Electrocardiographic markers for the prediction of ventricular arrhythmias in patients with systemic sclerosis

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Abstract
SSc is an autoimmune disease characterized by microvascular damage, endothelial dysfunction and fibrosis of the skin and the internal organs. Cardiac manifestation in patients with SSc is one of the major organ involvements. Approximately 20% of SSc patients suffer from primary cardiovascular disease and another 20% may have secondary cardiac involvement. Although cardiac arrhythmias are mostly linked to myocardial fibrosis, atrioventricular conduction abnormalities are secondary to the fibrosis of the pulse conduction system. Despite the severe consequences of ventricular rhythm disturbances in patients with SSc, the exact role of electrocardiographic markers in the prediction of these arrhythmias has not yet been clearly elucidated. Therefore, the question is whether certain ECG parameters reflecting ventricular repolarization may help to recognize scleroderma patients with increased risk for ventricular arrhythmias and sudden cardiac death.

Key words: systemic sclerosis, arrhythmias, sudden cardiac death

Introduction
SSc is an autoimmune disease characterized by diffuse microvascular damage, endothelial dysfunction, fibrosis of the skin and the internal organs [1]. SSc is four times more common in women than in men and its worldwide prevalence is ~150–300 cases per million [2]. Cardiac manifestation in patients with SSc is one of the major organ involvements as a direct consequence of autoimmune activity, microvascular abnormalities and fibrosis; however, it can also develop as a result of interstitial lung disease and pulmonary arterial hypertension. Approximately 20% of patients suffer from primary cardiovascular disease and another 20% may have secondary cardiac involvement [3, 4]. Signs of subclinical cardiac involvement can be detected with cardiac MRI in 75% of SSc patients [5], where pericarditis, myocarditis, arrhythmias, pulse conduction abnormalities, valvulopathies and heart failure (HF) can appear [6]. Unfortunately, 20% of patients with SSc die due to cardiac comorbidities [7]. According to the 2010 EULAR Scleroderma Trial and Research group (EUSTAR) database, 6% of SSc-related cardiovascular mortality was secondary to cardiac arrhythmias [8]. Based on the Spanish Scleroderma Registry, the relative frequency of cardiac involvement in SSc has tripled in the last decade, and patients with scleroderma heart disease had a
higher relative risk for mortality compared with patients with lung and renal involvement (2.8 vs 1.9 and 1.6) [9]. Among SSc patients, the occurrence of hypertension, ischaemic heart disease and dyslipidaemia was higher compared with the control group, and they also had a 2-fold higher need for the implantation of pacemakers and cardioverter-defibrillators [10].

Cardiac arrhythmias are mostly linked to myocardial fibrosis, while conduction abnormalities are secondary to the fibrosis of the pulse conduction system [11–13]. The exact role of electrocardiographic markers in the prediction of these arrhythmias has not yet been clearly elucidated. Therefore, the question is whether certain ECG parameters reflecting ventricular repolarization may help to recognize scleroderma patients with increased risk for ventricular arrhythmias.

Myocardial remodelling in SSc

As a consequence of electromechanical imparity, fibrosis of the myocardium leads to pulse generation and conduction disorders. Collagen deposition between cardiomyocytes can lead to patchy fibrosis in the heart. This pattern is different from the fibrosis due to ischaemic heart disease as the fibrotic tissue accumulates in the whole myocardium including the subendocardial region [4]. In addition, fibrotic patches disrupt the functional units of the heart and form non-conductive blockages that can serve as the electrophysiological substrate for re-entry mechanism and ectopic automaticity [4, 14]. Furthermore, SSc-related oblitative vasculopathy leads to myocardial hypoperfusion, which may aggravate electrical inhomogeneity [2, 15, 16]. Echocardiographic studies have shown that 69% of the SSc population had elevated right ventricular pressure, impaired left ventricular (LV) diastolic function and left atrial enlargement [17]. Simultaneous existence of lung fibrosis and systemic hypertension aggravates the cardiac dysfunction [18]. The hypertrophy and dilation of the right ventricle due to elevated pulmonary vascular resistance and increased right ventricular afterload may lead to malignant ventricular arrhythmias [19]. Systolic dysfunction has been shown to be secondary to structural myocardial deterioration in 5.4% of SSc patients with LV ejection fraction <55% [20]. In another study, symptomatic HF was associated with poor outcome as 75% of SSc patients had <5-year survival [9]. Early occurrence of HF, male gender, BMI <18.5 kg/m², forced vital capacity <50%, blood pressure ≥140/90 mmHg, coexisting pulmonary fibrosis or pulmonary arterial hypertension, the presence of carotid artery atherosclerosis, cardiac arrhythmias or digital ulcers, dcSSc subtype, fast progression of skin thickness, and an older age at disease onset are also known as unfavourable prognostic factors [8, 9, 21–25].

The EUSTAR database, which provides information about 11 193 SSc patients from 124 centres, was analysed by Elhai et al., showing that 27% of patients died of cardiac causes [26]. Ischaemic heart disease, dyslipidaemia, hypertension and diabetes mellitus have been described to aggravate the harmful effects of myocardial fibrosis. The consequent electrical instabiliy and anisotropy of the myocardial tissue (increased spatial dispersion of ventricular repolarization) are considered to play a role in arrhythmogenesis [27].

