Evaluation of Heart Rhythm Variability and Arrhythmia in Children with Systemic and Localized Scleroderma

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ABSTRACT. ***Objective.*** To evaluate possible disturbances in autonomic regulation and cardiac arrhythmias in children with localized and systemic scleroderma.

Methods. There were 40 children included in the study: 20 with systemic and 20 with localized scleroderma. The control group comprised 20 healthy children.

Results. In 24-hour Holter recording, the average rate of sinus rhythm was significantly higher in the groups with systemic and localized scleroderma than in the control group, but there was no significant difference between them. The variability of heart rhythm in both groups was significantly decreased. In the group with systemic scleroderma, single supraventricular ectopic beats were observed in 20% and runs were seen in 40% of patients. In the group with localized scleroderma, supraventricular single ectopic beats occurred in 35% of patients and runs in 45% of those studied. Ventricular arrhythmia occurred in 2 children with systemic scleroderma, but in 1 child, it was complex.

Conclusion. The most frequent cardiac arrhythmias in both types of scleroderma in children were of supraventricular origin, whereas ventricular arrhythmias did not occur very often. There were no significant differences in autonomic disturbances manifesting as a higher heart rate and decreased heart rate variability between localized and systemic scleroderma. (First Release Dec 1 2008; J Rheumatol 2009;36:191–6; doi:10.3899/jrheum.080021)

Key Indexing Terms:
SCLERODERMA
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Scleroderma is a chronic inflammatory disease of the connective tissue of unknown etiology, first described in the 18th century. It affects both adults and children, and is divided into 2 types: localized (morphea) and systemic (systemic sclerosis), which is associated with typical skin changes, immunological disturbances, and morbid involvement of internal organs. The clinical symptoms of scleroderma of the heart were described by Weiss, *et al* in 1943 as circulatory insufficiency and heart rate disturbances[1]. The criteria for diagnosing heart damage caused by scleroderma proposed by Medsger and Masi in 197l are in use to this day[2].

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In 1980, the American Rheumatism Association (ARA) proposed criteria for diagnosing scleroderma[3]. The causes and mechanisms of damage to the heart muscle remain unclear. Oram and Stokes believe that atrophy of the myocardial cells occurs as a result of pressure of the rapidly proliferating connective tissue. This leads to fibrosis of the heart muscle, which apart from being disseminated or striated may also be generalized, giving the picture of heart atrophy seen in scleroderma[4]. Fibrosis of the heart muscle secondary to ischemia arising in the mechanism of contraction of the vessels is to be explained by the theory of "intra-cardiac Raynaud's phenomenon" at the level of small intramuscular arteries proposed by Bulkley, *et al*[5,6]. The pathophysiology of arrhythmia in these patients may be related to the involvement of the autonomic nervous system, heart muscle, and atrioventricular conduction system. However, abnormal results of the 24-hour electrocardiogram (ECG) Holter recording in patients with scleroderma may occur in as many as 70% of those with the systemic form without clinically visible manifestations of heart involvement in the morbid process.

The aim of our study was to evaluate possible disturbances in heart rhythm, conduction, and autonomic regula-

tion in children with localized and systemic scleroderma. The study was approved by the Local Committee for the Supervision of Clinical Studies on Humans at the Institute of Cardiology in Warsaw (Approval no. NP/D-185/96 dated January 16, 1996). The trial registration number at the Institute of Cardiology is 2.10/1997.

MATERIALS AND METHODS

Subjects. Our study comprised successive children with systemic (n = 20) and localized (n = 20) scleroderma admitted to the Developmental Age Rheumatology Department at the Institute of Rheumatology in Warsaw from 1995 through 2001. In the systemic scleroderma group, there were 20 children, 17 (85%) girls and 3 (15%) boys, aged 6–18 years (mean 13.6 ± 2.9 yrs), and with mean body surface area (BSA) of 1.31 ± 0.27 m^2. In this group, the disease process had lasted 2–14 years (mean 6.3 ± 3.5 yrs; median 6.0).

