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Comparison of non-invasive assessment of arrhythmias, conduction disturbances and cardiac autonomic tone in systemic sclerosis and systemic lupus erythematosus

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Abstract

Systemic sclerosis (SSc) and systemic lupus erythematosus (SLE) are connective tissue diseases presenting cardiac complications including different arrhythmias, then direct electrocardiographic comparison may be useful in everyday clinical decision making. We examined 86 adult SSc patients, 76 with SLE and 45 healthy controls. Among other examinations all subjects underwent 24-h Holter monitoring with time-domain heart rate variability and heart rate turbulence evaluation. Patients with various co-existing conditions which might markedly influence arrhythmias and autonomic modulation were excluded from further analysis (SSc $n=12$, SLE $n=6$). Finally, 76 SSc and 70 SLE subjects were eligible for this study, mean age 51.9 ± 13.1 and 46.5 ± 12.7 years ($p=0.11$), with median disease duration 6.0 and 8.5 years ($p=0.15$), respectively. As compared to SLE, patients with SSc were characterised by more frequent incidence of various supraventricular and ventricular arrhythmias. As compared to SSc, patients with SLE presented prolonged corrected QT intervals and also significant correlations between corrected QT length and heart rate variability indices. Both SSc and SLE subjects presented impaired sympathetic cardiac autonomic modulation, while indices associated with parasympathetic activity in SLE were not diminished. Disease duration was not associated with arrhythmias' occurrence (except for ventricular tachycardia in SSc, $p=0.02$) and also with autonomic function in both groups of patients. Patients with SSc and SLE differ in terms of arrhythmias, conduction disturbances and cardiac autonomic tone. Regular Holter monitoring should be considered as a part of routine evaluation in connective tissue diseases patients, especially in systemic sclerosis.

Keywords Systemic sclerosis · Systemic lupus erythematosus · Arrhythmias · Conduction disturbances · Heart rate variability · Heart rate turbulence · Cardiac autonomic dysfunction

Introduction

Systemic sclerosis (SSc) and systemic lupus erythematosus (SLE) are connective tissue diseases which may involve numerous internal organs, including the heart. A wide spectrum of cardiovascular events is also the major cause of morbidity and mortality in both diseases [1, 2]. However, except for one small study, direct comprehensive comparison of incidence of arrhythmias and conduction disturbances in SSc and SLE was not performed so far, which might be useful for physicians in making everyday decisions concerning prophylaxis and treatment of the heart complications in these patients [3].

In the natural clinical course of the heart involvement in SSc, various mild or potentially life-threatening arrhythmias

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and also pulmonary hypertension leading to right ventricle failure are found as the most frequent. The symptomatic heart involvement in SSc was also revealed as the strongest factor increasing mortality [4, 5]. In contrast in a meta-analysis concerning over 17,000 SLE patients, arrhythmias or conduction disturbances were not even listed as one of the most important predictors of death [6]. In fact, arrhythmias were not taken into account because arrhythmias were not assessed in previous studies which were included in this meta-analysis. In another multicentre study by Garcia et al. including 1437 SLE patients with disease duration ≤ 2 years, arrhythmias (which were not precisely described) were reported in 23 patients only [7]. However, sinus tachycardia is frequently reported in SLE, while available data on arrhythmias' occurrence are limited and ambiguous. In addition, the latest assessments are missing [6, 8–10].

It is well-known that cardiac autonomic nervous system (cANS) imbalance in specific conditions may exacerbate or trigger potentially life-threatening ventricular arrhythmias [11]. Cardiac ANS dysfunction seems to be a significant component of the heart involvement both in SSc and SLE too [12–16]. Hitherto, diminished cANS modulation in SSc and SLE was described using various indirect electrocardiographic methods, i.e., heart rate variability (HRV) or heart rate turbulence (HRT) and also post-exercise heart rate recovery [12–16]. However, no direct comparison of results of above-mentioned methods was performed in SSc and SLE, therefore potential differences between cANS modulation in these diseases were not clearly evaluated.

It appears that rhythm abnormalities are less detected than they should be and hence this study is trying to find out what we miss in routine practice. Thus, we performed rheumatological and cardiac non-invasive examinations of SSc and SLE subjects and also healthy controls. Our assessment focused on selected electrocardiographic abnormalities, cardiac arrhythmias, conduction disturbances and indirect evaluation of cANS function. Besides, we also performed the assessment of potential association between disease duration and evaluated abnormalities in both disorders.

