of arrhythmias and conduction defects, we believe that 24-h Holter monitoring should be considered as part of routine evaluation in SSc patients, even if asymptomatic, every 1–2 years. A validation study to determine the possible impact of such an attitude and the ideal time interval is warranted. The patient should also be questioned about the presence of systemic illnesses that can be associated with arrhythmias such as chronic obstructive pulmonary disease, hyperthyroidism, pericarditis and congestive heart failure. Moreover, in SSc, several complications might favour arrhythmia, such as life-threatening infections related to severe motility disorders of the intestine or electrolyte imbalance because of gut or kidney involvement [23]. Measurement of HRT and HRV should be considered in selected patients after detailed clinical, echocardiographic and standard ECG and Holter monitoring evaluations. Invasive electrophysiological studies are indicated in patients who have atrioventricular block, intraventricular conduction disturbance, sinus node dysfunction, tachycardia and unexplained syncope or palpitations [24].

Treatment

Since different classes of anti-arrhythmics are available, and SSc patients may have multiple organs involved and take concomitant drugs, the choice of treatment must be personalized to the individual patient. Conduction abnormalities and arrhythmias may be an adverse effect of some drugs commonly used by such patients. Corticosteroids, in particular, high i.v. doses of methylprednisolone, although rarely used in SSc, are associated with tachyarrhythmias. MTX may rarely induce right bundle branch block and ventricular arrhythmias. HCQ is safer than chloroquine in terms of heart conduction disorders. Some epidemiological studies have reported the relation between domperidone and serious ventricular arrhythmia or sudden cardiac death. Because of the

TABLE 1 Cardiac diagnostic workup in patients with SSc for investigations of electrical disturbances

Clinical manifestation	Electrical assessment	Heart assessment
Fatigue Palpitations Syncope, fall Dizziness	Routine: CV risk factor assessment Standard 12-lead ECG 24-h Holter monitoring Second level: Exercise testing Upright tilt-table testing Invasive electrophysiological studies Measurement of HRT and HRV	Routine: Doppler echocardiography Tissue Doppler echocardiography Natriuretic peptides Second level: Coronary angiography Right heart catheterization Cardiac MRI

CV: cardiovascular; ECG: electrocardiogram; HRT: heart rate variability; HRV: heart rate turbulence.

frequency of gastrointestinal (GI) involvement and the widespread use of prokinetic drugs in SSc, clinicians must be aware of such risk. Moreover, potential harmful effects in SSc patients regarding other organ involvement might be a matter for future research [25, 26].

As no randomized controlled trials have been performed specifically in SSc patients, the choice of therapy should be similar to that of patients without SSc, but physicians should keep the following in mind:

(i) The negative effect of β-blockers on RP, except for the new molecules, such as metoprolol, that seem to reduce symptoms in patients suffering from RP when co-administered with calcium channel blockers [27].

(ii) The beneficial effect on RP offered by calcium channel blockers as well as their possible preventive effect on LV ejection fraction deterioration. Nifedipine has been associated with tachycardia, possibly through a sympathetic reflex. However, most of these occurred when nifedipine was used as a tocolytic at high dosage for preterm labour. Previous reports have shown that an increase in heart rate is of very limited impact except for patients with advanced coronary artery disease, rarely documented in SSc. In addition, an improvement in LV ejection fraction, LV contractility, LV filling and RV contractility after calcium channel blocker use in SSc has also been reported [28, 29]. Thus verapamil-like calcium channel blockers might be recommended in the treatment of atrial or intranodal tachycardia, although their efficacy is somewhat limited.

(iii) The prevalence of myocardial ischaemia and, as a consequence, the possible detrimental effect of class I anti-arrhythmic drugs.

(iv) Amiodarone is the most effective antiarrhythmic drug. Side effects include immuno-allergic pneumonia. There is no evidence that pre-existing pulmonary fibrosis increases the risk of immuno-allergic pneumonia, but it will worsen its consequences.

Implantable cardioverter defibrillators (ICDs), which monitor the cardiac rhythm and can deliver competing pacing stimuli and low- and high-energy shocks, have been used effectively in selected patients to prevent malignant ventricular arrhythmias. There is no specific recommendation in SSc patients; an ICD should be considered in patients at high risk of sudden death, in secondary prevention and in primary prevention for patients with an LV ejection fraction <30% (35% if ischaemic) and with proven symptomatic ventricular tachyarrhythmia. One should keep in mind that ICD should be considered only in patients without advanced organ failure other than the heart. An ICD was implanted in 10 patients with SSc who had cardiac involvement, mainly related to diastolic dysfunction. After 36 months, analysis of the device showed several episodes of ventricular tachycardia in three patients, which were promptly reverted by electrical shock delivery [30].

Catheter ablation therapy allows the destruction of a delimited atrial/ventricular zone. During the last decade, the risk of side effects has been reduced and its indication has been defined. Thus it should be considered as first-line therapy in patients with recurrent re-entrant tachycardia or atrial flutter, in patients with symptomatic, sustained, monomorphic ventricular tachycardia resistant or intolerant to pharmacological treatment and in patients with recurrent symptomatic atrial fibrillation despite anti-arrhythmic drugs.

Pacemaker implantation is the treatment of choice for complete heart block and other serious bradyarrhythmias [17].

Conclusion

Arrhythmias and conduction defects are important and frequent manifestations of cardiac involvement in patients with SSc. These abnormalities may be mild, but can also lead to a fatal outcome. The underlying arrhythmogenic mechanisms are not well understood, but myocardial damage and fibrosis seem to be the most important factors. Whether or not an appropriate treatment might affect the disease process in the myocardium remains to be confirmed. However, early recognition of life-threatening ventricular arrhythmias may be crucial in improving the overall prognosis of SSc patients.

> **Rheumatology key messages**
> - Arrhythmias and conduction abnormalities worsen the overall prognosis of SSc.
> - Patchy myocardial fibrosis could involve the conduction system in SSc.
> - Anti-arrhythmic treatment must be adapted to the individual SSc patient.

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