Abnormalities of heart rate turbulence and heart rate variability as indicators of increased cardiovascular risk in patients with systemic sclerosis

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Abstract

Introduction: Systemic sclerosis (SSc) is a connective tissue disease manifested by progressive fibrosis of many internal organs including the cardiovascular system and development of autonomic disorders with sympathetic predominance. These abnormalities can increase cardiovascular mortality.

Aim: To evaluate heart rate turbulence (HRT) and variability (HRV) parameters (indicator of autonomic imbalance) obtained from 24-hour ECG Holter monitoring, as predictors of the increased cardiovascular risk in patients with scleroderma.

Material and methods: Thirty-two scleroderma patients and 30 healthy people were included. After clinical examination, ECG, routine laboratory tests and echocardiography, participants performed 24-hour Holter-ECG at home. For HRT assessment, turbulence onset (To) and turbulence slope (Ts) parameters were used. Both time and frequency domain analysis of HRV was used. The HRV circadian rhythm was also evaluated.

Results: Time domain: SDNN, SDNN-ix, SDANN and frequency domain: LF, VLF, ULF, NHF, NLF, parameters were lower, while p50NN was higher in SSc as compared to the control group. There was also a loss of the circadian rhythm for r-MSSD and p50NN present in the control group. Abnormal HRT parameters To and/or Ts occurred in the SSc group only. The median value of To = –1.24% and Ts = 11.13 ms/RR did not differ significantly as compared to the control group.

Conclusions: The study confirmed the presence of HRV disturbances, including HRV circadian rhythm, as it may seem at an early stage of SSc. The HRT disorders may be characterized by the increasing changes with advancing disease. This indicates the presence of autonomic imbalance and an increased cardiovascular risk.

Key words: systemic sclerosis, autonomic disorders, heart rate variability, heart rate turbulence, cardiovascular risk, circadian rhythm.

Introduction

Systemic sclerosis (SSc) is a connective tissue disease manifested by involvement not only of the skin and subcutaneous tissue, but also many internal organs. It is characterized by progressive fibrosis and is associated with a significantly higher mortality compared with the general population [1–4]. The increased mortality is mainly due to involvement of the internal organs and the presence of specific autoantibodies [5]. The mortality rate in patients with SSc is from 1.5 to 7.2 times higher than that of the general population. Cardiac involvement appeared to increase the death rate by 2.8 times with no difference between disseminated and localized forms [5]. It is postulated that also microcirculation abnormalities, endothelial lesions and microvascular “Raynaud’s phenomenon” are involved in the intensification of changes within the myocardium [1, 6]. Fibrosis and its maldistribution result in a significant electrical heterogeneity of the heart and the increased risk of severe arrhythmia, including ventricle life-threatening arrhythmia [7]. It is postulated that the microvascular sympathetic-parasympathetic imbalance potentiates endothelial damage and accelerates the development of myocardial fibrosis [8–11].
One of the acknowledged methods of assessing the cardiovascular risk and efficiency of the autonomic nervous system is the measurement of heart rate variability (HRV) and heart rate turbulence (HRT) [12, 13]. Typically 24-hour Holter ECG recording is used. The assessment takes into account many parameters of HRV and HRT. Some data show a heightened risk of dangerous arrhythmias and increase in mortality in case of abnormal HRV and HRT values in various disease states, including heart failure, after myocardial infarction, cirrhotic cardiomyopathy and others [14–16].

The phenomenon of heart rate turbulence describes the short-term heart rate variability occurring during the sinus rhythm that appears after a premature or paced ventricular contraction. This leads to an initial acceleration (early acceleration) and then deceleration (late deceleration) of the heart rate. Measurement of these two consecutive phases is obtained through $T_0$ (turbulence onset) and $T_s$ (turbulence slope) parameters. Normal values of these parameters are $T_0 < 0\%$ and $T_s > 2.5\ ms$ [12]. There are divergent data regarding differences in HRV and HRT parameters comparing SSc patients with healthy people [8–11, 17, 18].

**Aim**

The aim of this study was to evaluate heart rate turbulence and heart rate variability parameters (indicator of autonomic imbalance) obtained from 24-hour ECG Holter monitoring, as predictors of the increased cardiovascular risk in patients with scleroderma.

