Ventricular Late Potentials in Systemic Sclerosis: Relationship with Skin Involvement

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ABSTRACT. ***Objective.*** To detect the myocardial involvement in patients with systemic sclerosis (SSc) by signal averaged electrocardiography method (SA-ECG) in relationship to the skin changes.

Methods. We selected 24 SSc outpatients according to American Rheumatism Association criteria, without clinical and instrumental evidence of cardiac disease, and compared them with 24 control subjects. All patients and controls underwent SA-ECG to detect ventricular late potentials (LP). The extent and severity of skin involvement in SSc patients was detected by modified Rodnan (m-Rodnan) skin score.

Results. SSc patients had higher prevalence of LP compared to controls (46 versus 8%, $p < 0.003$). Median skin score value in the overall SSc population was 7 [mean, SD (range): 7.8, 3.2, (4-18)]. Patients with LP had a higher median skin score value compared to SSc patients without LP [median (range): 10 (6-18) versus 6 (4-9); Mann-Whitney U test 22.5, $p < 0.005$]. A subset analysis was also performed to verify the correlation of antibodies positivity (anti-centromere and Scl 70) pattern and the presence of LP. Our findings showed that higher values of skin score correlated with the presence of LP independent of antibody subsets.

Conclusions. Our data suggest that diffuse abnormalities of the cardiac tissue detected by SA-ECG may be present, even in patients without cardiac symptoms. The relationship between LP and skin involvement in patients without clinical evidence of cardiac involvement may help detect of a subset of patients who may develop scleroderma heart disease. (J Rheumatol 2002;29:1388–92)

Key Indexing Terms:
SYSTEMIC SCLEROSIS SKIN SCORE LATE VENTRICULAR POTENTIALS

Systemic sclerosis (SSc) is a multisystem disease of unknown etiology characterized by microvascular abnormalities[1], enhanced fibroblastic activity[2], and collagen deposition in the skin and visceral organs. Visceral involvement (renal, pulmonary, and cardiac) is directly related to a poor prognosis[3]. The hallmark of primary myocardial disease in SSc is myocardial fibrosis, found in the majority of patients with SSc (77% in diffuse and 60% in limited disease) in autopsy studies[4-5]. In particular, 50% of patients had foci of myocardial fibrosis of varying magnitude, randomly distributed throughout the heart[4]. The coexistence of pulmonary and renal disease often represents a confounding variable in the study of cardiac involvement in SSc. Moreover, besides the difficulties of distinguishing secondary from primary cardiac involvement, it should be pointed out that it may exist without clinical evidence[3].

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Signal averaged electrocardiography (SA-ECG) is used for recording ventricular late potentials (LP), which are the expression of slowed and disorganized conduction through zones of myocardial scarring and represent a substrate for malignant reentrant ventricular arrhythmias[6]. Previous studies demonstrated that a significantly increased prevalence of LP can be found in SSc patients compared to controls[7,8]. However, to our knowledge, no data are available on the possible relationship between skin and cardiac involvement in patients with SSc. We studied myocardial involvement, using SA-ECG, in SSc patients without evidence of cardiac disease. Furthermore, performing skin score evaluation we assessed if a relationship exists between myocardial involvement and skin thickness.

MATERIALS AND METHODS

Patients. This study included 24 SSc outpatients [22 females and 2 males; aged from 23 to 61 (mean ± SD: 53 ± 12) yrs] and 24 healthy volunteers as controls [18 females and 6 males, aged from 35 to 58 (mean ± SD: 48 ± 6 yrs)]. Informed consent was obtained from all subjects enrolled, and the study was approved by the local ethics committee.

The diagnosis of SSc was made according to the criteria of the American Rheumatism Association[2]. Disease duration (mean ± SD: 12.3 ± 9.9 yrs) was calculated from the onset of Raynaud's phenomenon. All patients were taking low or moderate doses of calcium antagonists (nifedipine, 5-10 mg/day) or local (hands) transdermic nitrates (nitroglycerine, 5 mg/day) None of the patients included in the study had evidence of renal involvement, diabetes, or any other systemic disease.

