EJR European Journal of Rheumatology

DOI: 10.5152/eurjrheum.2020.19215

Original Article

Repolarization dispersion in patients with systemic sclerosis

Udi Nussinovitch[1-3], Gil Beeri[1, 3], Shiri Rubin[3], Merav Lidar[3, 4], Yair Levi[3, 5], Avi Livneh[3, 4, 6]

Abstract

Objective: Systemic sclerosis (SSc) is associated with increased cardiac morbidity and mortality. Whether some electrocardiographic markers of arrhythmias predispose to early cardiogenic death in SSc remains controversial. This study evaluated the occurrence of previously reported as well as unstudied markers of repolarization in patients with SSc and assessed their prognostic implications.

Methods: A total of 21 patients with SSc and 31 unaffected controls were included in this prospective study. Electrocardiograms were conducted under strict standards. Repolarization and dispersion parameters and markers of late ventricular potentials were determined using designated computer software. Results of multiple beats were averaged.

Results: There were no significant differences between the SSc and control groups in average QT intervals, average corrected QT intervals, average QT interval dispersion (QTd), average QT corrected dispersion (QTcd), and QT dispersion ratio. However, average QT apex dispersion, average JT dispersion, average JT corrected dispersion, and Tpeak-Tend corrected were significantly higher in patients with SSc than in controls. Late ventricular potentials were not found in patients with SSc or in controls. Increased QTd and QTcd were recorded in 1 patient who experienced ventricular arrhythmia before inclusion in the study. None of the remaining patients with SSc or the controls developed arrhythmia during the 9-year follow-up.

Conclusion: Abnormal repolarization parameters may be observed in patients with SSc. However, their prognostic significance with regard to increased risk for repolarization-associated ventricular arrhythmias and increased cardiac death could not be determined in this study. Our findings endorse additional studies on this matter.

Keywords: Systemic sclerosis, arrhythmia, electrocardiography (ECG)

ORCID iDs of the authors:
U.N. 0000-0002-3931-8003;
G.B. 0000-0003-3939-5217;
S.R. 0000-0003-4672-8315;
M.L. 0000-0001-5800-7860;
Y.L. 0000-0001-8371-4516;
A.L. 0000-0002-1970-5364.

Cite this article as: Nussinovitch U, Beeri G, Rubin S, Lidar M, Levi Y, Livneh A. Repolarization dispersion in patients with systemic sclerosis. Eur J Rheumatol 2021; 8(3): 144-9.

[1] Department of Cardiology, Meir Medical Center, Kfar Saba, Israel
[2] Applicative Cardiovascular Research Center (ACRC), Meir Medical Center, Kfar Saba, Israel
[3] Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[4] Unit of Rheumatology, Chaim Sheba Medical Center, Tel Hashomer, Israel
[5] Department of Medicine E, Meir Medical Center, Kfar Saba, Israel
[6] Department of Medicine and the Heller Institute of Medical Research, Chaim Sheba Medical Center, Tel Hashomer, Israel

Address for Correspondence:
Udi Nussinovitch; Department of Cardiology, Meir Medical Center, Kfar Saba, Israel; Applicative Cardiovascular Research Center (ACRC), Meir Medical Center, Kfar Saba, Israel; Sackler Faculty of Medicine, Tel Aviv University Tel Aviv, Israel

E-mail: udi.nussinovitch@gmail.com

Submitted: December 24, 2019
Accepted: October 23, 2020
Available Online Date: December 28, 2020

Copyright@Author(s) - Available online at www.eurjrheumatol.org.

Content of this journal is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

Introduction

Systemic sclerosis (SSc) is a rare chronic disease characterized by immune dysregulation, vascular damage, and increased collagen deposition in the skin and internal organs (1). Patients with SSc are usually classified into 2 main clinical subgroups according to the extent of the fibrosis. In patients with limited cutaneous SSc (lcSSc), skin fibrosis is restricted to the skin of the hands, forearms, and face, whereas in diffuse cutaneous SSc (dcSSc), fibrosis is more extensive. One or more visceral organs may be involved in both forms of scleroderma (2). Vascular abnormalities are generally more common in lcSSc (3), whereas dcSSc is usually associated with a worse overall prognosis (4).