Patients and methods

Study population

Initially 86 consecutive patients with SSc, 76 with SLE and 45 specially selected for this evaluation and the healthy volunteers (control group) were examined before inclusion into the study. The above patients were referred for routine cardiological assessment. Diagnosis of SSc and SLE (at least 1 year earlier) was performed by rheumatologists or dermatologists according to the defined international criteria [17, 18]. Subjects in the control groups were age-, sex- and body mass index-matched to the studied patients.

All examined persons were outpatients in stable condition who underwent detailed clinical cardiac and rheumatological examination, 12-lead electrocardiography, 24-h Holter monitoring, transthoracic echocardiography and basic laboratory tests (complete blood count, plasma levels of glucose, sodium, potassium, creatinine with estimated glomerular filtration rate total cholesterol, triglycerides and thyroid-stimulating hormone and also plasma activity of aspartate aminotransferase, alanine aminotransferase). Standards techniques were used to screen all patients for the following serological markers: anti-nuclear antibodies, anti-centromere antibodies, anti-extractable antigen antibodies including Scl-70 antibodies and antiphospholipid antibodies, when appropriate.

Systemic sclerosis patients were classified as having diffuse or limited form and the modified Rodnan skin score was used to assess the extent of skin involvement. Cumulative organ damage in SLE was assessed using SLICC/ACR Damage Index [19].

Since various factors may markedly influence both arrhythmias' occurrence and autonomic modulation, we excluded from further analysis patients with currently or previously detected coronary artery disease or history of myocardial infarction, left ventricular systolic dysfunction (ejection fraction < 50%), significant heart valvular abnormalities or left ventricle walls hypertrophy (> 12 mm). Treatment with antiarrhythmic drugs class I or III according to Vaughan–Williams classification and electrolytes abnormalities were also the exclusion criteria. Patients with significant anaemia (haemoglobin < 8.0 g/l), uncontrolled thyroid dysfunction and reduction in glomerular filtration rate < 30 ml/min were not included either. Only adult patients were included except for those > 80 years, as in older people arrhythmias' incidence substantially increases, while autonomic modulation decreases (irrespective of underlying systemic disease).

All patients and control subjects gave their written informed consent to participate in the study. This study was conducted in accordance with the amended Declaration of Helsinki. The study was approved by an independent ethics board (The Bioethics Committee in Medical University of Warsaw, Poland, no. KB 26/2012, 14-02-2012).

Standard electrocardiography and transthoracic echocardiography

Standard 12-lead tracings were acquired at 25 and 50 mm/s paper speed using electrocardiographic device (Philips, Page Trim III, NL). Precise assessment of all required features was performed. Intraventricular conduction defects were diagnosed, when QRS complexes' duration were > 110 ms

and specific criteria for complete or incomplete branch blocks or hemiblocks were fulfilled. The longest QT interval was used for corrected QT (QT_c) calculation with Bazett's formula. As various reports proposed different normal QT_c values (< 440–460 ms), the abnormal QT_c value for our study was defined as > 450 ms for all subjects. QT interval data were estimated for subjects without atrial fibrillation or intraventricular conduction disturbances. Analysis was performed by two qualified cardiologists according to aha/accf/hrs recommendations for the standardization and interpretation of the electrocardiogram.

Transthoracic echocardiography was performed using iE33 ultrasound system (Philips Medical System, USA). All standard dimensions and left ventricular ejection fraction were measured according to current recommendations. Pulmonary hypertension was considered likely when the tricuspid regurgitation peak gradient was > 31 mmHg. The analysis of echocardiographic data was performed by two independent qualified cardiologists.

24-h Holter monitoring with heart rate variability and turbulence

All subjects underwent 24-h Holter monitoring during normal everyday activity performed on a 3-channel digitized recordings (Lifecard-CF, Sentinel, USA). An evaluation of heart rate, arrhythmias, pauses and ischemia signs was performed (Impresario, Sentinel, USA). Non-sustained supraventricular and ventricular tachycardia were recognized when the heart rate was > 100 beat per minute for at least three consecutive beats and arrhythmia lasted < 30 s.

According to European and American Task Force 5 following indexes of time-domain HRV were measured: SDNN, SDNN-I, SDANN, RMSDD and pNN50 (abbreviations in Table 4) [20]. Turbulence onset (TO) describing early heart rate acceleration and turbulence slope (TS) describing late deceleration after ventricular premature beats were measured. HRT parameters were calculated using custom-designed software based on Schmidt et al.'s methodology (details in earlier publications) [13, 21]. Each Holter recording was analysed by a qualified cardiologist according to Standards of International Society for Holter and Noninvasive Electrocardiology [11, 21].

