Electrocardiographic Evaluation in Patients with Systemic Scleroderma and without Clinically Evident Heart Disease

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Background: In patients with systemic scleroderma (SSc), clinically evident cardiac involvement is recognized to be a poor prognostic factor. The aim of the study was to evaluate electrocardiographic changes, parameters of heart rate variability (HRV), and heart rate turbulence (HRT) in patients with SSc without evident symptoms of heart disease.

Methods: A group of 27 patients with SSc were subjected to standard electrocardiography (ECG) examination and 24-hour Holter monitoring. Analysis of HRV in time and frequency domains, HRT, and echocardiography were also performed.

Results: Holter monitoring revealed a larger number of premature supraventricular contractions (PSVCs), as well as premature ventricular contractions (PVCs) in the patients with systemic scleroderma, as compared with the control group. Moreover, the SSc patients showed decreased parameters of time and frequency domains, as referred to the controls, especially during night hours. In four patients, abnormal HRT values were present. On echocardiography, only slight changes were found, however in five patients left ventricle diastolic dysfunction was diagnosed.

Conclusions: The noninvasive electrocardiographic methods seems to be useful for detecting early heart involvement in course of SSc and could be recommended for routine used in clinical practice. Significance of HRT analysis in patients with SSc needs further elucidation.

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electrophysiology; autonomic nervous system; noninvasive techniques; heart rate variability; Holter/event recorders

Scleroderma is a systemic disease characterized by inflammation resulting in excess deposition of collagen, which leads to microvascular occlusion and clinical manifestation as fibrosis.¹ Visceral involvement results in renal, cardiac, and pulmonary disease with associated worsening of prognosis.² Cardiac complications in systemic sclero-

derma (SSc) contain congestive heart failure, myocardial disease, pericardial disease, conduction system disturbances and arrhythmias, nonspecific ST- and T-wave changes, also including sudden cardiac death.^{3–6} Heart involvement is an important complication affecting a prognosis of SSc, and scleroderma-related mortality might be associated

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with cardiovascular impairments, and particularly with heart failure.^{7,8} Because clinically evident cardiac involvement is considered as a poor prognostic factor regarding final outcome of scleroderma, all but none attempts to find noninvasive and feasible screening methods capable of determining SSc patients at high risk could be of great value.

In clinical practice, one of the easily available and noninvasive methods is 24-hour Holter ECG monitoring, containing heart rate variability (HRV) and heart rate turbulence (HRT) parameters. HRV is a useful measure of cardiovascular autonomic activity.⁹ Decreased HRV observed in patients after myocardial infarction is thought to be connected with increased cardiovascular risk.^{10,11} HRT means a fluctuation during sinus cycle length that occurs after a ventricular premature contraction (VPC) and is believed to be mediated via the baroreceptor reflex.¹² It is of documented predictive^{13,14} value in patients with previous myocardial infarction, however other applications of this method are also suggested.¹⁵

The aim of this study was to evaluate electrocardiographic changes, including parameters of HRV and HRT, in the patients with defined systemic scleroderma and without evident clinical presentation of heart involvement.

METHODS

A study population consisted of 27 patients (18 women and 9 men; mean age of 55.2 ± 11.3 years) with a prior diagnosis of systemic scleroderma according to the American College of Rheumatology criteria,^{16,17} who demonstrated no apparent symptoms of cardiac disease, and a control group of 23 healthy volunteers (11 women and 12 men age- and gender-matched; mean age: 49.7 ± 11.5 years). In 12 patients (44.4%), disseminated sclerosis was diagnosed contrary to 14 patients (51.8%), who manifested localized scleroderma. The examined patients complained of no serious diseases other than SSc and reported no symptoms related to cardiovascular system. Exclusion criteria included symptomatic cardiac condition (myocardial infarction, arterial hypertension, diabetes mellitus, or valvular disease), as well as pulmonary diseases. None of the examined patients declared symptoms of angina pectoris or syncope. A palpitations feeling was reported by 11 patients (40.7%). All the patients presented normal chest x-ray and spirometry results. None of the patients had a history

of smoking tobacco. The mean duration of SSc at the time of study entry, evaluated from the clinical file data, was 8.4 ± 5.3 years. Patients were not taking corticosteroids and/or D-penicillamine within the time of the study. The informed consent was taken from all the patients and the controls before enrollment to the study as well as the approval of the local ethics committee was obtained.