Assessment of cardiac involvement. Scleroderma patients with known cardiac

disease were excluded from this trial. History, physical examination and standard 12-lead ECG were performed in all eligible patients. Moreover, each patient underwent an echocardiographic study to exclude subjects with abnormal dimensions of cardiac chambers, valvular alterations, or pericardial effusion. A 24 h Holter ECG was performed to exclude patients with isolated atrial or ventricular arrhythmias (> 10/h), couplets, or runs. Patients with hypertension, cardiomegaly, arrhythmias and/or conduction abnormalities, pericardial effusion, valvular involvement, and heart failure were not eligible for the study.

The presence of LP by SA-ECG was checked in all subjects enrolled. SA-ECG was recorded using a computerized multichannel device (model AT-60 CEV 4.19, Schiller, Baar, Switzerland) with 4 kHz sampling frequency, 12 bit resolution, and 0-350 Hz (-3 dB) frequency response. During the first 10 seconds of the measurement, a sample beat (template) was selected. A signal averaging of the actual heart beat only took place when there was a correlation of more than 98% between the actual heart beat and the template. A number of 250 cardiac cycles was averaged to decrease noise to a level < 0.2 μV, with subjects lying quietly supine. After the signal averaging, the ECG data were filtered using a high pass with limit frequencies of 40 Hz and a low pass filtering at 250 Hz. According to the Simson method[9], the so-called vector magnitude was calculated after filtering for the data evaluation. The start of the vector magnitude was equal to the QRS start in the unfiltered leads; the end of the vector magnitude was the endpoint of a 6 ms duration in which the vector magnitude was larger than the sum of the noise plus 2.5 times the standard deviation. Finally, the highly frequent QRS duration of these vector amplitudes (QRS), the root mean square voltage of the last 40 ms (RMS), and the part of the vector amplitude below 40 μV (LAS) were calculated. Criteria for an abnormal SA-ECG included 2 of the following: (1) QRS > 114 ms; (2) RMS < 20 μV; and (3) LAS duration > 38 ms[10].

Assessment of skin score. All enrolled patients were submitted to physical examination to assess total skin score. For determining the extent and severity of skin involvement, modified Rodnan (m-Rodnan) total skin thickness score was used. Two independent observers examined 17 body areas (face, anterior chest, abdomen, right and left limbs separately, the fingers, hands, forearms, upper arms, thighs, lower legs, and feet) by clinical palpation, and graded them 0-3: 0 (normal skin), 1 (mild thickness), 2 (moderate thickness), 3 (severe thickness with inability to pinch). m-Rodnan score (range 0-51) was derived from the addition of the different gradings observed for all 17 areas[11,12]. SSc was defined as limited (lSSc) if skin thickening of any degree was limited to sites distal to the elbows and knees, with or without facial involvement. SSc was defined as diffuse (dSSc) if skin thickening of any degree was proximal to the elbows and knees, often involving the trunk[13].

Laboratory analysis. Antinuclear antibodies (ANA), including anti-centromere antibodies, were detected by immunofluorescence assay (IFI on Hep-2 cells, Sanofi Diagnostics, Pasteur, Redmond, USA). Anti-topoisomerase I (Scl 70) antibodies were determined by immunoblotting technique (Hep-2 Marblot, Arnika, Italy) according to the manufacturer's instructions.

Statistical analysis. Statistical analysis was performed by chi-square statistics or Fisher's exact test (if n < 5) for independence and by appropriate t test. Linear regression was used to study the different correlations. When necessary, appropriate nonparametric tests were employed. Data are presented as mean + SD and 95% confidence intervals (95% CI). Medians (range) are given for skin score because of appreciably skewed distribution. Only 2-tailed probabilities were used for testing statistical significance. P values lower than 0.05 were regarded as statistically significant. All calculations were made with the computer program Statistica (StatSoft Inc., Tulsa OK, USA).