Statistical analysis

The patients and controls were compared by either Student's *t* test or the Mann–Whitney–Wilcoxon test, according to parameters' distribution assessed by Kolmogorov–Smirnov test. Variables with a normal distribution are presented as mean followed by standard deviation. Variables not showing the normal distribution are presented as median with range values. Deletions of outliers' data were not performed. Categorical variables were compared by Fisher's exact test. All tests were double-sided. Correlations were evaluated by Spearman correlation coefficient. Values of $p < 0.05$ were considered statistically significant. Analyses were performed using a software package (STATISTICA-13, StatSoft Inc., USA).

Results

Clinical characteristics and echocardiography data of study populations

The general characteristics of the study populations are shown in Table 1. Eventually, 74 patients with SSc and 70 with SLE were enrolled into the current study. The remaining SSc patients were excluded due to coronary artery disease (4 pts), aortic stenosis (1 pt), ostium secundum atrial septal defect (1 pt), hyperthyroidism (1 pt), impaired renal function (3 pts) and age > 80 years (two patients). Due to predefined criteria, six SLE patients were not included either (five with coronary artery disease and one with left ventricular systolic dysfunction).

Diffuse SSc was diagnosed in 32 (43.2%), while limited in 42 (56.8%) patients. In SSc subjects a median of calculated modified Rodnan Score was 4.0 (0–35), while in SLE group SLICC/ACR-DI was 3.63 ± 1.99 points. In spite of similar age and disease duration, SLE patients presented more frequently systemic arterial hypertension ($p = 0.0006$), while SSc patients signs of pulmonary arterial hypertension ($p = 0.006$).

The observed differences between SSc and SLE subjects concerning anti-inflammatory drugs resulted from distinct commonly used long-term therapy. It should be noticed that the most frequently used cardiovascular drugs in SLE patients were various beta-blockers ($p < 0.0001$), in contrast to SSc subjects in whom these agents were avoided due to peripheral arteries dysfunction (including Raynaud's syndrome). In SLE patients, beta-blockers were usually used due to the previously diagnosed arterial hypertension and/or sinus tachycardia. No subject of the control group received any vital drugs prescribed by a physician.

Potentially arrhythmic-related or cANS dysfunction symptoms in a past medical history (palpitations, dizziness, presyncope or syncope) were present in 42 (56.7%) SSc and also in 25 (35.7%) SLE patients, while the other subjects were nearly asymptomatic. An unexpected additional observation was also the fact that our SLE patients were the most often current cigarettes smokers, both in relation to SSc ($p < 0.0001$), as well to controls ($p = 0.02$).

Table 1 The general characteristics of the studied populations: systemic sclerosis (SSc), systemic lupus erythematosus (SLE) and control group (CG)