Ventricular arrhythmias in SSc

Malignant ventricular arrhythmias (e.g. pulseless ventricular tachycardia and ventricular fibrillation) are the third most common death causes in SSc patients, and are responsible for 5% of mortality. In addition, sudden cardiac death (SCD) was registered in 28% of patients with pulmonary hypertension [8, 19, 21, 22]. In the Genetics versus Environment in Scleroderma Outcome Study (GENISOS) cohort study, SSc patients with ventricular arrhythmias had a hazard ratio of 2.18 for SCD compared with arrhythmia-free patients [24]. In a study by Bienias et al., premature ventricular couplets and non-sustained episodes of ventricular tachycardia (VT) were reported in 36% of the studied SSc patients [28]. Recent investigations described pathological ECG findings in 25–75% of SSc cases [29], where non-specific ST-T alterations (12%), pulse conduction abnormalities, bundle branch blocks, pathologic Q waves, signs of atrial and/or ventricular hypertrophy, and low voltage may be observed [24, 30]. According to Draeger et al., right bundle branch block caused a 5.3-fold increase in mortality risk in their scleroderma population [31]. In a study by Ferri et al., arrhythmias appeared in 30% of cases, and ventricular arrhythmias were recognized in 90% of patients [32]. In addition, multiform ventricular premature beats (VPBs) appeared in 40%, ventricular runs were observed in 28% and episodes of VT were detected in 13% of their population [32]. In a paper by De Luca et al., 100 SSc patients were investigated with new onset HF (dyspnoea, ankle oedema, palpitation and chest pain). According to their observations, 56% had electrocardiographic abnormalities and 24% presented frequent VPBs, which positively correlated with high-sensitive cardiac troponin, and negatively correlated with LV systolic function. >1190 VPBs/day has been reported to be a predictive factor of life-threatening ventricular arrhythmias (sensitivity 100%, specificity 83%) [14]. In another study by Muresan et al., 60% of 36 SSc patients had pulse conduction disorder and ventricular arrhythmias and 23.3% had only ventricular arrhythmia without conduction abnormalities. No significant differences have been shown between dcSSc and lcSSc with regard to the occurrence of ventricular arrhythmias [33]. Increased probability of ventricular arrhythmias during the first 3 years of SSc has been demonstrated [29, 30, 34, 35], while in another study higher ventricular arrhythmia frequency has been observed 6 years after the onset of the disease [36].

QT interval and QT dispersion for the prediction of ventricular arrhythmias

QT interval of the 12-lead surface ECG represents the repolarization of the ventricular myocardium. While
prolonged repolarization is linked to an increased susceptibility for ventricular rhythm disturbances, QT interval has been introduced as an electrocardiographic marker for the prediction of ventricular arrhythmias. The interlead difference between QT intervals is known as QT dispersion, which reflects the spatial dispersion of the ventricular recovery times. QT dispersion has also been seen to be different in homogeneous and in-homogeneous myocardial repolarization. Electrolyte imbalances, increased sympathetic tone, myocardial ischaemia or fibrosis, dyslipidaemia and administration of certain drugs (e.g. antiarrhythmics, antimicrobial agents and antidepressants) may prolong QT interval and dispersion [37–42]. The duration of QT interval is highly dependent on ventricular rate; therefore, it has to be corrected to heart rate [corrected QT interval (QTc)]. Bazett’s formula is commonly used for this purpose (QTc = QT/RR, where RR is the RR cycle length of the surface ECG, which represents heart rate). The QTc >450 ms value has been reported to show an increased risk for ventricular arrhythmias. Normal values of QT dispersion may vary in a wide range from 10 to 71 ms [43, 44].

QT interval and dispersion can be measured manually with callipers or by using computer software (Fig. 1). The manual determination of the end of the T wave is not always easy, thus different methods have been introduced for more accurate measurements. Using the threshold method, the end of the T wave is determined as the point where the T wave reaches the isoelectric line. Via the tangent method the end of the T wave is characterized by the intersection of a tangent line and the isoelectric line, where the tangent line is the terminal part of the T wave at the point of the maximum downslope. Three consecutive QT sections are recommended to be measured and averaged to determine the precise QT interval in the given ECG lead. QT measurements can also be performed by computer with the superimposed median beat method, where medians of all 12 leads are superimposed on each other [45–47]. According to previous data no significant differences have been confirmed between the specificity and sensitivity of the manual and computer-based methods [48].

**QT interval and QT dispersion in patients with SSc**

Recently, 14–25% of SSc patients have been reported to show QTc prolongation [49]. In a cohort study by Massie et al., 689 scleroderma patients were examined and QTc duration was found to be longer than 440 ms in 25% of their population. Importantly, QTc prolongation was described in 14.6% of patients with no cardiac symptoms [50, 51]. Rosato et al. described a linear correlation between QTc prolongation and the presence of digital ulcers [49]. De Luca et al. suggested that the prolongation of QT interval may correlate with the severity of SSc [52]. In another study the diagnostic importance of QT prolongation has also been confirmed, where reduced exercise tolerance could be detected together with the prolongation of the QTc interval [53]. Increased QT dispersion has been linked to fibrotic myocardial remodelling and perfusion abnormalities [54, 55]. Ciftci et al. examined QT dynamicity and heart rate variability in SSc patients. QT dynamicity (e.g. the slope of the linear regression line of QT/RR value) has been shown as a predictive factor of ventricular arrhythmias in patients with prolonged QT interval, where increased sympathetic activity and the inhomogeneous electrophysiological nature of the fibrotic myocardium have been assumed to be the underlying substrates [56]. Another ECG parameter, QT variability index, can be derived from the logarithmic ratio of the mean QTc interval and heart rate and the variability of QT interval and heart rate, indicating repolarizational inhomogeneity. Nussinovitch et al. found no significant difference regarding QT variability index between SSc patients and controls. However, the prolongation of QT variability index has been shown in a patient with VT during the follow-up period [57].