**Material and methods**

The initial qualification for the study included 54 consecutive ambulatory patients. Scleroderma was diagnosed in accordance with the criteria of the American College of Rheumatology [19]. All patients underwent a basic clinical examination, had the ECG, routine laboratory tests and echocardiography performed. In the past 12 months all the patients underwent a chest radiography or high-resolution computed tomography (HRCT) and spirometry. Furthermore, each participant had plasma autoantibodies typically present in SSc. Exclusion criteria included myocardial infarction, liver cirrhosis, heart failure class II and above, according to the NYHA classification, other than sinus heart rhythm assessed by ECG, uncontrolled hypertension, renal insufficiency (GFR $< 30\ ml/min/1.72\ m^2$), diabetes, autoimmune diseases other than scleroderma, current smoking and drinking alcohol. The study included only patients without significant changes in laboratory tests and echocardiography, without pulmonary hypertension (HP) and history of significant disorders, cardiovascular disorders, inflammatory diseases and cancer (patients with the history of successful treatment of cancer longer than 5 years were considered healthy). According to the above criteria, 32 people were qualified for the study.

The control group comprised 30 people selected according to sex and age, not treated for autoimmune diseases as these constitute exclusion criteria. People included in the study underwent 24-hour Holter ECG at home.

Because of the fact that the study included one male only, statistical analysis was performed only for the group of 31 women.

Written informed consent was obtained from all the participants.

**24-hour ECG Holter monitoring and further analysis**

All participants underwent the 24-hour ECG recording. This study was carried out using the Aspect 702 recorder by Aspel Zabierzów, Poland. The quality of obtained data was assessed and verified by a cardiologist experienced in non-invasive electrocardiology. Records with sufficient quality were subsequently subjected to automatic computer analysis—Holcard analysis system—by Aspel Zabierzów, Poland. This was followed by an automatic detection of QRS complexes, the parameters of heart rate turbulence and analysis of time and frequency domain heart rate variability.

The study used two most common HRT indices—$T_0$ and $T_s$ [20, 21]. Their analysis and calculation were performed automatically by applications, which were a part of a commercial Holter analysis system.

For the evaluation of HRV, the Fast Fourier Transformation test was used. The assessment was performed for the entire 24-hour observation period. For further comparisons, both time and frequency domain analyses of HRV were used. The study used the typical time domain parameters—the average RR intervals of sinus rhythm, SDNN, SDANN, SDNNi—SDNN index, r-MSSD, p50NN, Tri—HRV triangular index, TINN—the triangular interpolation of NN interval histogram and the following frequency domain parameters—total power of frequency domain heart rate variability.

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The obtained parameters were analysed separately for the whole day and for the morning activity hours—between 8:00 and 12:00 and night resting hours—between 24:00 and 4:00.

**Ethics**

The study was performed in agreement with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Bioethics Committee of the Medical University of Lodz No. RNN/591/09/KB.
Statistical analysis

Statistical analysis was performed using Statistica 8 PL (StatSoft Inc.). The distribution of the population was verified by the Shapiro-Wilk test. Continuous variables usually differed from normal distribution. To conclude, for the significance of differences between the groups, ANOVA, Kruskal-Wallis rank test, Mann-Whitney and Wilcoxon nonparametric tests were used. For the data of close to normal distribution, Student's and Wilcoxon nonparametric tests were used. Statistical significance was indicated for p < 0.05. As in some other works, frequency domain parameters were also presented in the form of a natural logarithm. Results were presented as mean and standard deviation and as median, and minimum and maximum values. The existence of any correlation between the parameters was tested using Spearman rank correlation test.

Results

Study groups did not differ significantly in terms of basic anthropometric parameters. Patients with scleroderma were characterized only by a higher minimum heart rate, compared with the control group (52.42/min vs. 47.73/min; p < 0.005). These data are presented in Table 1. The median duration of the disease was 5.5 (0.67–20.0) years. 73.3% of the women were post-menopausal and in the control group they accounted for 57.0% (p < 0.05). In the group of SSc, ANCA occurred in 16.6%, Acl-70 in 50% and anti-Ro-52 in 20%. Nineteen persons had the lSSc and 12 dSSc form. Bearing in mind the opinion presented in the current literature that there are no significant differences in the studied HRT and HRV parameters, the analysis was conducted jointly for both groups.