Characteristics	SSc ($n=74$)	SLE ($n=70$)	SSc vs SLE p value	CG ($n=45$)	SSc vs CG p value	SLE vs CG p value
Clinical and laboratory data						
Age (years)	51.9 ± 13.1	46.5 ± 12.7	0.11	48.3 ± 13.6	0.41	0.28
Body mass index (kg/m^2)	24.3 ± 4.56	24.47 ± 4.07	0.83	24.3 ± 2.9	0.97	0.85
Gender (female) (no. %)	67 (90.5%)	62 (88.6%)	0.79	37 (82.2%)	0.25	0.41
Current smokers (no. %)	4 (5.4%)	22 (31.4%)	**< 0.0001**	3 (6.7%)	1.0	**0.02**
Oxygen saturation at rest (%)[b]	96.9 ± 2.2	97.9 ± 1.0	**0.003**	98.1 ± 0.9	**0.001**	0.65
C-reactive protein (mg/l)[a]	2.5 (0.6–19.6)	1.3 (0.0–23.9)	**0.0006**	2.0 (0.1–7.0)	**0.04**	0.27
Haemoglobin concentration (g/dl)	13.3 ± 1.1	12.5 ± 1.5	**0.002**	13.6 ± 3.3	0.23	**0.0005**
SSc/SLE disease duration (years)[a]	6.0 (1.0–45.0)	8.5 (1.0–27.0)	0.15	–	–	–
Systemic arterial hypertension (no. %)	18 (24.3%)	37 (52.9%)	**0.0006**	0	–	–
Diabetes mellitus (no. %)	2 (2.7%)	3 (4.3%)	0.67	0	–	–
Pulmonary fibrosis (no. %)	28 (37.8%)	0	**< 0.0001**	0	–	–
Serological autoantibodies (no. %)[c]						
Anti-nuclear antibodies	72 (97.3%)	67 (95.7%)	–	–	–	–
Anti-centromere antibodies	22 (29.7%)	0	–	–	–	–
Anti Scl-70	40 (54.0%)	0	–	–	–	–
Other autoantibodies	6 (8.2%)	0	–	–	–	–
Antiphospholipid antibodies	0	14 (20.0%)	–	–	–	–
Transthoracic echocardiography						
Left ventricle ejection fraction (%)[a]	65.0 (50.0–73.0)	65.0 (55.0–70.0)	0.48	66.0 (60.0–71.0)	0.86	0.56
TRPG (mmHg)[d]	26.2 ± 6.2	21.5 ± 6.3	**0.0003**	17.4 ± 4.5	**< 0.0001**	**0.008**
TRPG > 31 mmHg[d] (no. %)	16 (23.9%)	4 (5.9%)	**0.006**	0	**0.02**	0.57
Pleural effusion (no. %)	2 (2.7%)	7 (10.0%)	**0.09**	0	0.53	**0.04**
Main anti-inflammatory and cardiological treatment (no. %)						
Glucocorticosteroids	6 (8.1%)	55 (78.6%)	**< 0.0001**	0	–	–
Immunosuppressive	4 (5.4%)	48 (68.6%)	**< 0.0001**	0	–	–
Antimalarial drugs	0	16 (22.9%)	**< 0.0001**	0	–	–
Peripheral arteries vascular drugs	53 (71.6%)	3 (4.3%)	**< 0.0001**	0	–	–
Angiotensin converting-enzyme inhibitors/sartans	17 (23.0%)	34 (48.6%)	**0.002**	0	–	–
Beta-blockers	4 (5.4%)	31 (44.3%)	**< 0.0001**	0	–	–
Calcium channel blockers[e]	13 (17.6%)	17 (24.3%)	0.41	0	–	–
Diuretics	9 (12.2%)	16 (22.9%)	0.12	0	–	–

Bold values are statistically significant

[a]Values presented as median with range

[b]Oxygen saturation at rest was possible to be measured in 67 SSc, 70 SLE and 45 CG subjects

[c]If the anti-nuclear antibody titer was below laboratory reference range in the latest assessment it was classified as absent

[d]TRPG = tricuspid regurgitation peak gradient (TRPG value was possible to be measured in 67 SSc, 67 SLE and 20 CG subjects)

[e]Predominatingly dihydropyridine-derived calcium channel blockers

Standard electrocardiography and Holter arrhythmias' data

Results of standard electrocardiography and Holter data are displayed in Table 2. Patients with SSc more frequently presented atrioventricular and intraventricular conduction disturbances (however not significantly) and the most frequent was right bundle brunch block coexisting with left anterior hemiblock (four patients). By contrast, in SLE

Table 2 Comparison of standard 12-lead electrocardiogram and 24-h Holter monitoring findings in studied groups: systemic sclerosis (SSc), systemic lupus erythematosus (SLE) and control group (CG)

Characteristics	SSc ($n=74$)	SLE ($n=70$)	SSc vs SLE p value	CG ($n=45$)	SSc vs CG p value	SLE vs CG p value
Standard electrocardiogram findings						
1st degree atrioventricular block (no. %)	4 (5.4%)	1 (1.4%)	0.37	0	0.30	1.0
Intraventricular conduction defects (no. %)	8 (10.8%)	3 (4.3%)	0.21	0	**0.02**	0.28
Corrected QT interval (ms)[a]	422 ± 21	432 ± 24	**0.02**	398 ± 22	**< 0.0001**	**< 0.0001**
Corrected QT interval ≥ 450 ms (no. %)[a]	6 (9.1%)	18 (26.5%)	**0.01**	0	0.08	**< 0.0001**
24-h Holter monitoring findings						
Mean heart rate (beat per min)	79 ± 10	72 ± 10	**0.0003**	75 ± 6	0.06	0.07
Supraventricular arrhythmias (no. %)						
Supraventricular premature beats > 100/24 h	19 (25.7%)	8 (11.4%)	**0.03**	5 (11.1%)	**0.06**	1.0
Non-sustained supraventricular tachycardia	37 (50.0%)	24 (34.3%)	**0.06**	5 (11.1%)	**< 0.0001**	**0.008**
Paroxysmal atrial fibrillation	4 (5.4%)	0	0.12	0	0.30	–
Ventricular arrhythmias (no. %)						
Ventricular premature beats > 100/24 h	18 (24.3%)	6 (8.6%)	**0.01**	4 (8.9%)	**0.05**	1.0
Bi-trigeminy and/or couplets	26 (35.1%)	10 (14.3%)	**0.004**	4 (8.9%)	**0.01**	0.56
Non-sustained ventricular tachycardia	10 (13.5%)	1 (1.4%)	**0.009**	0	**0.01**	1.0
Paroxysmal bradyarrhythmias (no. %)						
2nd degree atrioventricular block	7 (9.5%)	1 (1.4%)	**0.06**	1 (2.2%)	0.26	1.0
3rd degree atrioventricular block	2 (2.7%)	0	0.49	0	1.0	–
Sinus arrest or 2nd degree sinoatrial block	1 (1.3%)	0	1.0	0	–	–