**Further ECG markers for the prediction of ventricular dysrhythmias**

T wave peak-to-end interval (Tpe) is determined from the highest point of the T wave until it reaches the isoelectric line in lead V6 [58]. Tpe may refer to a transmural dispersion of the ventricular repolarization and its elevation was described in patients with increased ventricular arrhythmia susceptibility [59]. The arrhythmogeneity index is defined as the ratio of Tpe and QTc interval, and is a reliable predictor of SCD and ventricular arrhythmias [60]. Increased Tpe and arrhythmogeneity index have been
detected by Yayla et al. in 65 SSc patients [61]. Okutucu et al. found increased Tpe and arrhythmogeneity index regarding 107 SSc patients, which were correlated with the modified Rodnan skin severity score [62]. Fragmented QRS complexes have also been recognized in association with cardiac fibrosis. Bayar et al. detected fragmented QRS in more than half of their SSc patients. QRS fragmentation together with an elevated systolic pulmonary arterial pressure (≥24 mmHg) appeared to predict cardiac involvement in scleroderma with a sensitivity of 88% and a specificity of 79% [63]. Interestingly, 10% of SSc patients show an electrocardiographic morphology of septal infarction without the presence of a substantive myocardial infarction [13]. Wider spatial QRS-T angle recorded during Holter monitoring has also been introduced as an independent predictor for SCD [64]. Gialafos et al. examined 69 SSc patients and found a wider QRS-T angle in subjects who developed episodes of ventricular arrhythmias. A spatial QRS-T angle >19.3° had a sensitivity of 80% and a specificity of 68% in the prediction of non-sustained VT [65]. Another arrhythmia marker, heart rate variability, has been shown to significantly decrease in the case of autonomic dysfunction. Heart rate turbulence, e.g., the fluctuation of sinus cycle length mediated by baroreceptor reflex, has been detected after the occurrence of a VPB [27]. Analysing the data of 27 SSc patients, a decrease in heart rate variability and heart rate turbulence have been recognized, suggesting the arrhythmogenic role of autonomic dysfunction in SSc [66].

**Laboratory biomarkers in SSc**

According to the 2013 ACR/EULAR recommendation, positive tests for ANA, anti-Topoisomerase-I antibody (Scl-70), ACA and anti-RNA polymerase III antibody are classification criteria for SSc [67]. In a study by Priora et al. severe cardiac involvement has been recognized in anti-Scl70-positive SSc patients [68]. Further investigations showed that primary scleroderma heart disease is common in the case of anti-Scl70, anti-Ku, antihistone and anti-RNA polymerase (I, II and III) antibody positivity [69]. To evaluate the cardiac involvement in SSc serum troponin, creatine kinase-MB isofrom activity and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels must be measured as well [70]. Barsotti et al. analysed data from 65 SSc patients who underwent echocardiography, electrocardiography and serum high-sensitive troponin (HSTn) level measurement. HSTn level has been found to positively correlate with the occurrence of scleroderma heart involvement. Combined evaluation of HSTn and NT-proBNP levels was found to help in risk stratification. HSTn levels have also been shown to positively correlate with the number of VPBs obtained from 24-h Holter ECG recordings. However, HSTn level has low specificity and sensitivity (83% and 66.7%, respectively) [71]. In scleroderma heart disease, increased serum levels of NT-proBNP were determined, where NT-proBNP levels >50 pmol/l showed a positive correlation with the presence of cardiac involvement (sensitivity 90.5%, specificity 97.6%). Importantly, elevated right ventricle pressure, younger age and reduced kidney function, and the administration of angiotensin-converted enzyme inhibitors, angiotensin-receptor blockers, diuretics and Ca-channel blockers can lower the serum level of NT-proBNP, making the risk stratification more difficult [72]. In further investigations elevated serum levels of IL-6, TIMP-1 and TIMP-2 (MMP inhibitor molecules) were proven to correlate with the presence of LV diastolic dysfunction [73–75]. Among SSc patients an increased serum endostatin level (inhibitor of angiogenesis) was found, which may play a pathogenic role in microvascular damage [76]. Based on recent observations, the UK Systemic Sclerosis Study group suggests regular measurement (at 6-month intervals) of troponin (HSTnT or HSTnI), NT-proBNP and creatine kinase levels. Furthermore, Bissell et al. have also recommended the annual measurement of HbA1c and lipid profile in SSc patients with high cardiovascular risk [69].