Recordings of 12-lead electrocardiography (ECG) were collected in all of the examined SSc patients. Analysis of QTc was made using a Bazett formula, and the ECG lead with the longest QT period was chosen for analysis. In the SSc patients, 24-hour Holter monitoring was performed using 3-lead HolCARD 24W System (Aspel S.A., Zabierzow, Poland). All recordings were edited manually to exclude artifacts and noise. To evaluate cardiovascular autonomic function, HRV on 24-hour electrocardiogram recordings was analyzed as to time and frequency domains for 24 hours, separately for day activity hours (6.00–22.00) and for night resting hours (22.00–06.00).

The following parameters of HRV in the time domain were analyzed: standard deviation of all the normal sinus RR intervals in milliseconds (SDNN), standard deviation of the averaged normal sinus RR intervals for all 5-mm segments (SDANN), means of the standard deviations of all normal sinus RR intervals for all 5-minute segments in milliseconds (SDNNI), root-mean-square of successive normal sinus RR interval difference in milliseconds (rMSSD), percentage of successive normal sinus RR intervals >50 ms (pNN50). The following frequency domain variables were computed: ultra low frequency (ULF) power from 0 to 0.0033 Hz, very low frequency (VLF) power from 0.0033 to 0.04 Hz, low frequency (LF) power from 0.04 to 0.15 Hz, high frequency (HF) power from 0.15 to 0.4 Hz, likewise LF/HF ratio. The fast Fourier transformation method was used to evaluate the power spectral density of the RR series. The time and frequency domain measures of HRV were analyzed by the methods recommended by the Task Force of the European Society of Cardiology.⁹

For analysis, HRT, turbulence onset (TO) and turbulence slope (TS) were calculated according to the method described by Schmidt et al.¹² Echocardiography was performed with the SONOS 2000 ultrasound unit (Hewlett Packard, Andover, MA, USA) and SONOS 5500, (Agilent Technology, Santa Clara, CA, USA).

Statistical Analysis

Quantitative variables were expressed as the mean $\pm$ SD. Statistical analysis was performed using STATISTICA PL 6.0 package (StatSoft Polska, Krakow, Poland). Distribution of data was confirmed by the Shapiro-Wilk's W test. Because of the non-normal distribution of the data, the Mann-Whitney's test was performed. Qualitative data were expressed as percents. Qualitative nondependent variables were analyzed by chi-square test. P value less than 0.05 was considered statistically significant. Linear correlation was tested by use of the Sperman's r coefficient.

RESULTS

Analysis of the 12-lead ECG recordings revealed the following pathologies in 11 out of 27 (40.7%) patients with SSC: left anterior fascicular block (LAFH), incomplete right bundle branch block (RBBB), premature ventricular contractions (PVCs), pathological Q waves (>40 ms and $>25\%$ of the height of $R_{III,aVF}$ leads), right atrial enlargement (RAE), and prolonged corrected QT interval (QTc >440 ms). Changes in the 12-lead ECG tracings are shown in Table 1. None of the above-mentioned ECG pathologies were detected in the control group.

In the patients with SSC, the mean heart rate in 24-hour Holter monitoring was not significantly different from the normal individuals (75 ± 9 bpm vs. 77 ± 7 bpm; NS). There were statistically more numerous premature supraventricular contractions (PSVCs) and PVCs in the group with systemic scleroderma, as compared with the control group (198 ± 624 vs. 14 ± 27 , $P < 0.01$ and 112 ± 158 vs. 11 ± 16 , $P < 0.01$; respectively), as shown in Table 1. In only one patient (3.7%) from the

SSc group, a short episode (<1 second) of paroxysmal atrial fibrillation was present, and in four patients (14.8%) the short episodes of supraventricular tachycardia (SVT) were observed. These episodes were excluded from the HRV and HRT analysis. None of those findings were observed in the normal subjects. Other pathologies in systemic scleroderma group included: bigeminy in two patients (7.4%), and couplets in two patients (7.4%). In the control group, those disturbances were not detected. The analysis of ST-T changes in the study group revealed: in one patient (3.7%) 1-mm elevation of the ST segment, in two patients (7.4%) inverted T wave, in two patients (7.4%) depressed ST segment (>1 mm), and in two patients (7.4%) depressed ST segment due to SVT. In the control group, none of such ST-T abnormalities were noted.