Bold values are statistically significant

[a]Corrected QT interval value was possible to be measured in 66 SSc, 68 SLE and 45 CG subjects

more often repolarization abnormalities expressed by QTc interval prolongation were observed.

All types of arrhythmias, including non-sustained ventricular tachycardias were observed more commonly in SSc than in SLE or control subjects (except for atrial fibrillation). In SLE, only short supraventricular tachycardias were observed more often than in controls. No significant differences in ventricular arrhythmias between SLE and controls were observed either.

Since disease duration (in addition to age) seems to be one of the most important factor influencing arrhythmias' incidence, for additional analyses we divided patients into two subgroups depending on the median of disease duration: < 6.0 vs ≥ 6.0 years for SSc and < 8.5 vs ≥ 8.5 years for SLE patients. Results of comparison of selected characteristics in SSc and SLE according to diseases duration are presented in Table 3. Analysed subgroups of SSc were in similar age while SLE patients who were afflicted for a shorter period were younger. Our results indicate that disease duration, both for SSc and for SLE did not influence significantly the majority of evaluated abnormalities. However, the only important association was revealed for non-sustained ventricular tachycardia occurrence in SSc and this arrhythmia was observed much more frequently in patients who had been ill for a longer period ($p=0.02$).

Holter time-domain heart rate variability and turbulence data

Results of time-domain HRV and HRT data in Holter monitoring are presented in Table 4. All patients and healthy subjects had sinus rhythm during recordings. It should be underlined, that HRV parameters associated with sympathetic activity (SDNN, SDNN-I and SDANN) were similarly diminished in SSc and SLE patients, while parameters associated with vagal activity (RMSSD, pNN50) were not. In contrast to SSc patients, the values of RMSSD and pNN50 in SLE did not differ significantly when compared to healthy volunteers either. It should be noticed that mean heart rate in Holter monitoring was significantly higher in SSc than in SLE ($p=0.0003$), what would potentially influence HRV indices values. Likewise, both TO and TS values were significantly impaired in SSc as compared to controls. In SLE, only TS value (partly associated with sympathetic activity) was impaired, while TO value was not (mainly associated with vagal activity). Moreover, abnormal HRT occurrence was more often revealed in SSc than in SLE subjects.

Nevertheless, we did not demonstrate any correlations between disease duration and HRV or HRT parameters, both for SSc and also SLE patients. However, in SLE we demonstrated correlations between QTc length and HRV indices:

Table 3 Comparison of standard 12-lead electrocardiography and 24-h Holter monitoring findings in systemic sclerosis and systemic lupus erythematosus according to the median disease duration

Characteristics	Systemic sclerosis		*p* value
	Disease duration < 6 years (*n* = 34)	Disease duration ≥ 6.0 years (*n* = 40)	
Age (years)	50.5 ± 13.8	55.6 ± 15.1	0.13
Standard electrocardiography and Holter findings[a]			
Corrected QT interval (ms)[b]	420 ± 23	425 ± 20	0.27
1st degree AVB	0	4 (10.0%)	0.12
Intraventricular conduction defects	1 (2.9%)	7 (17.5%)	0.06
Supraventricular premature beats > 100/24 h	5 (14.7%)	14 (35.0%)	0.06
Non-sustained supraventricular tachycardia	18 (52.9%)	19 (47.5%)	0.82
Paroxysmal atrial fibrillation	2 (5.9%)	2 (5.0%)	1.0
Ventricular premature beats > 100/24 h	6 (17.6%)	12 (30.0%)	0.28
Bi-trigeminy and/or couplets	11 (32.3%)	15 (37.5%)	0.81
Non-sustained ventricular tachycardia	1 (2.9%)	9 (22.5%)	**0.02**
Paroxysmal 2nd degree atrioventricular block	3 (8.8%)	4 (10.0%)	1.0
Paroxysmal 3rd degree atrioventricular block	0	2 (5.0%)	0.50
Characteristics	Systemic lupus erythematosus		
	Disease duration < 8.5 years (*n* = 31)	Disease duration ≥ 8.5 years (*n* = 39)	
Age (years)	40.1 ± 12.8	49.6 ± 13.2	0.002
Standard electrocardiography and Holter findings[a]			
Corrected QT interval (ms)[b]	427 ± 27	436 ± 21	0.14
Supraventricular premature beats > 100/24 h	4 (12.9%)	4 (10.2%)	0.73
Non-sustained supraventricular tachycardia	12 (38.7%)	12 (30.8%)	0.61