There were 20 children in the group with localized scleroderma, including 16 (80%) girls and 4 (20%) boys, aged 11–19 years (mean 13.1 ± 4.2 yrs), mean BSA 1.43 ± 0.32 m^2. The disease process had lasted 2–17 years (mean 8.1 ± 4.1 yrs; median 8.0). The groups did not differ significantly in terms of the above-mentioned measures. The control group consisted of 20 healthy children aged 10–17 years (mean 13.8 ± 2.7 yrs; difference nonsignificant) with mean BSA 1.49 ± 0.17 m^2 (nonsignificant). Any cardiovascular diseases were excluded in this group by means of physical, ECG, and echocardiographic examinations. Interstitial lung disease was excluded by chest radiograph, spirometry, and clinical examination. High resolution computer tomography of the lungs was performed in 20% of children with systemic scleroderma and revealed no changes. The children who were suitable for the study had their diagnosis of systemic or localized scleroderma confirmed on the basis of generally accepted criteria, taking into particular account immunological studies such as rheumatoid factor (RF), antinuclear antibodies (ANA), and Scl-70 antibodies. The 24-h ECG Holter recording was analyzed using Reynolds Medical programming. During the study period, the children did not take any medication that could affect the 24-h recording. The following were described: minimal, maximal, and mean heart rate throughout the 24 h and during activity and sleep periods. Longterm variations in heart rate (due to parasympathetic activity) were analyzed by evaluating the standard deviation of mean R-R intervals in 5-min registrations (SDANN) and the SD of mean R-R intervals (SDNN). The assessment included disturbances in automaticity and conduction as well as supraventricular and ventricular rhythm disturbances. Supraventricular ectopic beats, with narrow QRS complexes (< 120 ms) in ECG, originate by the impulse formation above the bifurcation of the bundle of His, i.e., in the atria or atrioventricular node. Ventricular ectopic beats originate by the impulse formation distally to the bifurcation of the bundle of His, i.e., in the bundle branches or the Purkinje fibers, or rarely in the working myocardium of the ventricles, and have wide QRS complexes (> 120 ms).

Statistical analysis. The results were presented as the arithmetic mean ± SD, or as proportions. Statistical analysis was carried out using the SAS v 8.2 statistical system. After examining the characteristics of the distributions of continuous variables, the analysis of variance test was used with the post-hoc Scheffe test to compare the mean differences between the groups. Pearson's correlation coefficients were also calculated for all the measures with continuous variables, observed in particular groups of patients. In order to assess the differences in frequency of qualitative variables, Pearson chi-squared test was applied. If any expected cell values in a 2×2 table was less than 5, Fisher's exact test was performed. An association was sought between the 2 types of scleroderma (localized and systemic) and the analyzed factors with the aid of multiple logistic regression analysis. The statistical methods were verified, assuming a significance level of $p < 0.05$. All the analyzed tests were bilateral.

RESULTS

Characteristics of the groups. Echocardiography and other examinations were performed to identify potential associations with arrhythmia and disease progression. Echocardiographic examinations revealed no pathological changes, nor any impairment in the left ventricle systolic function and valves in the groups studied, according to Feigenbaum reference values for children. There were no cases of pulmonary hypertension and cardiac involvement in the groups studied.

Spirometry, carried out in both groups of children in order to measure vital capacity and lung compliance, showed decreased vital capacity in 13 (65%) of the children with systemic scleroderma, and in 5 (25%) of the group with localized scleroderma. In the systemic group, 60% of ventilation disturbances were restrictive and in 5% restrictive-obliterative. In the localized scleroderma group, 25% of ventilation disturbances were restrictive. No child had interstitial lung disease. There were no symptoms of kidney disease in any child. Creatinine concentrations did not exceed normal values (1.4 mg%). All children had signs of skin involvement of the morphea type.