**Imaging techniques for the diagnosis of scleroderma heart disease**

2D and M-mode echocardiography is necessary for the evaluation of the structure and function of the heart, since echocardiographic abnormalities have been described in 69% of the scleroderma population [19]. Impaired relaxation of both ventricles based on the tissue Doppler determination of Tei index has been detected in 30% of SSc patients [74]. In the case of high-risk subjects the measurement of pulmonary arterial pressure, the evaluation of systolic and diastolic ventricular function, and the detection of wall motion abnormalities and pericardial effusion are suggested every 6 months [23, 69]. According to Ferri et al., these echocardiographic abnormalities show a stronger correlation with the occurrence of ventricular arrhythmias than the alterations appearing on the 12-lead surface ECG [32]. The application of more accurate imaging techniques, such as speckle-tracking echocardiography, cardiac MRI and SPECT methods are also recommended for the precise assessment of cardiac anatomy and function of patients with scleroderma [29]. During speckle-tracking echocardiography, determination of global longitudinal strain examined from the apical view shows the change of longitudinal length of the studied myocardial segments [77]. Guerra et al. found reduced global longitudinal strains of both ventricles in SSc, thus, speckle-tracking echocardiography may be a valuable method in the determination of subclinical cardiac involvement even at the early stages of the disease [78, 79]. According to Bissell et al., cardiac MR is suggested not only to determine left and right ventricular function, but to clarify the presence of myocardial oedema and inflammation, and to follow the progression of fibrosis [69]. In their cardiac MR study, a significantly higher extracellular volume was recognized after ventricular arrhythmia episodes of 20 SSc patients. Moreover,
extracellular volume showed a positive correlation with the serum levels of HSTnI and NT-proBNP [80].

**Antiarrhythmic management of SSc patients**

Management of scleroderma is highly dependent on the extension, subtype, severity and comorbidities, and the time elapsed from the diagnosis of the disease [81]. In the Very Early Diagnosis of Systemic Sclerosis , multicentre study the ‘red flags’ in the diagnosis of very early scleroderma were defined as ANA positivity, presence of RP and development of puffy fingers. Puffy fingers are considered to be an early symptom of connective tissue disease, which can predict the evolution of RP into SSc [82]. In the case of a longer existing SSc, a pretreatment evaluation should be performed to differentiate between the diffuse and the limited cutaneous forms of SSc. Specific internal organ involvements should also be taken into consideration before determining the therapy [81]. In the case of myocarditis, moderate and severe LV dysfunction and malignant ventricular arrhythmias, the administration of low-dose CS (<15 mg daily) together with CYC therapy can improve the cardiac status and the survival of patients with SSc [69].

Due to a lack of studies with appropriate evidence levels, the antiarrhythmic therapy of scleroderma patients remains empiric. Since amiodarone may enhance pulmonary fibrosis, its use is limited in this particular indication. The sodium channel blockers (Class I antiarrhythmic drugs, e.g. propafenone, quinidine, flecainide, etc.) should also be avoided, as they may cause ischaemia–reperfusion effect and proarhythmia [29]. In autoimmune diseases the beta adrenoceptor antagonist metoprolol and its combination with a dihydropyridine type calcium channel blocker (CCB) (e.g. felodipine) is applicable without the worsening of RP [83]. The beta adrenoceptor antagonists carvedilol and nebivolol have been shown to be applied the most effectively as a treatment for cardiac rhythm disturbances due to their vasodilator properties, without having a harmful effect on Raynaud’s symptoms and peripheral arterial circulation [84]. In the case of scleroderma heart disease, angiotensin-converting enzyme inhibitors and CCBs are thought to be useful therapeutic tools. According to a retrospective study based on the data of 7000 SSc patients, CCBs have been shown to decrease the prevalence of LV dysfunction [85]. The application of dihydropyridine-type CCBs (e.g. nifedipine, felodipine, amlodipine, etc.) in SSc can be favourable; their vasodilator effect improves the peripheral circulation, which increases the perfusion of the myocardium [28, 29]. Furthermore, the beneficial property of nifedipine on myocardial perfusion in SSc patients may appear even after 2 weeks of treatment [86]. Valenti et al. found that 448 out of 601 SSc patients took CCBs combined with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (mainly valsartan and candesartan). During the follow-up period, the vasodilator therapy had to be terminated or modified in only 15 cases due to peripheral vascular adverse effects. Importantly, the administration of vasodilator treatment was associated with a reduced occurrence of ventricular arrhythmias \((P = 0.03)\) [87]. Regarding angiotensin-converting enzyme inhibitors, the use of ramipril (2.5–5 mg/day) may be favourable; in addition to its positive cardiovascular effects, it can also reduce the progression of scleroderma kidney disease [88]. Among non-dihydropyridine CCBs, verapamil is preferred for the treatment of supraventricular arrhythmias in SSc. Digoxin, spironolactone, furosemide, procarcinamide or mexiletine can also be administered in the case of recurrent ventricular arrhythmias [84, 89]. Wada et al. have shown that in SSc patients with cardiac amyloidosis, combined diuretic, angiotensin-receptor blocker and beta-blocker treatment alongside anti-TNF therapy could also improve cardiac function [90]. A novel agent, C188-9, may reduce the fibrotic activity in scleroderma, as it inhibits STAT3 phosphorylation. Consequently, it significantly decreases the activity of TGF-β1 and IL-6 pathways. During phase 1 investigations with C188-9 in an SSc mouse model, a definitive reduction of cardiac fibrosis has been detected [91].