The mean SDNN value on 24-hour Holter recordings was significantly lower in the SSc group than in the control group ($P < 0.01$). The remaining parameters of a time domain analysis did not differ significantly in comparison with normal subjects, though there was a clear tendency toward lower values in the group of SSc patients (Table 2).

In the HRV frequency analysis, VLF and LF values were significantly lower in the patients with SSc, as compared with the healthy subjects (Table 2). LF and VLF parameters as well as LF/HF ratio taken from the day activity HRV were significantly lower in the SSc patients than in the control group ($P < 0.05$, $P < 0.05$, and $P < 0.01$, respectively), but there were no significant differences in the time domain parameters between the SSc patients and the normal subjects (Table 3). During the night hours, SDNN, SDNNI, SDANN, rMSSD, pNN50 as well as VLF, LF, and HF were significantly lower in the group with SSc than in the controls (Table 4).

In all the patients with systemic scleroderma, the mean TS and the TO values were 21 ± 11 ms/RR-interval and $0.095 \pm 0.01\%$, respectively. According to a definition, the mean TS was abnormal (TS < 2.5 ms/RR-interval) in two patients (7.4%) with values of 2.04 and 1.61 ms/RR-interval. The mean TO was out of limits ($>0\%$) in three patients with SSc (11.1%) with values of 0.0155, 0.0045, and 0.0015%. In the majority of the controls, the values of TO and TS could not be calculated because of absence of the required number of PVCs.

Table 1. Analysis of 12-Lead ECG Recordings in the Patients with SSc

ECG Abnormalities	No. of Patients
Normal ECG	16
Incomplete right bundle branch block	1
Left anterior fascicular block	5
Pathological Q waves (in III and aVF)	2
Premature ventricular contractions	1
Right atrial enlargement	1
Prolonged corrected QTc (>440 ms)	1

Table 2. Results of HRV Time and Frequency Analyses in the Patients with SSc in Comparison with the Control Group

Parameter	Patients with SSc (n = 27)	Control Group (n = 23)	P Value
SDNN (ms)	128.40 ± 48.05	167.17 ± 31.09	P < 0.01
SDNNi (ms)	48.00 ± 22.23	61.04 ± 15.55	NS
SDANN (ms)	111.50 ± 40.46	149.26 ± 28.68	NS
rMSSD (ms)	48.60 ± 41.20	52.13 ± 25.44	NS
pNN50 (%)	9.58 ± 10.84	16.50 ± 11.32	NS
ULF (ms ²)	999.40 ± 582.06	1049.39 ± 232.99	NS
VLF (ms ²)	2893.90 ± 1076.48	3968.26 ± 793.35	P < 0.01
LF (ms ²)	3116.80 ± 1895.71	4703.13 ± 1161.35	P < 0.01
HF (ms ²)	4186.90 ± 3668.42	5661.83 ± 3269.11	NS
LF/HF	0.90 ± 0.30	0.95 ± 0.28	NS

NS = statistically nonsignificant.

Table 3. Results of HRV Time and Frequency Analyses in the Patients with SSc in Comparison with the Control Group during Day Hours (06.00–22.00)

Parameter	Patients with SSc (n = 27)	Control Group n = 23	P Value
SDNN (ms)	71.85 ± 33.76	91.39 ± 29.31	NS
SDNNi (ms)	44.46 ± 16.73	54.83 ± 16.13	NS
SDANN (ms)	52.69 ± 25.92	67.39 ± 26.89	NS
rMSSD (ms)	43.00 ± 31.41	41.96 ± 20.56	NS
pNN50 (%)	7.93 ± 9.02	12.33 ± 12.60	NS
ULF (ms ²)	314.86 ± 304.22	186.74 ± 65.72	NS
VLF (ms ²)	549.79 ± 230.08	706.83 ± 183.23	P < 0.05
LF (ms ²)	706.71 ± 405.91	982.61 ± 317.90	P < 0.05
HF (ms ²)	960.50 ± 696.18	924.57 ± 424.63	NS
LF/HF	0.84 ± 0.27	1.17 ± 0.34	P < 0.01

NS = statistically nonsignificant.