Myocardial fibrosis is the main pathogenic feature of cardiac involvement in SSc. Although cardiac involvement may be observed early in the disease course and is suggested to occur in almost all patients with SSc, fibrosis-driven clinical manifestations are usually a late sequel (5). Once the clinical manifestations have emerged (in 10%-35% of patients with SSc), prognosis is usually poor and the 5-year mortality rate may reach 70% (5, 6). Cardiac arrhythmias, valvular defects, myocardial ischemia, and pericardial effusion and constriction have all been reported in SSc. Heart failure may occur when cardiac fibrosis is extensive or secondary to pulmonary hypertension (6, 7). Sudden cardiac death affects 5% of patients with SSc, and arrhythmias lead to 6% of all-cause mortality in SSc (8, 9). Nevertheless, the role of electrocardiogram (ECG) markers in the prediction of this risk is not yet established.

Several possible early markers of arrhythmia have been studied. Ventricular late potentials (LPs) are high-frequency and very-low-intensity signals localized at the end of the QRS complex that can be detected by signal averaged ECG (SAECG). The detection of LPs may signify increased risk for re-entrant arrhythmias (10). LPs were reported to be more prevalent in patients with SSc and are considered to be a marker of adverse

prognosis (11-14). The association between prolonged corrected QT (QTc), commonly found in SSc (15-20), and disease prognosis is not clearly established. Some studies have suggested that prolonged QTc is not necessarily associated with major arrhythmic complications (16). QT dispersion (QTd) is a marker of repolarization heterogeneity reported to be associated with increased rate of arrhythmias (21). However, it is still disputed whether increased QTd is more frequent in SSc (18, 22). These controversies only highlight the need for additional arrhythmic markers and more studies on arrhythmia predisposition markers in SSc. Furthermore, the precision of many previous studies, which have been managed manually rather than by designated computerized programs, is argued. In this study, we explored the presence of previously studied and unstudied repolarization markers in SSc and evaluated their role in predicting cardiac outcome in these patients.

Methods

Study design

A comparative cross-sectional study design was used. The research protocol was approved by the Sheba Medical Center (Approval Date: February 05, 2008; Approval Number: 5003/07). Before inclusion, all participants provided written informed consent. Patients were recruited in December 2010 and have been followed up since then.

Study subjects

The study cohort included 21 patients with SSc recruited from the rheumatology outpatient clinic. All patients with SSc were routinely examined every 12 months and underwent follow-up studies, including ECG, tissue Doppler echocardiography, pulmonary function tests (including diffusion capacity), routine laboratory blood tests, and SSc autoantibody profile. Additional studies were performed if needed. The diagnosis of SSc was based on the American Rheumatism Association classification criteria for SSc, which were the standard classification criteria at subject recruitment (23).

A total of 31 healthy controls who were followed up at the executive health screening program clinic of the hospital (a preventive program for early detection and treatment of health problems) and were found to be free of cardiopulmonary disease, SSc, or other autoimmune or inflammatory disorders (based on medical history, physical examination, cardiac stress test, resting ECG, chest X-ray, complete blood count, and blood chemistry) were randomly recruited in 2010. They served as the reference group for normal ECG parameters.

Procedure

Participants were asked not to smoke, drink caffeinated beverages, or take other stimulants for at least 3 hours before the study and to avoid strenuous exercise for 24 hours before the test. They were also asked to discontinue any drugs that might affect ECG results at least 12 hours before the study. In all cases, ECG was conducted between 9:00 a.m. and 12:00 p.m. Room temperature was maintained at ~22°C. Participants were asked to lie quietly for 10 minutes before the exam.