RESULTS

The findings of SA-ECG showed the presence of LP in 11 out of 24 Ssc patients (46%) versus 2 out of 24 controls (8%). The difference between the 2 groups was statistically significant (p < 0.004). The mean QRS, RMS, and LAS recorded among the SSc patients did not statistically differ from those found in normal controls (QRS: 85.73 ± 14.09 versus 88.24 ± 8.27 ms; RMS: 28.51 ± 22.84 versus 29.92 ± 17.35 μV; LAS: 33.69 ± 19.74 versus 31.28 ± 6.89 ms). A comparative analysis was performed between SSc patients with (n = 11) and without LP (n = 13). As shown in Table 1, age, gender, and disease duration were similar between the 2 subgroups of interest. The mean values of QRS, RMS, and LAS statistically differ among 2 subgroup (QRS: 95.5 ± 14.51 versus 77.36 ± 6.32 ms, p = 0.0003; RMS: 11.67 ± 3.09 versus 42.95 ± 22.56 μV, p = 0.0001; LAS: 45.67 ± 5.45 versus 23.43 ± 6.40 ms, p < 0.0001).

The median value of skin score (m-Rodnan) in the overall population was 7 (range: 4-18). Age and disease duration did not correlate with skin score. LP positive patients had higher median value of skin score compared to SSc patients free from LP [median (range): 10 (6-18) versus 6 (4-9); Mann-Whitney U test 22.5, p < 0.005].

Nine out of 24 SSc patients had diffuse and 15 had limited disease. LP was present in 67 and 33% of the 2 groups respectively. ANA were present in 23 (96%), anti-centromere antibodies in 8 (31%), and Scl-70 antibodies in 7 (29%) of 24 SSc patients. A comparative analysis of SSc patients with and without LP showed that ANA and anti-centromere antibodies percentages were similar between the 2 groups (Table 1). Scl-70 antibodies were found in 5 of 11 (45%) patients with LP

Table 1. Clinical, laboratory and ECG characteristics of 24 SSc patients according to the presence of LP.

	LP present (n = 11)	p value	LP absent (n = 13)
Age (years) mean ± SD	53.25 ± 10.67	0.940	52.86 ± 13.81
Females n (%)	9 (82)	0.199	13 (100)
Disease duration mean ± SD	12.3 ± 12.4	0.367	12.4 ± 7.7
QRS, ms mean ± SD	95.5 ± 14.51	0.0003	77.36 ± 6.32
RMS, μV mean ± SD	11.67 ± 3.09	0.0001	42.95 ± 22.56
LAS, ms mean ± SD	45.67 ± 5.45	0.0001	23.43 ± 6.40
m-Rodnan score skin median (range)	10 (6–18)	0.005	6 (4–9)
ANA n (%)	10 (91)	0.267	13 (100)
Anti-centromere antobodies n (%)	2 (18)	0.211	6 (46)
Scl 70 n (%)	5 (45)	0.182	2 (15)