Bold values are statistically significant

[a]No. (%)—except for QT interval data

[b]Corrected QT interval value was possible to measure in 66 SSc and 68 SLE patients

with SDNN ($r = -0.289$, $p = 0.02$), SDNN-I ($r = -0.431$, $p < 0.0001$), with RMSSD ($r = -0.364$, $p = 0.002$) and with pNN50 ($r = -0.355$, $p = 0.003$). No equivalent correlations for QTc in SSc were revealed.

Discussion

Cardiac arrhythmias, conduction disturbances and other electrocardiographic abnormalities in connective tissue diseases were described in several studies until now, usually performed on relatively small groups of patients. The issues discussed in our paper were also frequently summarized in various reviews or meta-analyses concerning mainly SSc, but not giving proper attention to SLE patients so far [1, 2, 10, 22].

In general, our Holter monitoring results revealed that various arrhythmias in SSc occur much more often than in SLE, especially ventricular arrhythmias including non-sustained tachycardia ($p = 0.009$). Interestingly, our SLE patients were characterised by relatively frequent incidence of short supraventricular tachycardia, but not frequent supraventricular premature beats. Moreover, atrial fibrillation was not observed in our SLE group at all. This small incidence of atrial fibrillation is thought-provoking, especially in relation to performed by Chen et al.'s meta-analysis which showed that in most SLE patients a significant increase in the left atrial diameter is observed, which is one of the most important risk factors increasing atrial fibrillation incidence (weighted mean difference 0.18, 95% CI 0.06–0.29) [8]. In the recent and one of the largest Holter evaluation of 142 Brazil SLE patients, paroxysmal atrial fibrillation was observed in 2.8% of cases, while the remaining results were similar to our assessment [23]. The similar incidence of atrial fibrillation (3%) was also revealed by Myung et al. during analysis of 235 SLE electrocardiograms at a single academic centre [24].

The precise mechanism of structural heart abnormalities in SLE remain unclear and is considered to be related to myocarditis and coronary artery disease. Then, it may

Table 4 Comparison of time-domain heart rate variability and heart rate turbulence in 24-h Holter monitoring in studied populations: systemic sclerosis (SSc), systemic lupus erythematosus (SLE) and control group (CG)

Characteristics	SSc ($n=74$)	SLE ($n=70$)	SSc vs SLE p value	CG ($n=45$)	SSc vs CG p value	SLE vs CG p value
Holter time-domain heart rate variability parameters[b]						
SDNN (ms)	120 ± 31	130 ± 36	0.09	156 ± 34	**< 0.0001**	**0.0002**
SDNN-I (ms)	40 ± 15	42 ± 16	0.51	56 ± 13	**< 0.0001**	**< 0.0001**
SDANN (ms)	110 ± 30	118 ± 34	0.13	145 ± 33	**< 0.0001**	**< 0.0001**
RMSSD (ms)[a]	22.2 (9.3–167.1)	27.8 (14.5–150.1)	**0.002**	32.5 (14.9–72.5)	**0.003**	0.81
pNN50 (%)[a]	2.9 (0.1–65.9)	5.5 (0.1–64.9)	**0.006**	7.3 (0.8–28.3)	**< 0.0001**	0.12
Holter heart rate turbulence parameters[c]						
TO (%)[a]	− 0.20 (− 5.38 to 5.96)	− 1.67 (− 8.66 to 4.87)	**0.002**	− 2.88 (− 10,43 to − 0,63)	**< 0.0001**	0.11
TS (ms/RR)[a]	5.96 (0.76–19.50)	7.81 (0.31–76.56)	**0.04**	13.36 (2.77–47.9)	**< 0.0001**	**0.03**
Abnormal HRT (no. %)[d]	28 (48.3%)	9 (25.7%)	**0.04**	0	**< 0.0001**	**0.002**
VPB/HRT (n)[a,c]	5 (2–1343)	4 (2–621)	0.43	2 (2–668)	0.07	0.34