Table 4. Results of HRV Time and Frequency Analyses in the Patients with SSc in Comparison with the Control Group during Night Hours (22.00–06.00)

Parameter	Patients with SSc (n = 27)	Control Group (n = 23)	P Value
SDNN (ms)	69.14 ± 30.92	114.65 ± 43.39	P < 0.01
SDNNi (ms)	45.14 ± 18.18	76.96 ± 31.16	P < 0.01
SDANN (ms)	52.57 ± 22.93	75.78 ± 33.00	P < 0.05
rMSSD (ms)	42.07 ± 29.99	69.09 ± 41.95	P < 0.05
pNN50 (%)	13.68 ± 17.40	29.27 ± 21.76	P < 0.05
ULF (ms ²)	353.57 ± 322.62	204.52 ± 108.55	NS
VLF (ms ²)	572.57 ± 214.47	959.17 ± 325.81	P < 0.001
LF (ms ²)	571.64 ± 291.93	1182.87 ± 517.59	P < 0.001
HF (ms ²)	824.43 ± 554.00	1462.39 ± 835.30	P < 0.05
LF/HF	0.84 ± 0.42	0.94 ± 0.33	NS

NS = statistically nonsignificant.

The linear regression analysis in the SSc group showed a negative linear correlation between TS and age ($r = -0.60$; $P < 0.05$), positive linear correlations between the night TS and LF, and the night TS and VLF ($r = 0.89$, $P < 0.05$ and $r = 0.85$, $P < 0.05$, respectively).

As to echocardiography, the results were quite normal in five patients of the SSc group. In two patients, interventricular septum diastolic diameter was thickened (IVSDd > 11 mm), and in one patient enlargement of right ventricle was present (RVDD > 26 mm). Mild pulmonary hypertension was diagnosed in two patients (maximal systolic pressure in pulmonary artery: 35 and 47 mmHg, respectively). Only mild, hemodynamically insignificant valvular lesions were observed in 12 patients, and only in one patient it was of clinical significance (moderate insufficiency of tricuspid valve). In five patients, left ventricle diastolic dysfunction was recognized. It should be stressed that there were no significant pathologies on echocardiography in the control group.

DISCUSSION

Clinically overt symptoms of heart involvement were described in 20–25% of patients with SSC, although autopsy studies have revealed changes, such as myocardial fibrosis and pericardial effusion, ranging from 30 to 80% of those patients.^{1,8} Clinically evident cardiac disease is assessed as poor prognostic factor, and especially serious arrhythmias can be life threatening for SSc patients.¹⁸ Heart involvement in course of SSc may stay undiagnosed for a long time. In this context, it seems reasonable to search for signs of early changes in cardiovascular system in patients with SSc.

Our analysis of 12-lead ECG in the SSc group revealed left anterior fascicular block in six patients, pathological Q in the leads representing inferior wall in two patients, and in one patient prolonged corrected QT interval was found. In a similar group of SSc patients, Wranicz et al. also reported no prolongation of QTc.¹⁹ The electrocardiographic changes in patients SSc with more advanced heart disease are often secondary to pulmonary hypertension. Wokhlu correlated P wave findings on the 12-lead ECGs with mean pulmonary artery pressure measured by right heart catheterization in patients with SSc and found it helpful in assessment of pulmonary hypertension in course of this disease.²⁰ In our study, only in two patients the fea-

tures of mild pulmonary hypertension were found, including 12-lead ECG changes in one patient with RAE.