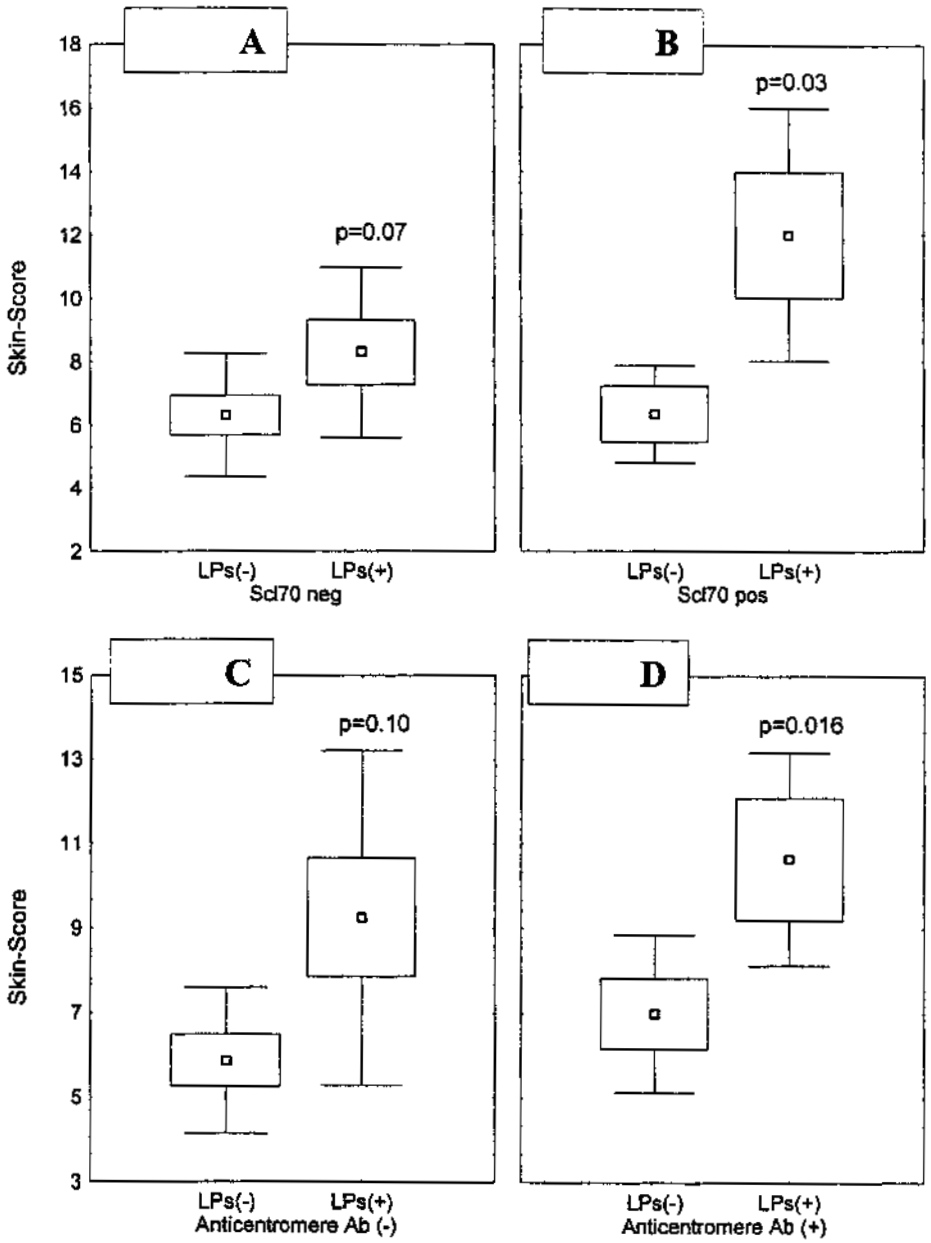

Figure 1. Skin score values in patients according to the presence of LP. Patient subset without Scl 70 (A), with Scl 70 (B), without anticentromere antibodies (C), with anticentromere antibodies (D).

and in 2 of 13 (15%) patients without LP, but the difference did not reach the statistical significance.

The only patient with negative ANA had a skin score value of 11. The median m-Rodnan value of patients positive for anti-centromere antibody was higher than patients without these antibodies [median (range): 8.5 (5-13) versus 6.5 (4-18); Mann-Whitney U test 48.5, p = 0.337]. Patients with Scl-70 positive antibody showed increased levels of skin score compared to patients without Scl-70, but the difference did not reach statistical significance [median (range): 10 (5-18) vs. 6 (4-13); Mann-Whitney U test 35.5, p = 0.123]. A subset analysis was performed to verify the correlation of antibody positivity and the presence of LP. As shown in Figure 1, higher values of skin score correlated with the presence of LP independently of antibody subsets.