Table 1. Comparison of basic parameters of the tested groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SCL (n = 31)</th>
<th>Control (n = 30)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>53.94 ±10.64</td>
<td>53.53 ±10.53</td>
<td>0.863</td>
</tr>
<tr>
<td>Weight</td>
<td>66.07 ±13.40</td>
<td>68.12 ±10.73</td>
<td>0.360</td>
</tr>
<tr>
<td>Height</td>
<td>160.74 ±8.51</td>
<td>162.87 ±6.18</td>
<td>0.155</td>
</tr>
<tr>
<td>BMI</td>
<td>25.61 ±5.22</td>
<td>25.73 ±4.37</td>
<td>0.735</td>
</tr>
<tr>
<td>Waist</td>
<td>84.15 ±12.68</td>
<td>84.22 ±9.63</td>
<td>0.795</td>
</tr>
<tr>
<td>Max HR [beats/min]</td>
<td>125.94 ±10.20</td>
<td>123.00 ±7.99</td>
<td>0.983</td>
</tr>
<tr>
<td>Min HR [beats/min]</td>
<td>52.42 ±6.22</td>
<td>47.73 ±5.33</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>Mean HR [beats/min]</td>
<td>83.65 ±7.19</td>
<td>80.63 ±6.76</td>
<td>0.106</td>
</tr>
</tbody>
</table>

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The HRT parameters were classified in accordance with current standards [13]. Among patients with SSc – 19 had at least 5 ventricular beats suitable for analysis. Abnormal values of To ≥ 0% and/or Ts ≤ 2.5 ms/RR occurred only in this group. One person had two abnormal parameters – To = 0.63% and Ts = 2.2 ms/RR and only one abnormal To = 2.58 ms/RR. All the control group had correct To and Ts parameters. The median values were To = –1.24% (min. –10.71; max. 2.58) and Ts = 11.13 ms/RR (min. 2.20; max. 28.65). These values did not differ significantly as compared with the control group, where the median values were To = –1.36% (min. –4.53, max. –0.41), and Ts = 11.46 ms/RR (min. 2.60; max. 31.80).

Statistically significant differences were noted in the majority of evaluated HRV parameters between women with SSc and the control group (Table 2). These were lower in the case of SDNN, SDNN-ix and SDANN and higher for p50NN. In turn, the frequency domain parameters were generally lower in SSc patients.

Table 2. Comparison of HRV parameters in time and frequency domains between the study and the control group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SCL (n = 31)</th>
<th>Control (n = 30)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean NN [ms]</td>
<td>797.7 ±81.4</td>
<td>838.3 ±89.2</td>
<td>0.096</td>
</tr>
<tr>
<td>SDNN [ms]</td>
<td>136.1 ±39.9</td>
<td>156.6 ±29.8</td>
<td>0.024</td>
</tr>
<tr>
<td>SDNN-ix [ms]</td>
<td>41.0 ±12.2</td>
<td>48.5 ±11.7</td>
<td>0.031</td>
</tr>
<tr>
<td>SDANN [ms]</td>
<td>122.9 ±37.8</td>
<td>143.2 ±29.5</td>
<td>0.017</td>
</tr>
<tr>
<td>r-MSSD [ms]</td>
<td>34.0 ±20.5</td>
<td>35.7 ±16.3</td>
<td>0.264</td>
</tr>
<tr>
<td>p50NN (%)</td>
<td>11.2 ±26.4</td>
<td>10.5 ±7.8</td>
<td>0.035</td>
</tr>
<tr>
<td>Tri</td>
<td>75.9 ±20.0</td>
<td>81.8 ±16.7</td>
<td>0.223</td>
</tr>
<tr>
<td>TINN</td>
<td>694.7 ±237.3</td>
<td>726.8 ±107.4</td>
<td>0.283</td>
</tr>
<tr>
<td>TP [ms²]</td>
<td>11845.3 ±6029.8</td>
<td>12746.2 ±4289.9</td>
<td>0.093</td>
</tr>
<tr>
<td>HF [ms²]</td>
<td>3372.90 ±2535.19</td>
<td>3762.67 ±1677.68</td>
<td>0.082</td>
</tr>
<tr>
<td>LF [ms²]</td>
<td>2894.5 ±1673.8</td>
<td>3379.4 ±1060.7</td>
<td>0.011</td>
</tr>
<tr>
<td>VLF [ms²]</td>
<td>2853.5 ±871.7</td>
<td>3450.6 ±787.6</td>
<td>0.003</td>
</tr>
<tr>
<td>ULF [ms²]</td>
<td>854.4 ±211.7</td>
<td>1002.4 ±211.7</td>
<td>0.018</td>
</tr>
<tr>
<td>NHF</td>
<td>39.7 ±5.4</td>
<td>42.7 ±5.3</td>
<td>0.035</td>
</tr>
<tr>
<td>NLF</td>
<td>36.8 ±6.5</td>
<td>40.2 ±5.3</td>
<td>0.025</td>
</tr>
<tr>
<td>LF/HF</td>
<td>0.95 ±0.26</td>
<td>0.96 ±0.23</td>
<td>0.746</td>
</tr>
</tbody>
</table>
A separate analysis for the morning activity hours and for night resting hours are shown in Table 3. In the morning activity, SSc patients had significantly lower proved average NN, SDNN-ix, p50NN, TP, LF and VLF. In the bedtime, in SSc group all of the time domain, and most frequency domain parameters were statistically significantly lower compared to the healthy group. Next, circadian variations of HRV were evaluated (Table 4). In the control group all of time domain parameters were significantly different between the morning activity
and night resting hours. Also among the parameters of frequency domain there were significant differences for HF, LF, ULF and NHF noted. In women with SSc, there were no such differences for r-MSSD and p50NN. In turn, of the frequency domain parameters such differences occurred only for ULF and NHF.