ECG strips were recorded in the resting supine position using a commercial machine (Meigaoyi Co.; Beijing, China). Electrodes were placed in standard positions. ECGs were repeated if the results were of poor quality. QT, JT, QT dispersion, and JT dispersion parameters were measured and calculated using a designated computer software program (ECGLAB 3.0, Meigaoyi Co.). QTc was automatically calculated using the Bazett's formula. QT interval dispersion (QTd) was computed from 1 randomly selected beat in a steady state by subtracting the minimum QT interval from the maximum QT interval in 12 leads. QTc dispersion (QTcd) was calculated similarly. The QTd ratio (QTdr) was calculated by correcting QTd for the corresponding RR interval. JT dispersion (JTd) and corrected JT dispersion (JTcd) were calculated analogous to the QTcd but for the JT interval. QT apex (QTa) was measured from the onset of QRS to the apex of the T wave. Thereafter, QTa dispersion (QTad) was measured similar to QTd (24). All calculations were automatically performed for 5 consecutive beats. The average QT interval length for the 5 complexes, including average QTc, average QTd, average QTcd, average QTad, average JTc, and average JTcd, was computed. The interval between T wave peak to T wave end (Tpe) was measured using a semi-automatic on-screen caliper software (Measurements, version 5.0.33, Norav Medical Ltd.; Yokneam, Israel) from lead V5. T wave end was measured automatically using the tangent method (that is, the intersection of the tangent to the down slope of the T wave and the isoelectric line when not followed by a U wave or if distinct from the following U wave). If a U wave followed the T wave, the T-wave offset was measured as the nadir between the T and U waves. If the T-wave amplitude was <1.5 mm, that measurement was excluded from analysis. Automatic measurements were manually reviewed by a blinded investigator for any errors of measurements. Rate correction of Tpe interval (Tpe-c) was performed using the Bazett's formula (Tpe/√RR).

LPs were measured with a different designated software (LPs, Norav Medical; Israel). The subject's skin was cleansed with alcohol before electrode placement in an attempt to decrease noise level to less than 0.7 μV. Leads were positioned according to the Frank's corrected orthogonal lead system, representing the X, Y, and Z bipolar axes. A minimum of 200 consecutive beats were digitally recorded and averaged. A commercial algorithm was used to calculate the following parameters: 1) duration of filtered QRS complex (fQRS); 2) root-mean-square voltage of the terminal 40 (RMS40) ms; and 3) time during which the low-amplitude QRS signal (LAS) remained below 40 μV. LP measurements were considered abnormal when 2 of the following 3 criteria were met: 1) fQRS duration >114 ms; 2) RMS40 <20 μV; 3) LAS duration >38 ms (25).

Statistical analysis

Data were analyzed using JMP, version 7.0 (SAS Institute; Cary, NC, USA). Results were presented as means and standard deviations. Abnormal results were defined as more than 2 standard deviations from the normal range. Findings were compared between the groups using the Kruskal-Wallis one-way analysis test and Fisher's exact test. A p-value less than 0.05 was considered statistically significant. Figures were created with MedCalc version 19.1.5 (MedCalc Software bvba; Ostend, Belgium; https://www.medcalc.org).

Results

A total of 21 patients with SSc and 31 healthy controls were included in the study. The clinical and demographic background information of participants in the study and control groups is presented in Table 1. As seen, patients with SSc and individuals in the control group were comparable in terms of most of the study parameters, including those considered as cardiovascular risk-factors, such as age, sex, smoking habits, and long-term metabolic dis-

Main Points

- Systemic sclerosis (SSc) is associated with previously unreported markers of abnormal repolarization, including high QT apex dispersion, average JT dispersion, and average JT corrected dispersion values.
- Normal signal-averaged electrocardiogram parameters are found in patients with SSc without overt cardiac disease.
- The prognostic implications of these parameters merit further clinical study.

Table 1. Clinical and demographic characteristics.