On 24-hour Holter recordings taken from SSc patients, several pathologies were observed by various authors. In our study, the major findings concerned significantly higher number of premature contractions (supraventricular and ventricular) indicating a possible arrhythmogenic substrate within myocardium. Those results are consent with observations of Morelli et al., who additionally confirmed higher incidence of supraventricular tachycardia in patients with SSc, as compared to controls.²¹ In our study, four patients manifested also supraventricular tachycardia and in one case a short episode of atrial fibrillation appeared.

In our SSc patients, we did not observe any significant differences in the mean heart rate as compared with the normal subjects, contrary to the others.²²

HRV analysis revealed the decreased parameters of time and frequency domains, like SDNN, VLF and LF, in the reported SSc patients in comparison with the controls. Similar results were obtained by Wranicz et al. in 24-hour Holter monitoring.¹⁹ In our observations, VLF, LF, and LF:HF ratio during day hours were statistically reduced in relation to the normal subjects. However during night hours, majority of parameters of time and frequency HRV analysis were significantly lower in the SSc group than in the control group. Reduction in LF and HF power in the patients with SSc, although described by some authors in 24-hour Holter monitoring, were not confirmed by the others.^{19,21}

SDNN parameter represents joint sympathetic and parasympathetic modulation of the heart rate.⁹ The efferent vagal activity is a major contributor to the HF component.^{22,23} Some studies suggest that LF component is a quantitative marker of sympathetic modulations and the others consider LF as reflecting both sympathetic activity and vagal activity.^{9,23,24} Consequently, the LF:HF ratio is thought to reflect sympathovagal balance or sympathetic modulations.^{11,23,24} Physiological interpretation of VLF oscillations is still a subject of debate; however reduction in VLF is associated with increased risk of cardiac death.²⁵ Different physiological mechanisms for VLF have been proposed, among others: physical activity, thermoregulation, renin-angiotensin-aldosterone alterations; however it is mainly regarded to reflect parasympathetic activity.^{26–28}

HRT, describing the short-term fluctuation in sinus cycle length that promote premature ventricular contractions, has a proven clinical significance based on its ability to predict mortality and sudden cardiac death following myocardial infarction.¹² In the present studies, we made an attempt to apply HRT analysis; however considering our results, there are too few data to decide, whether it could be routinely used in patients with scleroderma. Only in four SSc patients, we found abnormal TS or TO parameters, and in one patient both HRT parameters were impaired. This subgroup of the SSc patients was not characterized by either higher heart rate, higher number of PSVCs and PVCs, or by any other specific features.

In the examined SSc patients, no signs of systolic cardiac dysfunction were found, whereas in five patients, left ventricle diastolic dysfunction (impaired relaxation) was recognized. The impaired relaxation of the left ventricle was earlier reported as a feature of scleroderma heart disease.²⁹ Initial phase of myocardial damage, investigated with 99m Tc methoxyisobutylisonitrile (MIBI) gated perfusion SPECT and 123I metaiodobenzylguanidine (MIBG), showed in patients with SSc a high prevalence of diastolic dysfunction and sympathetic abnormality.⁷ SSc patients often show angiographically normal epicardial coronary arteries and normal left ventricular function, despite decreased coronary flow and resistance reserve.³⁰

Valvular lesions were observed by us in 13 patients, but only in one case it was hemodynamically important. Only two patients had mild pulmonary hypertension. This pathology is a serious complication of SSc and constitutes a leading cause of death in SSc patients.³¹ WHO recommends annual echocardiography screening for pulmonary arterial hypertension in patients with SSc.³¹ However, considering electrocardiographic changes in patients with SSc, it seems reasonable to recommend rest 12-lead ECG examination, as well as 24-hour Holter monitoring in patients with SSc and repeating them periodically, as it is indicated by echocardiography findings.

CONCLUSIONS

The decreased parasympathetic and sympathetic tone of the autonomic activity along with the significantly higher number of PSVCs and PVCs observed in the patients with SSc without overt clinical manifestations of heart involvement confirms a

thesis that electrocardiographic evaluation, including Holter monitoring and HRV analysis, could be helpful in stratifying and treating SSc patients. As of now, there are insufficiently reliable data collected to decide whether HRT could be applicable in early stages of heart involvement in SSc.

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