**Immunomodulatory therapy of SSc and consequential ECG alterations**

According to the latest EULAR recommendation, immunosuppressive drugs may be useful to treat different organ manifestations of patients with SSc [81]. The administration of MTX, MMF, CYC, glucocorticoids or biological agents are important therapeutic options [92, 93]. However certain concerns have also been raised about the cardiac side effects of these drugs.

In a case study of a 28-year-old patient reported by Dhesi et al., the cardiotoxic effect of CYC has been demonstrated. Secondary to the medication interstitial fibrin deposition, ventricular hypertrophy and consequent diastolic dysfunction have been diagnosed. Furthermore, fibrin-platelet microthrombus formation led to myocardial necrosis and myocarditis. Due to excessive pericardial effusion, cardiac tamponade occurred. According to their observations, early evaluation of heart damage due to CYC can be diagnosed with abnormal prolongation of QTc interval as well as an increase in QT dispersion [94].

In a study by Pieroni et al. the acute myocarditis of scleroderma patients improved due to combined immunosuppressive therapy. Interestingly, Holter ECG monitoring showed fewer VPBs. Normalization of cardiac enzymes and altered expression of adhesion molecules (VCAM-1, ICAM-1) during immunohistochemistry have also been confirmed. These findings highlight that intense immunosuppressive therapy slows down the progression of fibrosis of the myocardium in SSc patients with acute myocarditis [95].

In an animal study by Tavares et al., ciclosporin and specifically its cardiac effects have been examined. Its
administration (<5 mg/day) resulted in prolongation of QTc and increased the amplitude of the T wave, and the use of a higher dose (30 mg/day) contributed to the appearance of ischaemic ECG signs [96].

Taking all these data into consideration it can be concluded that there is conflicting and limited information available on the cardiac effects of immunomodulatory therapy. Data are limited mainly to animal experiments and human case reports.

Antiarrhythmic device therapy and radiofrequency ablation

In the case of severe myocardial fibrosis and secondary ventricular dysfunction the implantation of a cardiac defibrillator (implantable cardioverter-defibrillator) and/or the application of cardiac resynchronization therapy (biventricular pacing) are also to be considered [29, 34].

Initiating the effective medical and/or device therapy within 3 years after the onset of SSC is crucial for a good prognosis and is able to slow down the progression of the disease [84].

In the cases of recurrent and drug-resistant VT and ventricular fibrillation, the radiofrequency ablation of triggers and substrates of life-threatening ventricular arrhythmias should also be performed in order to avoid the consequences of frequent implantable cardioverter-defibrillator shocks. According to recent case reports the ablation of VT substrates (located mainly in the right ventricle) after cardiac pace and substrate mapping has been successfully performed [97–100]. Regarding non-inducible and rare ventricular arrhythmias, the implantation of a loop recorder can also be a useful diagnostic tool [80].

Summary

In patients with scleroderma the underlying factors leading to cardiac symptoms are commonly secondary to impulse-generating and conductive disorders driven by structural and cellular alterations of the myocardium. The measurement of certain parameters of the 12-lead ECG may be of help in the prediction of ventricular arrhythmias and SCD. There are contradictory data on the applicability of QT interval and dispersion in patients with SSC; however, all studies agree that the prolongation of these electrocardiographic parameters can predict the occurrence of ventricular arrhythmias and SCD. Besides the measurement of NT-proBNP and HSTnT, further novel laboratory markers are available that may help to establish the diagnosis and to evaluate the current inflammatory activity of the disease. Laboratory markers and echocardiography are cornerstones of the diagnosis, which may highlight the extent of cardiac damage and predict the long-term outcome of these patients. The simultaneous determination of the abovementioned clinical parameters can result in a more accurate risk stratification and management of SSC.

In conclusion, investigating the ECG alterations together with echocardiographic findings and laboratory parameters may result in the building of a more effective risk stratification and management strategy of patients with SSC.

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References

1 Geyer M, Müller-Ladner U. The pathogenesis of systemic sclerosis revisited. Clin Rev Allergy Immunol 2011;40:92–103.
2 Allanore Y, Meune C, Vonk MC et al. Prevalence and factors associated with left ventricular dysfunction in the EULAR Scleroderma Trial and Research group (EUSTAR) database of patients with systemic sclerosis. Ann Rheum Dis 2010;69:218–21.
3 Kahan A, Allanore Y. Primary myocardial involvement in systemic sclerosis. Rheumatology (Oxford) 2006;45(Suppl 4):14–7.
4 Lambova S. Cardiac manifestations in systemic sclerosis. World J Cardiol 2014;6:993–1005.
5 Hachulla AL, Launay D, Gaxotte V et al. Cardiac magnetic resonance imaging in systemic sclerosis: a cross-sectional observational study of 52 patients. Ann Rheum Dis 2009;68:1876–84.
6 Abraham DJ, Krieg T, Distler J, Distler O. Overview of pathogenesis of systemic sclerosis. Rheumatology (Oxford) 2006;48:i3–7.
7 Komócsi A, Vorobcsuk A, Faludi R et al. The impact of cardiopulmonary manifestations on the mortality of SSC: a systemic review and meta-analysis of observational studies. Rheumatology (Oxford) 2012;51:1027–36.
8 Tyndall AJ, Bannert B, Vonk M et al. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. Ann Rheum Dis 2010;69:1809–15.
9 Ioannidis JP, Vlachoyiannopoulos PG, Haidich AB et al. Mortality in systemic sclerosis: an international meta-analysis of individual patient data. Am J Med 2005;118:2–10.
10 Butt SA, Jeppesen JL, Torp-Pedersen C et al. Cardiovascular manifestations of systemic sclerosis: a Danish nationwide cohort study. J Am Heart Assoc 2019;8:e013405.
11 Lubitz SA, Goldbarg SH, Mehta D. Sudden cardiac death in infiltrative cardiomyopathies: sarcoidosis, scleroderma, amyloidosis, hemachromatosis. Prog Cardiovasc Dis 2008;51:58–73.
12 Ridolfi RL, Bulpkley BH, Hutchins GM. The cardiac conduction system in progressive systemic sclerosis. Clinical and pathologic features of 35 patients. Am J Med 1976;61:361–6.
13 Follansbee WP, Curtiss EI, Rahko PS et al. The electrocardiogram in systemic sclerosis (scleroderma).
Study of 102 consecutive cases with functional correlations and review of the literature. Am J Med 1985;79:183–92.