Parameter	SSc (n=21)	Control (n=31)	p
Age (years)	45.9±12.0	41.5±14.2	NS
Sex (F/M)	19/2	24/7	NS
BMI (kg/m^2)	22.5±4.7	22.9±2.2	NS
Current smoker (%)	23.8	22.6	NS
Ventricular arrhythmias (%)	4.8	0	NS
Former smoker (%)	14.3	9.7	NS
Family history of IHD (%)	66.7	45.2	NS
Diabetes mellitus (%)	4.8	0	NS
Hypertension (%)	4.8	0	NS
Dyslipidemia (%)	19.0	22.6	NS
Hypothyroidism (%)	4.8	0	NS
Aspirin intake (%)	9.5	0	NS
ACEI intake (%)	14.3	0	NS
ARB intake (%)	4.8	0	NS
CCB intake (%)	38.1	0	<0.001
Beta-blockers intake (%)	9.5	0	NS
Statins intake (%)	4.8	12.9	NS
Fibrates intake (%)	4.8	0	NS
Insulin intake (%)	4.8	0	NS
Other anti-diabetic drugs (%)	4.8	0	NS
Anti-depressants intake (%)	19.0	0	0.022
Levothyroxin intake (%)	4.8	0	NS
Immunosuppressive therapy* (%)	47.6	0	<0.001
Prostacyclin therapy (%)	14.3	0	NS

*Immunosuppression therapy refers to methotrexate, prednisone, or immunoglobulins.
SSc: systemic sclerosis; BMI: body-mass index; IHD: ischemic heart disease; ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin-II receptor blockers; CCB: calcium-channel blockers; NS: non-significant.

Table 2. Repolarization and dispersion parameters in study subjects.

QTd result	SSc (n=21)	Control (n=31)	p
Average QT (ms)	400.9±33.9	397.6±27.4	NS
Average QTc (ms)	434.3±32.3	421.6±24.9	NS
QTd (ms)	47.0±15.1	41.7±9.8	NS
QTcd (ms)	50.9±16.2	44.2±10.1	NS
QTdr (%)	5.5±1.8	4.7±1.1	NS
QTad (ms)	85.5±29.9	67.9±23.2	0.032
JTd (ms)	20.5±6.5	17.1±4.2	0.038
JTcd (ms)	22.1±6.9	18.2±4.5	0.021
V5 Tpe (ms)	81.4±10.7	78.1±7.3	NS
V5 Tpe-c (ms)	89.7±12.9	82.0±7.0	0.021

SSc: systemic sclerosis; QTc: corrected QT interval; QTd: QT dispersion; QTcd: corrected QT dispersion; QTdr: QT dispersion ratio; QTad: QT apex dispersion; JTd: JT dispersion; JTcd: JT corrected dispersion; Tpe: T wave peak to end; Tpe-c: Tpe corrected; NS: non-significant.

orders. Moreover, the difference in the medications consumed between the 2 groups did not reach statistical significance for most agents. However, the rates of participants using calcium-channel blockers (38.1% vs. 0%, p<0.01), anti-depressants (19.0% vs. 0%, p=0.03), and immunosuppressive drugs (47.6% vs. 0%, p<0.01) were much higher in the SSc group; 2 patients with SSc had lcSSc, and the remaining 19 had dcSSc.

During the 9-year follow-up period, 1 patient with SSc died of malnutrition and 2 died from an infectious disease; 5 were lost to follow-up. In addition, 3 developed pulmonary hypertension (mean pulmonary arterial pressure of 48-59 mm Hg), 1 patient incurred a cerebrovascular event (5 years after inclusion), and another (who was 58 years old at inclusion) had wide complex non-sustained ventricular tachycardia (VT) 1 year before inclusion and has had recurrent episodes of atrioventricular nodal reentry tachycardias. She has been treated continuously with Flecainide (3M Pharmaceuticals; Minnesota, USA) and has had no recurrence of arrhythmia. This particular patient had QTd of 60.4 ms and QTcd of 57.1 ms, which are above the suggested normal threshold, whereas other dispersion parameters, such as QTdr (5.4%), QTad (82.6 ms), JTd (21 ms), and JTcd (19.9 ms) (26), were not increased.