Bold values are statistically significant

[a]Values presented as median with range

[b]*Heart rate variability parameters* SDNN = the standard deviation of N–N (normal-to-normal) interval; SDNN-I (index)—mean of the standard deviations of all N–N for all 5 min periods of the entire recording; SDANN = the standard deviation of the average of N–N in all 5 min periods of the entire recording; RMSSD = the square root of the mean of the sum of the squares of differences between adjacent N–N; pNN50 = number of pairs of adjacent N–N differing by more than 50 ms in the entire recording divided by the total number of all N–N [19]

[c]*Heart turbulence parameters* TO = turbulence onset; TS = turbulence slope; VPB/HRT = number of ventricular premature beats used for heart rate turbulence calculation; HRT values were possible to measure in 58 SSc, 35 SLE and 31 CG subjects

[d]As proposed by International Society for Holter and Noninvasive Electrocardiology, abnormal HRT was recognized if TO value was ≥ 0% and/or TS value was ≤ 2.5 ms/RR [20]

potentially be that often prescribed beta-blockers (in our SLE group in 44.3%) may play one of the crucial roles in the low occurrence of atrial fibrillation. It would be noticed that in above-mentioned Latin American SLE cohort just antimalarial treatment was negatively associated with the occurrence of primary cardiac disease risk (OR 0.62, 95% CI 0.44–0.89) [7]. Similarly, Teixeira et al. revealed potential protective role of chloroquine in cardiac arrhythmias and conduction disturbances in SLE [23]. Why such a treatment does not prevent supraventricular tachycardia in our study remains unclear.

Nevertheless, the lack of clear answer also concerns the relatively small incidence of ventricular arrhythmias in SLE (maybe also frequent beta-blockers treatment?). Then, one may speculate that the occurrence of various tachyarrhythmias in SSc might be reduced by more frequent use of beta-blockers, especially highly beta-1 selective ones (bisoprolol or nebivolol). However, concerns about the use of beta-blockers in SSc patients result from the potential deterioration of Reynaud's symptom or pulmonary function, as well as the possibility of advanced atrioventricular conduction disorders.

Actually, bradyarrhythmias in SSc patients occur relatively rarely, but it should be underlined that more often than in SLE or healthy subjects. The presence of atrioventricular, including complete heart blocks may also be associated with the presence of anti-Ro/SSA antibodies, what was proved both in SSc and in SLE patients [25, 26]. In contrast, the above-mentioned Myung et al. did not notice any bradyarrhythmias in theirs 235 SLE group at all [24].

Considering the treatment of ventricular arrhythmias with beta-blockers, it is worth mentioning that an improvement in beta-blocker tolerance in SSc may be obtained using them together with nondihydropyridine calcium channel blockers [27]. Others antiarrhythmic drugs should be reserved for cases with potentially life-threatening tachyarrhythmia only (especially amiodarone due to potential provoking or exacerbating interstitial lung disease). The potential necessity of invasive electrotherapy procedures should not be forgotten either, whereby detailed indications for SSc/SLE patients do not differ from those for general population.

Atherosclerosis progression and vascular complications in SLE are closely related to disease duration, in addition to higher damage index score and less aggressive immunosuppression [9]. In contrast, no strict association between diseases' duration and arrhythmia incidence or other selected electrocardiographic alternations was displayed in our SLE evaluation, similarly to the majority of estimated features in

SSc patients. It should be underlined that in our SSc subjects potentially life-threatening ventricular tachycardias were observed almost exclusively in long-lasting disease, i.e., in our study ≥ 6.0 years (in 22.5 vs 2.9%, $p = 0.02$). In contrast, such relationship was not observed for supraventricular tachycardia or paroxysmal atrial fibrillation. We did not find any other studies in which relationships between diseases' duration and arrhythmias' occurrence were estimated, both in SSc and in SLE patients. The high occurrence of various, including asymptomatic and potentially life-threatening arrhythmias in SSc patients (regardless from disease duration) may suggest the need for regular cardiological testing, including both electrocardiography and Holter monitoring. Recently published and concerning SSc cardiac disease recommendations provide detailed guidelines on this issue [28].