Immunological tests showed the presence of immunological complexes in 4 (20%) children in the group with systemic scleroderma, and in 2 (10%) of the group with the localized form. ANA were present in 13 (65%) patients with systemic scleroderma and in 8 (40%) with localized scleroderma, and RF in 4 (20%) and 4 (20%), respectively. Scl-70 antibodies were present only in the group with systemic scleroderma, in 5 of the children (25%).

Results of 24-h Holter recording. In 24-h ECG recording, the mean rate of sinus rhythm throughout the 24 h was significantly higher in the group with systemic and localized scleroderma than in the control group: 88.0 ± 12.1/min versus 78.7 ± 10.7/min ($p < 0.005$) and 84.0 ± 10.0/min versus 78.7 ± 10.7/min ($p < 0.01$), respectively. There were no significant differences between the heart rate throughout the 24 h in the 2 types of scleroderma. But the rate of sinus rhythm during the activity period was significantly higher in the group with systemic scleroderma compared with the controls: 96.6 ± 4.5/min versus 86.4 ± 3.7/min ($p < 0.0001$) as well as in the group with localized scleroderma: 90.9 ± 3.3/min versus 86.4 ± 3.7/min ($p < 0.0005$). The heart rate during the activity period was significantly higher in the systemic form in comparison with the localized form: 96.6 ± 4.5/min versus 90.9 ± 3.3/min ($p < 0.001$).

During sleep the rate of sinus rhythm was higher in both groups — with systemic scleroderma, 76.8 ± 4.4/min ($p < 0.005$), and with the localized form, 72.2 ± 3.4/min — than in the control group, 65.9 ± 3.5/min ($p < 0.005$). But there was no significant difference in this measure between the 2 types of scleroderma (Figure 1).

In the 24-h profile of sinus rhythm analyzing hourly intervals, significantly higher heart rate occurred during the

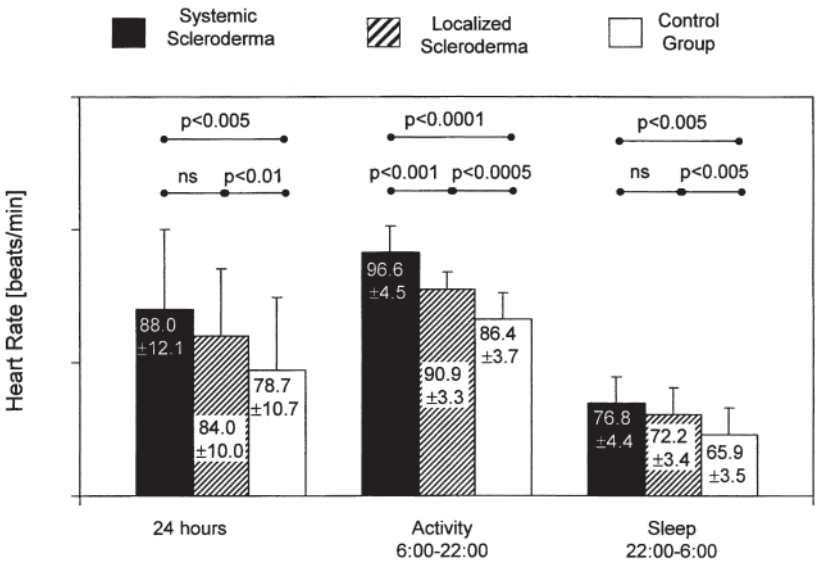

Figure 1. Mean rate of sinus rhythm during activity and during sleep in children with scleroderma in 24-h ECG Holter monitoring. ns: nonsignificant.

activity period between 9:00 AM and 2:00 PM in children with systemic scleroderma versus those with the localized form (Figure 2).