It revealed the presence of a statistically significant ($p < 0.05$) positive correlation between To and Ix-Triangle ($R = 0.463$), and a negative correlation between To and NLF ($R = -0.666$), To and LF/HF ratio ($R = -0.468$), Ts and Ix-Triangle ($R = -0.456$) and between Ts and TINN ($R = -0.467$). In addition, there was a negative correlation between the duration of the disease and To ($R = -0.530$) and between waist circumference and To ($R = -0.471$) and a positive correlation between the body weight and To ($R = 0.468$).

**Discussion**

Cardiac involvement including arrhythmia and conductivity disturbance, have an important prognostic value in patients with SSc [1, 4, 8, 23–26]. The main causes of cardiac abnormalities include the autonomic disorders, vasomotor disturbances on the small coronary vessels, including vascular endothelium and progressive fibrosis [27–30]. The early symptoms of cardiac involvement are very uncharacteristic, however, approx. 5% of deaths are sudden [31–33]. Simple and non-invasive method of assessment of the cardiovascular risk and function of the autonomic nervous system is to estimate the HRT and HRV parameters. Among them SDANN and LF the best reflect the function of the sympathetic, r-MMSD, p50NN and HF – parasympathetic nervous function [12, 34, 35]. Low values of SDNN are furthermore associated with a higher risk of developing arterial hypertension and progression of atherosclerotic lesions [36]. The HRT is a reflection of the total sympathetic-parasympathetic balance, and also reflects baroreflex sensitivity [12, 14].