Repolarization measurements of 21 patients with SSc and 31 controls are presented in Table 2. Despite a persistent trend toward higher mean values of QT, QTc, QTd, QTcd, and QTdr in the SSc group than in the control group, the differences were not significant. However, QTad was significantly higher in the SSc group than in controls (85.5±29.9 ms vs. 67.9±23.2, respectively; p=0.032, Table 2, Figure 1a). JTd and JTcd were significantly higher in the SSc group than in controls (20.5±6.5 ms vs. 17.1±4.2 ms, p=0.038; and 22.1±6.9 ms vs. 18.2±4.5 ms, p=0.021, respectively, Table 2 and Figure 1b and c). Tpe could not be computed in 1 patient with SSc and 2 healthy volunteers because of low voltage. Despite seemingly higher Tpe results in SSc, the difference between the groups did not reach statistical significance. However, patients with SSc had significantly higher Tpe-c values (89.7±12.9 ms vs. 82.0±7.0, p=0.021; Figure 1d). Methodologically acceptable SAECG was completed in 11 patients with SSc and 27 controls. Tests that were methodologically insufficient for analysis (owing to noise level less than 0.7 μV) were excluded from analysis. LPs were not detected in any of the patients with SSc or controls (Table 3).

Table 3. Late potentials in 11 patients with SSc.

Patient #	Age (years)	Sex (F/M)	SSc type	fQRS duration (ms)	RMS40 (μV)	LAS duration under 40 μV (ms)	Abnormal LPs result*
1	25	F	Diffuse	75	69	15	No
2	28	F	Diffuse	100	9	49	No
3	32	F	Diffuse	69	74	25	No
4	32	F	Diffuse	80	81	29	No
5	39	F	Diffuse	81	44	28	No
6	40	F	Diffuse	60	89	19	No
7	45	F	Diffuse	70	53	20	No
8	55	F	Limited	75	66	16	No
9	58	F	Diffuse	93	11	48	No
10	62	F	Diffuse	63	196	26	No
11	40	M	Diffuse	76	44	26	No

*LPs were determined using signal-averaged electrocardiogram. The LP test was considered abnormal when 2 of 3 criteria were met: 1) fQRS >114 ms; 2) RMS40 <20 μV; and 3) LAS >38 ms.
SSc: systemic sclerosis; F: female; M: male; fQRS: filtered QRS complex; RMS40: root-mean-square voltage of the terminal 40 ms; LAS: low-amplitude signal; LPs: late potentials.

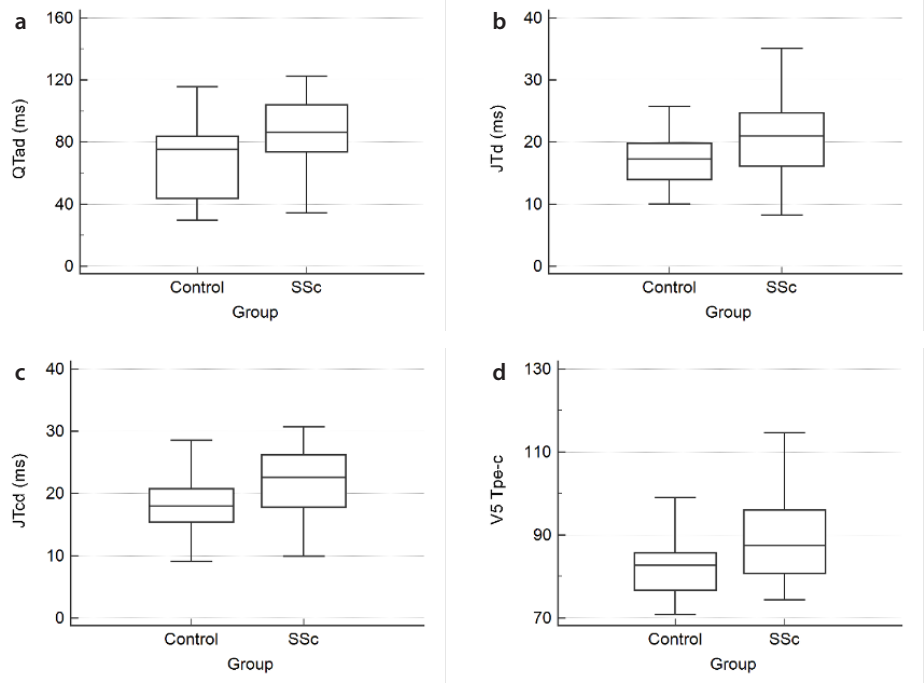

Figure 1. a-d. Increased QT interval dispersion parameters in scleroderma QT apex dispersion (a), JT dispersion (b), JT corrected dispersion (c), and V5 corrected Tpeak-Tend interval (d). All comparisons were statistically significant (p<0.05).