14 De Luca G, Bosello SL, Gabrielli FA et al. Prognostic role of ventricular ectopic beats in systemic sclerosis: a prospective cohort study shows ECG indexes predicting the worse outcome. PLoS One 2016;1:1:e0153012.

15 Schicchi N, Valeri G, Moroncini G et al. Myocardial perfusion defects in scleroderma detected by contrast-enhanced cardiovascular magnetic resonance. Radiol Med 2014;119:885–94.

16 Krummen DE, Ho G, Villongco CT, Hayase J, Schricker et al. Ventricular fribillation: triggers, mechanisms and therapies. Future Cardiol 2016;12:373–90.

17 Smith JW, Clements PJ, Levisman J, Furst D, Ross et al. Echocardiographic features of progressive systemic sclerosis (PSS). Correlation with hemodynamic and postmortem studies. Am J Med 1979;66:28–33.

18 Vemulapalli S, Cohen L, Hsu V. Prevalence and risk factors for left ventricular diastolic dysfunction in a scleroderma cohort. Scand J Rheumatol 2017;46:281–7.

19 Muresan L, Petcu A, Pamfil C et al. Cardiovascular profiles of scleroderma patients with arrhythmias and conduction disorders. Acta Reumatol Port 2016;41:26–39.

20 Meune C, Allanore Y, Pascal O et al. Myocardial contractility is early affected in systemic sclerosis: a tissue Doppler echocardiography study. Eur J Echocardiogr 2005;8:351–7.

21 Follansbee WP, Zerbe TR, Medsger TA Jr. Cardiac and skeletal muscle disease in systemic sclerosis (scleroderma): a high risk association. Am Heart J 1993;125:194–203.

22 Rajdev A, Garan H, Biviano A. Arrhythmias in pulmonary arterial hypertension. Prog Cardiovasc Dis 2012;55:180–6.

23 Desai CS, Lee DC, Shah SJ. Systemic sclerosis and the heart: current diagnosis and management. Curr Opin Rheumatol 2011;23:545–54.

24 Assassi S, Del Junco D, Sutter K et al. Clinical and genetic factors predictive of mortality in early systemic sclerosis. Arthritis Rheum 2009;61:1403–11.

25 Coppi F, Giuggioli D, Spinella A et al. Cardiac involvement in systemic sclerosis: identification of high-risk patient profiles in different patterns of clinical presentation. J Cardiovasc Med (Hagerstown) 2018;19:393–5.

26 Elhai M, Meune C, Boubaya M et al. Mapping and predicting mortality from systemic sclerosis. Ann Rheum Dis 2017;76:1897–905.

27 Vacc A, Meune C, Gordon J et al. Cardiac arrhythmias and conduction defects in systemic sclerosis. Rheumatology (Oxford) 2014;53:1172–7.

28 Bienias P, Ciurzyński M, Glińska-Wielochowska M et al. Heart rate turbulence impairment and ventricular arrhythmias in patients with systemic sclerosis. Pacing Clin Electrophysiol 2010;33:920–8.

29 Bournia VK, Tountas C, Protogerou AD et al. Update on assessment and management of primary cardiac involvement in systemic sclerosis. J Scleroderma Relat Disord 2018;3:53–65.

30 Clements PJ, Furst DE, Cabeen W et al. The relationship arrhythmias and conduction disturbances to other manifestations of cardiopulmonary disease in progressive systemic sclerosis (PSS). Am J Med 1981;71:38–46.

31 Draeger HT, Assassi S, Sharif R et al. Right bundle branch block: a predictor of mortality in early systemic sclerosis. PLoS One 2013;8:e78808.

32 Ferri C, Bernini L, Bongioni MG et al. Noninvasive evaluation of cardiac dysrythmias, and their relationship with multisystemic symptoms, in progressive systemic sclerosis patients. Arthritis Rheum 1985;28:1259–66.

33 Muresan L, Oancea I, Mada RO et al. Relationship between ventricular arrhythmias, conduction disorders, and myocardial fibrosis in patients with systemic sclerosis. J Clin Rheumatol 2018;24:25–33.

34 Bernardo P, Conforti ML, Bellando-Randone S et al. Implantable cardioverter defibrillator prevents sudden cardiac death in systemic sclerosis. J Rheumatol 2011;38:1617–21.