In the assessment of heart rate variability (HRV), significantly lower values of SDANN were seen both in the systemic scleroderma group, 122.1 ± 41.0 ms, and in the localized scleroderma group, 122.8 ± 26.4 ms, compared with the control group, 153.3 ± 29.7 ms ($p < 0.005$). Significantly lower values of SDNN were observed in systemic scleroderma, 137.5 ± 42.6 ms ($p < 0.05$), and in localized scleroderma, 139.3 ± 28.4 ms ($p < 0.01$), compared with the control group, 168.3 ± 37.3 ms. There were no significant differences between values in the 2 types of scleroderma. In no child with either form of scleroderma was there an SDNN value < 100 ms (Figure 3).

Supraventricular ectopic beats were observed in the group with systemic scleroderma at a frequency of over 50/24 h in 4 (20%) of the children studied (maximum of 3638/24 h); and episodes of nonsustained supraventricular tachycardia were seen in 8 (40%), with a mean frequency of 135.5/min (maximum 192/min). A significant number of ventricular extrasystoles occurred in 2 (10%) of the children studied. In 1 child (5%), a severe arrhythmia was observed in the form of multiple ventricular ectopic beats, maximum 4213 per 24 h, 405 ventricular couplets and nonsustained ventricular tachycardia episodes manifesting as short-lasting

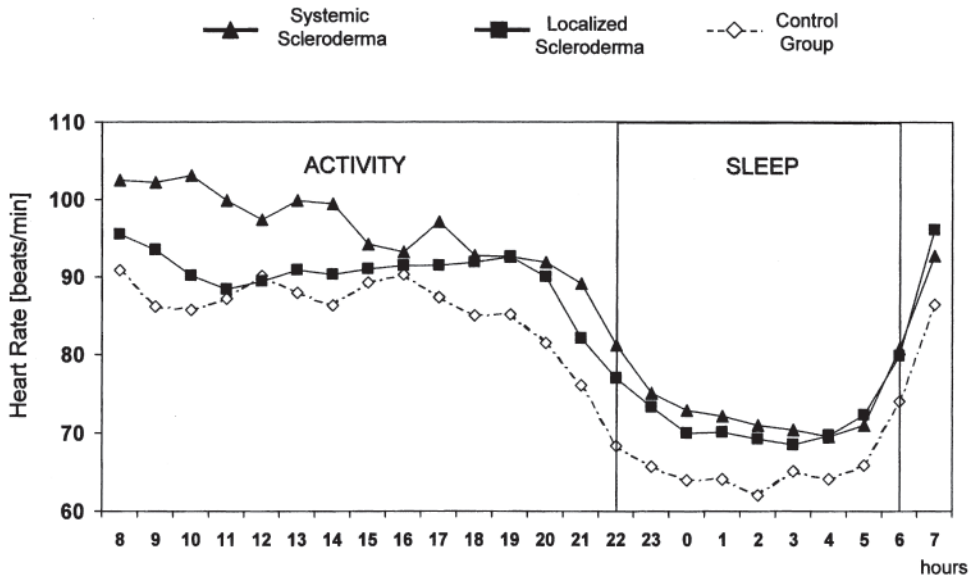

Figure 2. 24-h profile of sinus rhythm in children with scleroderma in 24-h ECG Holter monitoring.