Discussion

In this study, we evaluated the repolarization parameters in 21 patients with SSc to detect the markers known to predict arrhythmia and predispose the patients to increased cardiac morbidity and mortality. We found that some markers, including QTad, JTd, JTcd, and Tpe-c, had increased compared with those of the controls. Other dispersion parameters, such as QT, QTd, Tcd, and QTdr, were not increased in these patients. During 9 years of follow-up, none of the patients developed arrhythmia or died of cardiac causes and 1 patient with increased QTd developed VT before inclusion in the study.

Overt cardiac disease in patients with SSc is uncommon and usually emerges at a late stage in the course of the disease. However, subclinical cardiac involvement in SSc may be widespread (4, 27). Recently, Meduri et al. (5) have reported that abnormal cardiac magnetic resonance imaging (MRI) findings are apparent in approximately 80% of patients with SSc. These include myocardial edema, dilated ventricles or reduced contractile function, delayed contrast enhancement, and pericardial effusion. Some of these findings may make the myocardium more susceptible to develop arrhythmia. However, because routine cardiac MRI is expensive and may be difficult to perform, alternative markers of cardiac involvement and risk stratification in SSc, such as those associated with repolarization instability, are needed.

Increased QTd and QTcd in SSc have been previously reported by Sgreccia et al. (18). In contrast, Karaahmet et al. (22) have found that QTcd was similar in patients with SSc and in controls. Our results regarding QTcd are similar to those in the study by Karaahmet et al (22). QTad, JTd, and JTcd have not yet been studied in patients with SSc. Notably, JTd has been suggested to be more accurate than QTd in identifying patients with repolarization abnormalities (28). Nevertheless, over a 9-year follow-up period, the increase in QTad, JTd, and JTcd was not associated with arrhythmia in our study group, implying that their role in predicting arrhythmias is yet to be determined as our study sample was too small to draw definite conclusions. Our results of increased transmural repolarization dispersion (manifested in our cohort as increased Tpe-c values in SSc) are in line with those reported by Okutucu et al. (29) and Yayla et al. (30), although in the latter, Tpe interval was not corrected for heart rate.

The role of the various medications used in excess by patients with SSc compared with con-

trol subjects appears to be negligible. Calcium-channel blockers do not seem to influence repolarization dispersion (31). Most of the serotonin reuptake inhibitors do not influence QTc (32). Although repolarization abnormalities were linked to citalopram (Forest Laboratories; New York, USA), escitalopram (Allergan; Dublin, Ireland), venlafaxine (Wyeth Pharmaceuticals Company; Madison, NJ, USA), and tricyclic antidepressants (33), these were not prescribed to any of our patients. Accordingly, the mean QTc values were similar in both the study groups and within normal limits. The influence of anti-depressants on repolarization heterogeneity and repolarization dispersion parameters is largely unknown.

The negative LP results in this study disagree with those previously reported (11-14). Certain patient characteristics, poor compliance with the requirement to remain motionless for several minutes, and vulnerability to external and internal electrostatic interferences may underlie the discrepancy between the studies.

This study had some limitations. The relatively small number of study patients owing to the rarity of SSc could have affected the results. A trend to increased values of most repolarization parameters was observed; it is entirely plausible that with a larger sample size, results of patients with SSc would have reached statistical significance. However, the results of our study highlight the possible superiority of specific dispersion parameters over others in SSc. Furthermore, a 9-year follow-up period might be too short to elucidate the deleterious outcomes of increased dispersion parameters in SSc. The role of using automated versus manual, averaged versus single beat, and tangent versus the trapezium area (or the integration operation methods) in determining study outcome is yet to be found.

In conclusion, an association between SSc and an increase in some repolarization dispersion parameters was observed. A longer duration of follow-up and larger population of patients with scleroderma are needed to determine the prognostic value of these markers with regard to malignant ventricular arrythmias and increased risk of sudden cardiac death.

Ethics Committee Approval: Ethics committee approval was received for this study from the Sheba Medical Center (Approval Date: February 05, 2008; Approval Number: 5003/07).