35 Steen VD, Medsger TA. Severe organ involvement in systemic sclerosis with diffuse scleroderma. Arthritis Rheum 2000;43:2437–44.

36 Bienias P, Ciurzyński M, Kisiel B et al. Comparison of non-invasive assessment of arrhythmias, conduction disturbances and cardiac autonomic tone in systemic sclerosis and systemic lupus erythematosus. Rheumatol Int 2019;39:301–10.

37 Yap YG, Camm AJ. Drug induced QT prolongation and torsades de pointes. Heart Br Card Soc 2003;89:1363–72.

38 Frothingham R. Rates of torsades de pointes associated with ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin, and moxifloxacin. Pharmacotherapy 2001;21:1468–72.

39 Owens RC, Ambrose PG. Antimicrobial safety: focus on fluoroquinolones. Clin Infect Dis 2005;41(Suppl 2):S144–57.

40 Taylor DM. Antipsychotics and QT prolongation. Acta Psychiatr Scand 2003;107:85–95.

41 Haddad PM, Anderson IM. Antipsychotic-related QTc prolongation, torsade de pointes and sudden death. Drugs 2002;62:1649–71.

42 Vieweg WVR, Wood MA. Tricyclic antidepressants, QT interval prolongation, and torsade de pointes. Psychosomatics 2004;45:371–7.

43 Moss AJ. QTc prolongation and sudden cardiac death. The association is in the detail. J Am Coll Cardiol 2006;47:368–9.

44 Sebestyén V, Szabó Z. The role of electrocardiographic markers in the prevention of atrial and ventricular arrhythmias. In: Lakshmanados ed. Echocardiography in heart failure and cardiac electrophysiology, Chapter 2. Rochester, NY: InTechOpen, 2016:13–26.

45 Salvi V, Karnad DR, Panicker GK et al. Comparison of 5 methods of QT interval measurements on electrocardiograms from a thorough QT/QTc study.
effect on assay sensitivity and categorical outliers. J Electrocardiol 2011;44:96–104.

46 Postema PG, Wilde AA. The measurement of the QT interval. Curr Cardiol Rev 2014;10:287–94.

47 Panicker GK, Karnad DR, Natekar M et al. Intra- and interreader variability in QT interval measurement by tangent and threshold methods in a central electrocardiogram laboratory. J Electrocardiol 2009;42: 348–52.

48 Savelleia I, Yi G, Guo X, Hnaktova K, Malik M. Agreement and reproducibility of automatic versus manual measurement of QT interval and QT dispersion. Am J Cardiol 1998;81:471–7.

49 Rosato E, Gigante A, Liberati M et al. QTc interval prolongation in systemic sclerosis: correlations with clinical variables. Int J Cardiol 2015;182:20–2.

50 Massie C, Hudson M, Tatibouet S et al. Absence of an association between anti-Ro antibodies and prolonged QTc interval in systemic sclerosis: a multicenter study of 689 patients. Semin Arthritis Rheum 2014;44:338–44.

51 Foocharoen C, Pussadhamma B, Mahakkanukrauh A, Suwannaroj S, Nanagara R. Asymptomatic cardiac involvement in Thai systemic sclerosis: prevalence and clinical correlations with non-cardiac manifestations (preliminary report). Rheumatology (Oxford) 2015;54:1616–21.

52 De Luca G, Bosello SL, Canestrari G et al. QTc interval prolongation in systemic sclerosis: correlations with clinical variables and arrhythmic risk. Int J Cardiol 2017;239:33.

53 Gigante A, Rosato E, Liberati M et al. In systemic sclerosis prolonged QTc interval is associated with reduced exercise tolerance. Int J Cardiol 2016;203: 570–2.

54 Karaahmet T, Tigen K, Gurel E et al. Impact of systemic sclerosis on electromechanical characteristics of the heart. Heart Vessels 2010;25:223–8.

55 Sgreccia A, Morelli S, Ferrante L et al. QT and QT dispersion in systemic sclerosis (scleroderma). J Intern Med 1998;243:127–32.

56 Ciftci O, Onat AM, Yavuz B et al. Cardiac repolarization abnormalities and increased sympathetic activity in scleroderma. J Natl Med Assoc 2007;99:232–7.

57 Nussinovitch U, Rubin S, Levy Y, Lidor M, Linveah A. QT variability index in patients with systemic sclerosis. Eur J Rheumatol 2019;6:179–83.

58 Yamaguchi M, Shimizu M, Iho H et al. T wave peak-to-end interval and QT dispersion in acquired long QT syndrome: a new index for arrhythmogenicity. Clin Sci (Lond) 2003;105:671–6.

59 Tse G, Gong M, Wong WT et al. The Tpeak - Tend interval as an electrocardiographic risk marker of arrhythmic and mortality outcomes: a systematic review and meta-analysis. Heart Rhythm 2017;14:1131–7.

60 Gupta P, Patel C, Patel H et al. Tp(p-e)/QT ratio as an index of arrhythmogenesis. J. Electrocardiol 2008;41: 567–74.

61 Yayla C, Yayla ME, Yayla KG et al. The assessment of Tp-e interval and Tp-e/QT ratio in patients with systemic sclerosis. Arch Rheumatol 2016;31:139–44.
Electrocardiographic markers in SSc

77 Yingchoncharoen T, Aganwal S, Popović ZB, Marwick TH. Normal ranges of left ventricular strain: a meta-analysis. J Am Soc Echocardiogr 2013;26:185–91.