DISCUSSION

Symptomatic myocardial involvement in SSc is much less common than histopathological findings, suggesting a high incidence of subclinical disease. Atrial and ventricular arrhythmias, detected by 24 h ambulatory ECG, are present in more than half of SSc patients[14]. Roberts, *et al* using invasive

intracardiac electrophysiological studies showed conduction abnormalities in 70% of SSc patients examined[15]. Furthermore, Rokas, *et al* found a high prevalence of electrophysiologic abnormalities in SSc patients without detectable organic heart disease and without cardiac arrhythmias[16].

SA-ECG is a simple, non invasive, and reproducible technique to detect the presence of low-amplitude and high-frequency waveforms termed LP on the body surface. In this study we selected SSc patients without clinical evidence of cardiac disease. SA-ECG results showed significant differences in the presence of LP between patients with SSc and controls, suggesting a myocardial involvement also in those patients without clinical evidence of cardiac disease. Despite the lack of age and gender matched controls, no statistically significant differences for age were found between patients and controls. Body size and left ventricular mass that relate to gender did not show significant differences between patients and controls. Moreover, age-related changes in SA-ECG were significant only in the elderly patients, due to a generally slower propagation of excitation wave fronts within the myocardium. The delayed conduction that manifests itself as an LP can be caused primarily by one of 2 factors: slow conduction velocity and/or a long path length of conduction. Experimental studies have shown that ventricular LP are representative of slowed conduction within an area of depressed myocardium in acute ischemia[17]. In chronic infarction, the morphology of LP is typically fractionated with multiple high frequency and low amplitude deflections. The term fractionated defines the morphologic characteristics of signals that can occur after the terminal portion of QRS in the SA-ECG. The microanatomy of regions where the fractionated electrograms are recorded is characterized by large amounts of fibrous tissue[18]. Moreover, myocardial fibrosis has been associated with LP even in the absence of myocardial infarction[4,19]. In fact, myocardial activation may be delayed because the pathway of excitation is lengthened by islands of fibrosis. The higher incidence of LP in SSc shown in our study is in agreement with the reports by others[7,8,20], and may be considered as expression of myocardial fibrosis. However, in SSc the underlying disease process responsible for the myocardial fibrosis is not well understood. The most plausible etiology is vasospasm, alone or superimposed on fixed structural or functional abnormalities of the coronary microvasculature. The primary immunological alterations may be responsible for the initial vascular damage[21,22]. Classic pathological changes of contraction band necrosis seen in scleroderma are similar to the findings in hearts subjected to prolonged ischemia and subsequent reperfusion[4].

Our results showed a correlation between the presence of LP and skin involvement. Patients with LP had a higher skin score compared to patients without LP ($p = 0.005$). Moreover, no significant differences were found between the presence of LP and scleroderma antibody subsets, even if LP incidence was higher in patients with anti-topoisomerase antibodies compared to anti-centromere antibodies, which is in agreement with the prevalence of visceral involvement in patients with Scl-70 antibodies[23].

It has been shown that extensive skin involvement is correlated with decreased survival and a greater risk of developing scleroderma renal crisis, and myocardial or interstitial pulmonary disease[24]. Recently, Steen, *et al* demonstrated that severe organ involvement occurs early in diffuse scleroderma, worsening the survival of these patients. In that study, although higher skin score remains a significant risk factor for organ involvement, it did not independently affect a poor outcome[25]. A prospective study carried out by Clements, *et al* showed that SSc patients with severe cardiac involvement were more likely to have high skin score[26].

In our patients with SSc, the median skin score was not high, but this may be due to the exclusion of those patients with any obvious cardiac disease. Nevertheless, our data demonstrate a significant correlation between ventricular LP and skin score even in symptom free SSc patients. Furthermore, we suggest that SA-ECG is an accurate and noninvasive technique that can easily detect diffuse abnormalities of the cardiac tissue and might be helpful particularly in those patients in whom no cardiac symptoms are evident. Although at the present the prognostic value of LP in SSc is unknown, the relationship between LP and skin involvement may help identify a subset of patients who could develop clinically important scleroderma heart involvement.

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