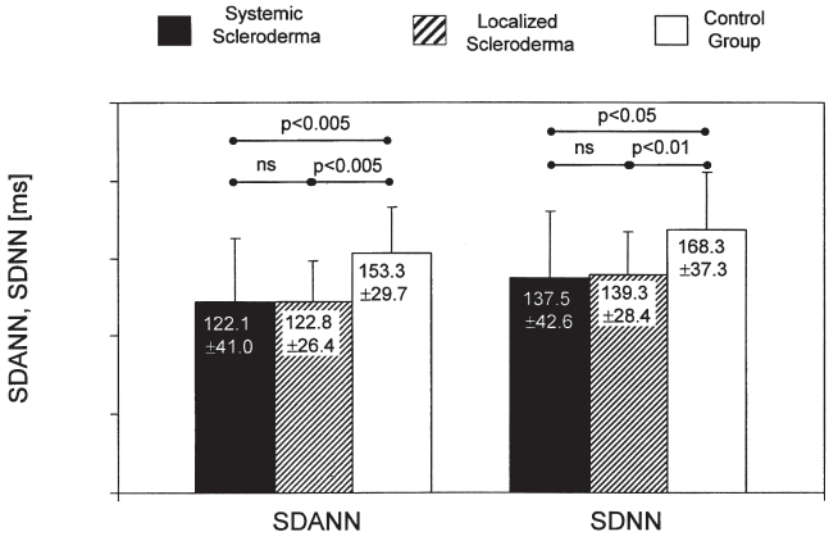

Figure 3. Heart rhythm variations in children with scleroderma in comparison with control group. SDNN: standard deviation of all normal RR-intervals; SDANN: SD of 5-min mean RR-intervals. ns: nonsignificant.

periods of syncope. In the other child, 232 premature ventricular beats were observed throughout the 24 h, without complex forms. In 2 cases of systemic scleroderma (10%) sinus arrest episodes lasting over 1700 ms (maximum 2200 ms) were observed, with no clinical symptoms (Table 1).

In the group with localized scleroderma, supraventricular ectopic beats at a frequency of over 50/24 h (maximum 378) occurred in 7 (35%) children. Episodes of nonsustained supraventricular tachycardia were observed in 9 (45%) cases, with a frequency of 120/min (maximum 149/min). The number of ventricular ectopic beats detected was insignificant and so was their complexity. Sinus arrest lasting longer than 1700 ms occurred in 2 (10%) cases, and never was it longer than 1740 ms (Table 1).

In the control group, only sporadic ventricular ectopic beats below 50/24 h were observed in 3 cases. In other children single ventricular extrasystoles occurred sporadically. No sinus arrest episodes were observed (Table 1).

An association was sought between the 2 types of scleroderma and the analyzed factors and measures using multiple logistic regression analysis. In multiple analysis there was no correlation observed between the presence of ANA, immunological complexes, RF, and organ changes and changes in the 24-h ECG recording in either type of scleroderma.

DISCUSSION

Pediatric scleroderma, either systemic or localized, is a diagnostic challenge for both the cardiologist and the rheumatologist, since the pathophysiology of the disease process is not fully known. There are few publications on the subject of systemic scleroderma in children, and they refer to case reports. Singsen reports that 1.5% of cases occur before the age of 10 and 7.2% between the ages of 10 and 19[7]. Foeldvari and Wulffraat, in their study on pediatric scleroderma, showed that the occurrence of localized scleroderma was 0.2–0.4 cases per 100,000 children, and the systemic form was even rarer[8].

Epidemiological data show the difficulty in amassing a large, representative group to analyze the disease process at a young age. Despite these difficulties, we managed to gather 2 comparable groups of children: one with systemic and

Table 1. Heart rhythm disturbances in children with systemic and localized forms of scleroderma and in controls in 24-h ECG recording using the Holter method.

Disturbance	Systemic Scleroderma, n (%)	Localized Scleroderma, n (%)	Control Group, n
Pauses > 1700 ms	2 (10)	2 (10)	0
Supraventricular ectopic beats > 50/24 h	4 (20)	7 (35)	0
Supraventricular tachycardia episodes	8 (40)	9 (45)	0
Ventricular ectopic beats > 50/24 h	2 (10)	0	0
Ventricular tachycardia episodes	1 (5)	0	0

the other with localized scleroderma. In children, the range of pathological processes in the cardiac muscle and the symptoms accompanying this remain a difficult and hitherto not fully explained clinical problem. Although cardiac changes are quite frequent in this group, they usually follow a subclinical course. Cardiac insufficiency caused by fibrosis of the cardiac muscle may make itself evident only in the ultimate phase of the disease and may be the direct cause of death. There is proof that disturbances in the circulatory system may also occur in children with localized scleroderma, which is still regarded as a milder form of the disease, and involvement of the organs is described sporadically[3,9-15].