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - U.N., A.L.; Design - U.N., A.L.; Supervision - U.N.; Data Collection and/or Processing - S.R.; Analysis and/or Interpretation - U.N., G.B., S.R.; Literature Search - G.B., M.L., Y.L., A.L.; Writing Manuscript - U.D., M.L., Y.L., A.L.; Critical Review - U.D., M.L., Y.L., A.L.

Acknowledgments: We wish to thank Faye Schreiber, MS for editorial assistance.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Acosta-Herrera M, Lopez-Isac E, Martin J. Towards a better classification and novel therapies based on the genetics of systemic sclerosis. Curr Rheumatol Rep 2019; 21: 44. [Crossref]
2. Grosicka A, Manasar A, Kucharz EJ, Kotyla PJ. Serum concentration of surfactant protein D in patients with systemic sclerosis: The potential marker of the interstitial lung disease severity. Best Pract Res Clin Rheumatol 2018; 32: 541-9. [Crossref]
3. Wan MC, Moore T, Hollis S, Herrick AL. Ankle brachial pressure index in systemic sclerosis: Influence of disease subtype and anticentromere antibody. Rheumatology (Oxford) 2001; 40: 1102-5. [Crossref]
4. Belch JJ, McSwiggan S, Lau C. Macrovascular disease in systemic sclerosis: The tip of an iceberg? Rheumatology (Oxford) 2008; 47 Suppl 5: v16-7. [Crossref]
5. Meduri A, Di Molfetta DV, Natale L, Manfredi R. Cardiac magnetic resonance in systemic sclerosis patients with cardiac symptoms. Eur Rev Med Pharmacol Sci 2017; 21: 4797-803.
6. Marques-Alves P, Baptista R, Canha C, Franco F, Santos L, Pego M. Early manifestation of myocardial involvement in systemic sclerosis. Rev Port Cardiol 2019; 38: 299-303. [Crossref]
7. Wangkaew S, Prasertwittayakij N, Euathrongchit J. Clinical manifestation and incidence of cardiopulmonary complications in early systemic sclerosis patients with different antibody profiles. J Clin Med Res 2019; 11: 524-31. [Crossref]
8. 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. [Crossref]
9. Tyndall AJ, Bannert B, Vonk M, Airo P, Cozzi F, Carreira PE, 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. [Crossref]
10. Gadaleta M, Giorgio A. A method for ventricular late potentials detection using time-frequency representation and wavelet denoising. ISRN Cardiol 2012; 2012: 258769. [Crossref]
11. Paradiso M, Di Franco M, Musca A, Basili S, Riccieri V, Paoletti V, et al. Ventricular late potentials in systemic sclerosis: Relationship with skin involvement. J Rheumatol 2002; 29: 1388-92.
12. Pignone A, Matucci-Cerinic M, Becucci A, de Leonardis V, Lombardi A, Fabiani D, et al. Patterns of ventricular late potentials in systemic sclerosis: A noninvasive method in the study of cardiac involvement. Ann Ital Med Int 1994; 9: 141-5.
13. Morelli S, Sgreccia A, De Marzio P, Perrone C, Ferrante L, Gurgo AM, et al. Noninvasive assessment of myocardial involvement in patients with systemic sclerosis: Role of signal averaged electrocardiography. J Rheumatol 1997; 24: 2358-63.
14. Paradiso M, Gabrielli F, Coppotelli L, Aguglia G, Pergolini M, Leonardo M, et al. Signal-averaged electrocardiography and echocardiography in the evaluation of myocardial involvement in progressive systemic sclerosis. Int J Cardiol 1996; 53: 171-7. [Crossref]
15. Rosato E, Tubani L, Gigante A. QTc interval prolongation in systemic sclerosis. Int J Cardiol 2017; 239: 34. [Crossref]
16. De Luca G, Bosello SL, Canestrari G, Cavalli G, Dagna L, Ferraccioli G. QTc interval prolongation in systemic sclerosis: Correlations with clinical variables and arrhythmic risk. Int J Cardiol 2017; 239: 33. [Crossref]
17. Rosato E, Gigante A, Liberatori M, Gasperini ML, Sardo L, Amoroso A, et al. QTc interval prolongation in systemic sclerosis: Correlations with clinical variables. Int J Cardiol 2015; 182: 20-2. [Crossref]
18. Sgreccia A, Morelli S, Ferrante L, Perrone C, De Marzio P, De Vincentiis G, et al. QT interval and QT dispersion in systemic sclerosis (scleroderma). J Intern Med 1998; 243: 127-32.
19. Massie C, Hudson M, Tatibouet S, Steele R, Huynh T, Fritzler MJ, 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. [Crossref]
20. Morelli S, Sgreccia A, Ferrante L, Barbieri C, Bernardo ML, Perrone C, et al. Relationships between electrocardiographic and echocardiographic findings in systemic sclerosis (scleroderma). Int J Cardiol 1996; 57: 151-60. [Crossref]
21. Nussinovitch U, Livneh A, Volovitz B, Nussinovitch M, Ben-Zvi I, Lidar M, et al. Normal QT dispersion in colchicine-resistant familial Mediterranean fever (FMF). Clin Rheumatol 2012; 31: 1093-6. [Crossref]
22. Karaahmet T, Tigen K, Gurel E, Takir M, Avci A, Cevik C, et al. Impact of systemic sclerosis on electromechanical characteristics of the heart. Heart Vessels 2010; 25: 223-8. [Crossref]
23. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: An American College of Rheumatology/European League against Rheumatism collaborative initiative. Arthritis Rheum 2013; 65: 2737-47. [Crossref]