78 Guerra F, Stronati G, Fischietti C et al. Global longitudinal strain measured by speckle tracking identifies subclinical heart involvement in patients with systemic sclerosis. Eur J Prev Cardiol 2018;25:1598–606.

79 Zaïr I, Mzoughi K, Nifene Z et al. Speckle tracking echocardiography in systemic sclerosis: a useful method for detection of myocardial involvement. Ann Cardiol Angeiol (Paris) 2019;68:226–31.

80 Bissell LA, Dumitru RB, Erhayiem B et al. Incidental significant arrhythmia in scleroderma associates with cardiac magnetic resonance measure of fibrosis and hs-TnI and NT-proBNP. Rheumatology (Oxford) 2019;5:1221–6.

81 Kowal-Bielecka O, Fransen J, Avouac J et al. Update of EULAR recommendations for the treatment of systemic sclerosis. Ann Rheum Dis 2017;76:1327–39.

82 Minier T, Guiducci S, Bellando-Randone S et al. Preliminary analysis of the Very Early Diagnosis of Systemic Sclerosis (VEOSS) EUSTAR multicentre study: evidence for puffy fingers as a pivotal sign for suspicion of systemic sclerosis. Ann Rheum Dis 2014;73:2087–93.

83 Csiki Z, Garai I, Shemirani AH et al. The effect of metoprolol alone and combined metoprolol-felodipin on the digital microcirculation of patients with primary Raynaud’s syndrome. Microvasc Res 2011;82:84–7.

84 Denton CP, Hughes M, Gak N et al. BSR and BHPR guideline for the treatment of systemic sclerosis. Rheumatology (Oxford) 2016;55:1906–10.

85 Steen VD, Medsger TA. Case-control study of corticosteroids and other drugs that either precipitate or protect from the development of scleroderma renal crisis. Arthritis Rheum 1998;41:1613–9.

86 Vignaux O, Allanore Y, Meune C et al. Evaluation of the effect of nifedipine upon myocardial perfusion and contractility using cardiac magnetic resonance imaging and tissue Doppler echocardiography in systemic sclerosis. Ann Rheum Dis 2005;64:1268–73.

87 Valentini G, Huscher D, Riccardi A et al. Vasodilators and low-dose acetylsalicylic acid are associated with a lower incidence of distinct primary myocardial disease manifestations in systemic sclerosis: results of the DeSScipher inception cohort study. Ann Rheum Dis 2019;78:1576–82.

88 Schuster J, Moinzadeh P, Kurschat C et al. Proteinuria in systemic sclerosis: reversal by ACE inhibition. Rheumatol Int 2013;33:2225–30.

89 Seferovic PM, Ristic AD, Maksimovic R et al. Cardiac arrhythmias and conduction disturbances in autoimmune rheumatic diseases. Rheumatology (Oxford) 2006;45:iv39–42.

90 Wada Y, Kobayashi D, Murakami S et al. Cardiac AA amyloidosis in a patient with rheumatoid arthritis and systemic sclerosis: the therapeutic potential of biological reagents. Scand J Rheumatol 2011;40:402–4.

91 Pedroza M, To S, Assassi S et al. Role of STAT3 in skin fibrosis and transforming growth factor beta signalling. Rheumatology (Oxford) 2018;57:1838–50.

92 Pope JE, Bellamy N, Seibold JR et al. A randomized controlled trial of metotrexaee versus placebo in early diffuse scleroderma. Arthritis Rheum 2001;44:1351–8.

93 Tashkin DP, Elashoff R, Clements PJ et al. Cyclophosphamide versus placebo in scleroderma lung disease. N Engl J Med 2006;354:2655–66.

94 Dhesi S, Chu MP, Blevins G et al. Cyclophosphamide-induced cardiomyopathy a case report, review, and recommendations for management. J Investig Med High Impact Case Rep 2013;1:2324709613480346.

95 Pieroni M, De Santis M, Zizzo G et al. Recognizing and treating myocarditis in recent-onset systemic sclerosis heart disease: potential utility of immunosuppressive therapy in cardiac damage progression. Semin Arthritis Rheum 2014;43:526–35.

96 Tavares P, Reis F, Ribeiro CA, Teixeira F. Cardiovascular effects of cyclosporin treatment in an experimental model. Rev Port Cardiol 2002;21:141–55.

97 Rankin AC, Oswald S, McGovern BA, Ruskin JN, Garan H. Mechanism of sustained monomorphic ventricular tachycardia in systemic sclerosis: reversal by ACE inhibition. J Am Coll Cardiol 2014;63:633–6.

98 Chung HH, Kim JB, Hong SH et al. Radiofrequency catheter ablation of hemodynamically unstable ventricular tachycardia associated with systemic sclerosis. J Korean Med Sci 2012;27:215–7.

99 Casella M, Carbucicchio C, Russo E et al. Electrical storm in systemic sclerosis: inside the electroanatomic substrate. World J Cardiol 2014;6:1127–30.

100 Lacroix D, Brugade F, Marquié C, Klug D. Electroanatomic mapping and ablation of ventricular tachycardia associated with systemic sclerosis. Europace 2004;6:336–42.