An interesting problem is whether the process described in systemic or localized scleroderma in adults runs the same course in both types of scleroderma in children. The time from the start of disease to diagnosis in children is much shorter than in adults and hits the period of rapid development of the organism, when the compensatory mechanisms of the circulatory system are great. In the literature, all authors stress the disproportions existing in children with scleroderma between the changes in the circulatory system and slight or indeed lack of clinical manifestations[11].

Studies on 24-h heart Holter recording to evaluate heart rate variability in both types of scleroderma mostly concern adults. The participation of the autonomic nervous system has been noted for many years, seeking in this theory a neuro-autonomic mechanism for the start of scleroderma. Noninvasive tests are used to evaluate autonomic disturbances, such as the tilt test and the Valsalva test, but the commonly accepted method is the assessment of HRV. Disturbances in autonomic regulation are more frequently present as the first symptom of autonomic disturbances in the course of both systemic and localized scleroderma in adults and in children. Many authors have noted a higher sinus rate and heart rate variations in adults with both systemic and localized scleroderma[13,16,17]. In our study on children with systemic and localized scleroderma, we demonstrated higher values of heart rate in relation to healthy children both in the activity-sleep periods and in the whole 24-h sinus rhythm profile. We found an association between the decreased total sinus rhythm variability in 5-min R-R intervals and increased mortality. This shows that it is a reflection of the influence of the autonomic nervous system on the sinus node, and that a factor permitting the prediction of cardiac death was a value for SDNN < 100 ms. In neither group of children with scleroderma were there patients in whom the SDNN value was below this figure. Lagana, *et al*, studying sinus rate variability in a group of adults with diseases of the connective tissue (systemic lupus erythematosus, rheumatoid joint inflammation, Sjögren's syndrome, and systemic scleroderma), demonstrated lower values of SDNN in the groups studied than in the control group[18]. Morelli, *et al*, assessing HRV in 50 adults with systemic scleroderma, showed dysfunction of the autonomic nervous system[19]. Similar conclusions are drawn from the study of Wranicz, *et al*, who observed lower values for SDNN and SDANN in 19 patients with scleroderma than in the control group[16]. The significantly lower values for SDNN and SDANN in systemic and localized scleroderma compared with our group of healthy children confirm the occurrence of disturbances in autonomic regulation in both systemic and localized scleroderma in children as well. However, there were no significant differences between the values in both types of scleroderma in children. Our results confirm the researchers' theories, pointing to the occurrence of disturbances in autonomic regulation in scleroderma. An original finding in our study is that the level of occurrence of these disturbances in children with localized scleroderma is similar to that in children with systemic scleroderma.

The issue of ventricular arrhythmia in patients with scleroderma is clinically important. In a group of 18 adult patients with systemic scleroderma, Anvari, *et al* showed symptomatic ventricular tachycardia in 1 case, 5 patients exhibited nonsustained ventricular tachycardia, and in 6 cases tachycardia was supraventricular[20]. In a group of 19 adults with scleroderma, conduction disturbances occurred in 3% of cases and ventricular rhythm disturbances in 6%[16]. In another study, ventricular rhythm disturbances were observed in as many as 53.3% of 17 patients with systemic scleroderma[21]. Other authors showed the presence of arrhythmia to a minor extent[13,22,23]. Our observations showed rare occurrence (10%) of ventricular rhythm disturbances in children with scleroderma, but in 1 child we observed multiple single ventricular extrasystoles, couplets of ventricular ectopic beats, and episodes of nonsustained ventricular tachycardia with syncope episodes. In this case, treatment with amiodarone was initiated. The results of our study show that supraventricular arrhythmia is the most common type in systemic and localized scleroderma in children. This confirms earlier reports[23,24].

Autonomic disturbances manifesting as a higher heart rate and decreased heart rate variability were observed in both the localized and systemic forms of scleroderma in children. The most frequent cardiac arrhythmias in the localized and systemic type of the disease were of supraventricular origin, whereas ventricular arrhythmias occurred infrequently, but might have complex forms.

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