In our study we found significantly lower SDANN and LF values in patients with SSc, which reflects an increase in sympathetic activities. In turn, parameters of parasympathetic activity did not change significantly, or in case of the value of p50NN slightly, but are statistically significantly increased. These results are consistent with observations of Di Franco et al. [9], who showed significantly lower values of SDNN, SDANN and p50NN, indicators of overexpression of the sympathetic nervous system and the lack, or only slight impairment, of parasympathetic activity. The authors also suggest that sympathetic hyperactivity might disturb the balance between vasoconstriction and vasodilatation in favour of the first one. In contrast to these results, Suarez-Almazor et al. [37] do not confirm cardiovascular autonomic insufficiency in SSc patients and CREST syndrome, but they used other available methods, rather than HRT and HRV. Time and frequency domain parameters were significantly lower compared with the control group in Othman et al. study [38]. The authors found no significant correlation between HRV parameters and the subtype and duration of the disease. This is consistent with our observations: we found no significant correlations between the HRV parameters and time after diagnosis. Othman puts an interesting hypothesis: changes in the HRV and arrhythmias may occur at a very early, asymptomatic stage of SSc, even when there is no change in the cardiovascular system detected by routine diagnostic methods. Similar observations were obtained by Sielańczyk et al. [17]. They found no statistically significant difference in HRV parameters between the two groups of subjects with SSc duration of less than 8 and more than 10 years. Bienias et al. [18], using HRT and HRV parameters, also showed dominance of the sympathetic nervous system in SSc patients. However, the average duration of the disease was 11.7 years in this case. It can therefore be assumed that the subjects were in a more advanced stage of the disease. No differences depending on the subtype of the disease were found. Deterioration of HRT with the duration of illness was found. These authors suggest that the autonomic nervous system disorders in patients with SSc assessed by HRT and HRV, increased with the progress of the disease. This was not confirmed by the results of our studies as there was no correlation between HRT and HRV parameters and duration of SSc. Furthermore, HRT parameters did not differ significantly as compared with the control group. It is possible that changes of HRT may appear only in the later stages, as opposed to aberrant HRV. Abnormal HRT correlates with the escalation of arrhythmia, which is characteristic in the overt involvement of the cardiovascular system. In the study of Bienias et al. [22], a decrease in the value of Ts was associated with a higher incidence of ventricular arrhythmias. The frequency of this type of arrhythmia, including nsVT, increases with the duration and severity of lesions. As it is known, abnormal HRT parameters are the reflection of a greater risk of death, especially sudden deaths, associated with serious ventricular arrhythmias. Such a clear relationship was demonstrated for many diseases and clinical conditions [12, 14, 16, 39, 40]. Bienias et al. showed that among SSc patients most people with HP are characterized by abnormal To and/or Ts values. The presence of HP was itself an independent factor affecting the HRT disturbances. It seems that the appearance of abnormal HRT values is a strong risk factor for sudden cardiac death. In our observation, only two people were in the risk group.

Another problem is the loss of diurnal variation of the autonomic nervous system, which is associated with a higher cardiovascular risk. In the general population, a normal circadian rhythm of HRV occurs, with predominantly sympathetic nervous system during the day and parasympathetic at night. In our study, at night there was a significant decrease in the values of SDANN, r-MMSD and p50NN as well as HF. There was an indicator of sig-
significant dominance of the sympathetic nervous system and decreasing the activity of the parasympathetic nervous system. A similar issue was highlighted by Di Franco et al. [9] on the basis of reduced SDNN and SDANN-index. Similar findings were observed for patients with diabetes, as well as in the offspring of diabetic patients who are not yet diagnosed with diabetes [41]. It is characterized by the lack of the increase in the value of SDNN and r-MMSD and p50NN [34]. Similarly, this is the case of decompensated liver cirrhosis [42]. The loss of diurnal variation HRV appears in the early stages of SSC.

The study has its limitations. It was performed on a relatively small, but homogeneous population. We used data available only in the female population. There are reports that menopause alters autonomic balance. Moidathaya et al. [43] have shown a decrease in HF and LF values in postmenopausal women. However, these authors indicate the key effect of age on the parameters of autonomic function. Similarly, Tezini et al. [44] indicate a lack of correlation between the autonomic function and ovarian hormone deprivation in the case of natural menopause. In turn, Neufeld et al. [45], despite showing a significant difference in HF and LF values, do not find a clinically important relationship between cardiovascular autonomic control and menopausal status in women. So, despite a slightly higher number of postmenopausal women in our study, we decided that this fact did not have a significant impact on the results we obtained. Authors have tried to minimize the impact of other factors beyond the SSC, including co-morbidities and medications on HRT and HRV. However, it seems that the results are promising and could become a contribution to further investigations.

Conclusions
Cardiovascular system involvement is referred to as Scleroderma Heart Disease (SHD) by Ferri et al. [8]. The study confirmed the presence of HRV disturbances, including HRV circadian rhythm, as it may seem at an early stage of SSC. HRT disorders may be characterized by the increasing changes with advancing disease. This indicates the presence of autonomic imbalance and the increased cardiovascular risk. Use of the 24-hour ECG Holter monitoring with HRV and HRT appears to be completely safe and inexpensive. This requires further studies.

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Conflict of interest
The authors declare no conflict of interest.

References
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