24. Perkiomaki JS, Ikaheimo MJ, Pikkujamsa SM, Rantala A, Lilja M, Kesaniemi YA, et al. Dispersion of the QT interval and autonomic modulation of heart rate in hypertensive men with and without left ventricular hypertrophy. Hypertension 1996; 28: 16-21. [Crossref]
25. Breithardt G, Cain ME, el-Sherif N, Flowers NC, Hombach V, Janse M, et al. Standards for analysis of ventricular late potentials using high-resolution or signal-averaged electrocardiography. A statement by a Task Force Committee of the European Society of Cardiology, the American Heart Association, and the American College of Cardiology. Circulation 1991; 83: 1481-8. [Crossref]
26. Lutfi MF. QT interval derived measurements in patients with cardiac syndrome x compared to coronary artery disease. Front Physiol 2016; 7: 422. [Crossref]
27. Akram MR, Handler CE, Williams M, Carulli MT, Andron M, Black CM, et al. Angiographically proven coronary artery disease in scleroderma. Rheumatology (Oxford) 2006; 45: 1395-8. [Crossref]
28. Shimizu H, Ohnishi Y, Inoue T, Yokoyama M. QT and JT dispersion in patients with monomorphic or polymorphic ventricular tachycardia/ventricular fibrillation. J Electrocardiol 2001; 34: 119-15. [Crossref]
29. Okutucu S, Karakulak UN, Aksoy H, Sabanoglu C, Hekimsoy V, Sahiner L, et al. Prolonged Tp-e interval and Tp-e/QT correlates well with modified Rodnan skin severity score in patients with systemic sclerosis. Cardiol J 2016; 23: 242-9. [Crossref]
30. Yayla C, Yayla ME, Yayla KG, Ilgen U, Akboga MK, Duzgun N. The assessment of Tp-e Interval and Tp-e/QT Ratio in patients with systemic sclerosis. Arch Rheumatol 2016; 31: 139-44. [Crossref]
31. Zhao G, Pu J, Zhang C, Ma Y, Li B, Quan X. Effect of calcium-channel antagonist on repolarization heterogeneity of ventricular myocardium in an in vitro rabbit model of long QT syndrome. J Huazhong Univ Sci Technolog Med Sci 2007; 27: 516-9. [Crossref]
32. Ojero-Senard A, Benevent J, Bondon-Guitton E, Durrieu G, Chebane L, Araujo M, et al. A comparative study of QT prolongation with serotonin reuptake inhibitors. Psychopharmacology (Berl) 2017; 234: 3075-81. [Crossref]
33. CredibleMeds. QTdrugs Lists [Internet]. Available from: https://crediblemeds.org.