Our study was not focusing on a detailed standard electrocardiography assessment, because some interesting and accurate articles about various electrocardiographic abnormalities were published recently, both in SSc and SLE [24, 29–31]. In general, our results confirmed earlier observations indicating that in comparison to healthy controls SSc patients are characterised by more frequent incidence of various intraventricular conduction defects (in 10.8 vs 0%, $p = 0.02$), while SLE patients by more frequent prolongation of QTc (in 26.5 vs 9.1%, $p < 0.0001$) [24, 29–31]. The incidence of QTc prolongation in our SLE group (26.5%) is slightly higher as found by Myung et al. (17.0%) and it is probably associated with different applied criteria [24]. The precise mechanism of QTc prolongation in SLE remains unknown. It might be partly due to longer cardiac repolarization associated with cANS involvement, and our results of significant correlations between QTc length and HRV indices in SLE might indirectly confirm that hypothesis (but not in SSc patients).

It is worth noting that as described in previous studies and confirmed in the current evaluation cANS dysfunction in SSc and SLE might be an additional and important contributor to arrhythmias occurrence. So far, many studies presented results of Holter-derived assessment of cardiac autonomic function, both in SSc and in SLE patients [14–16, 32–34]. Therefore, we did not focused on comprehensive discussion on this issue either. Ours HRV and HRT results in SSc indicate an all-encompassing involvement of cANS. Interestingly, in SLE subjects decreased values of SDDN, SDDN-I, SDANN and also TS mainly indicate dysfunction of sympathetic part of autonomic regulation. However, in other reports when frequency-domain HRV analysis was used in SLE, impaired vagal modulation was also suggested [35].

Our study has also some limitations. It is a single-centre cross-sectional study which included a relatively limited number of cases. One of potential limitation of our evaluation is predominance of women both in SSc and in SLE groups, but such sex ratio is typical. It should also be underlined that various drugs, especially beta-blockers or antimalarial might influence heart rhythm, arrhythmias' prevalence and QTc interval length, so treatment with these medicines might influence obtained results. However, in the recent evaluation of 55 SLE patients, no significant influence of beta-blocker treatment on time-domain HRV parameters was observed [12]. Moreover, in spite of similar environment conditions during Holter monitoring, repetitive and the same conditions are possible in autonomic laboratory only. Therefore, an influence of various environment conditions on HRV and HRT parameters should be also taken into consideration in results interpretation. It could also be speculated that the duration of the diseases might be associated with more abnormalities than was revealed in our study. A regression analysis or dividing patients into three groups depending on the disease duration might be more suitable. However, due to many of examined parameters and relatively small number of examined patients and also a relatively small number of some categorical variables, we think that such evaluations would not be suitable for our evaluation. A definite limitation of our study is the fact that a presumably different pulmonary function, a different saturation with possible exercise desaturation and also even benign anaemia might have an influence on arrhythmias' occurrence and cANS function in presented groups of patients. However, the goal of our study was not to perform detailed evaluation concerning various factors influencing examined heart abnormalities. A systemic review of literature performed by Gowd and Thompson revealed that women have faster resting heart rates, longer QTc intervals and are two times likely to experience atrioventricular nodal reentry tachycardia than men. In addition, it was proved that supraventricular tachycardia before menopause varies with menstrual cycle, which was not determined in our study either [36].

Conclusions

In our study involving subjects without conditions strongly influencing arrhythmias occurrence, we revealed that SSc patients presented frequent incidence of various arrhythmias, as compared to SLE and healthy volunteers. On the other hand, SLE patients were characterised by prolonged QTc, which might be associated with compromised cardiac autonomic tone. Both SSc and SLE subjects presented impaired sympathetic modulation, while indices associated with parasympathetic activity in SLE were not diminished. Importantly, disease duration was not associated with arrhythmias' occurrence in both groups of patients, except for non-sustained ventricular tachycardia in SSc ones. Therefore, we think that our observations imply the need for routine cardiac screening of patients with connective tissue diseases, irrespective of disease duration (especially SSc subjects).

Author contributions All authors whose names appear on the submission have contributed sufficiently to the scientific work and therefore share collective responsibility and accountability for the results. All authors also fulfil ICMJE recommendations concerning authorship based on the following four criteria: (1) substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; (2) drafting the work or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Dr. Piotr Bienias as the main author had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

Ethical approval All procedures in this study were conducted in accordance with the amended Declaration of Helsinki. The study was approved by an independent ethics board (The Bioethics Committee in Medical University of Warsaw, Poland, no. KB 26/2012, 14-02-2012).

Informed consent All patients and control subjects gave their written informed consent to participate in the study.

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