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Original Article

Cardiac autonomic modulation at rest and during orthostatic stress among different systemic sclerosis subsets

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ABSTRACT

Objective: To compare autonomic heart rate variability (HRV) parameters at rest and during active stand in a population of SSc patients, taking into account SSc subsets age-matched to healthy control subjects.
Methods: Sixty-nine consecutive SSc patients were enrolled in study; these included 12 subjects with early SSc, 39 with limited cutaneous (lcSSc) and 18 with diffuse cutaneous SSc (dcSSc) along with 36 age- and sex-matched healthy controls (HC). ECG and respiration were recorded in supine position and in orthostatism (ORT). HRV analysis was performed on samples of 300 beats. Spectral analysis identified two oscillatory components, low frequency (LFnu, sympathetic) and high frequency (HFnu, vagal). Symbolic analysis identified three patterns, 0 V%, (sympathetic) and 2UV% and 2LV%, (vagal). The %ΔORT was calculated from the differences between HRV in ORT and SUP, normalized (%) by the HRV values at rest.
Results: SSc as a whole had higher markers of sympathetic (LF, 0 V%) and lower markers of vagal modulation (HR, 2UV%, 2LV%) compared to HCs. In addition, %ΔLFnu, %ΔHFnu, %Δ0 V, %Δ2UV and %Δ2LV were lower in SSc than HC. dcSSc and lcSSc were dissimilar to HC as far as rest indexes were concerned (↑LF/HF, ↑LFnu, ↓HFnu, ↑0 V% and ↓2UV%) while no differences could be detected between HC and EaSSc.
Conclusion: SSc showed a reduced vagal and increased sympathetic modulation at rest and a blunted autonomic response to ORT in comparison to HC. These alterations were mostly detectable in the advanced and fibrotic forms of SSc (dcSSc and lcSSc), while EaSSc were similar to HC.

1. Introduction

Systemic Sclerosis (SSc) is an autoimmune disease characterized by vascular damage, autoantibodies production and fibrosis of the skin and internal organs. Heart is frequently affected in SSc with variable manifestations including conduction abnormalities, myositis of myocardium, coronary artery disease, pericardial manifestation and myocardial fibrosis [1]. Cardiac involvement has a cumulative risk of death of 3.15 [2], and it may occur independently from other typical complications of SSc [3]. According to MRI investigations, myocardial fibrosis occurs in about 45–60% of SSc patients with a higher prevalence in the diffuse cutaneous SSc (dcSSc) subgroup [4,5]. From autoptic studies, the prevalence of ventricular fibrosis is even higher, about the 80% [6,7]. Although ventricular fibrosis could induce arrhythmias due to cardiac structural and functional remodeling, conduction system abnormalities are not always detectable in SSc myocardial fibrosis [5,8].

Autonomic dysfunction is an early marker of SSc progression and could precede cardiac fibrosis occurrence helping to identify subclinical cardiac involvement [9]. Heart rate variability (HRV) has been described as a powerful non-invasive tool to access heart sympathetic and vagal modulation. Interestingly, HRV at rest is associated with the risk of arrhythmic complications and mortality in SSc patients [10]. Two studies described an impaired cardiac autonomic modulation at rest in

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SSc patients through vagal-mediated HRV [14,15]. One additional study assessed HRV during orthostatic stress (ORT) test, a maneuver used to describe the autonomic responses during physiological challenges [11], showing an impaired response for vagal- and sympathetic-mediated HRV in SSc patients compared to healthy controls [16].

In addition to classical linear spectral tools, new non-linear tools, such as symbolic dynamics and conditional entropy, have been proposed to overcome some important limitations of linear methods [12,13]. No study to date performed symbolic dynamics and conditional entropy as additional evaluation tools in SSc patients stratified for their disease subsets and severity.

In the present study, we aimed to compare autonomic HRV parameters at rest and during active stand in a population of SSc disease, taking into account SSc subsets age-matched to healthy control subjects (HC).

2. Methods

2.1. Study population and clinical features

The present case-control study included 69 SSc patients, (18 men and 51 women, aged 58 ± 12 [mean ± standard deviation] years) and 36 age- and sex-matched healthy controls (HC; 13 men and 23 women; aged 57 ± 12 years). All the patients fulfilled the 2013 American college of Rheumatology/European league against rheumatism classification criteria for SSc [17] or the LeRoy and Medsger criteria for early SSc (EaSSc) [18]. EaSSc were defined as patients with a pre-clinical stage of disease solely presenting with Raynaud's phenomenon, SSc-specific autoantibodies and/or typical abnormalities at nail-fold videocapillaroscopy [18]. SSc patients were classified into diffuse cutaneous SSc (dcSSc) or limited cutaneous SSc (lcSSc) subsets based to the extent of their skin fibrosis [19]. Finally, patients with a definite SSc but without skin fibrosis yet with puffy fingers were categorized in the lcSSc group.

Clinical and laboratory parameters within 3 months from study visit were extracted from medical records, and included the determination for total lung capacity (TLC), forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), diffusing capacity for carbon monoxide (DLCO), the left ventricular ejection fraction (LVEF) computed using the modified Simpson's formula, the Tricuspid annular plane systolic excursion (TAPSE) and the pulmonary artery pressure (PAPs), the erythrocyte sedimentation rate (ESR), the C-reactive protein (CRP), the presence of hypergammaglobulinemia and creatinine and glucose levels.

All the subjects underwent recording of ECG and respiration using a thoracic belt record at rest (supine position for 10 min) and during active standing (orthostatic stress for 10 min) between 8 a.m. and twelve noon. The cardiovascular variables were acquired using an *ad hoc* telemetric system device (BT16 Plus, Marazza Spa, Monza, ITA). All measurements were performed in a quiet and temperature-controlled room (between 22 °C and 24 °C), and all patients had a normal body temperature during the recordings (between 35,5 °C and 36,5 °C). During the recordings, subjects were in spontaneous breathing. The absence of a stable sinus rhythm on ECG and an ongoing therapy with beta-blocker drugs were considered exclusion criteria for this study.

The protocol was approved by the local Ethics Committee (Comitato Etico Milano Area 2) and it was developed in accordance with the Declaration of Helsinki. All the subjects signed an informed written consent before the participation to the study.

2.2. HRV analysis

The HRV was evaluated through specific software (Heart Scope II, AMPS, ITA.) on short samples of 300 beats at rest and orthostatism. To evaluate the autonomic dynamic response to ORT, we calculated the ΔORT% (HRV in SUP position – HRV in ORT position)/HRV in SUP position).

Spectral analysis was performed through the autoregressive model, with a Hanning window and 50% overlap to obtain the spectral power in the low frequency (LF, frequency band bounded between 0.04 and 0.15 Hz) and high frequency (HF, frequency band bounded between 0.15 and 0.40 Hz and synchronous with respiration) components. The LF and HF components can also be expressed in normalized units (LFnu and HFnu). The normalized components are obtained dividing each band power by the total power subtracted the very low component (< 0.04 Hz). The autonomic balance was calculated as the LF/HF ratio.

Nonlinear dynamics were evaluated by symbolic analysis. The R-R dynamics were classified into 3 patterns families referred to as a) patterns with no variation (0 V; all 3 symbols will equal); b) patterns with 1 variation (1 V; 2 consequent symbols were equal and the remaining symbol was different); and c) patterns with 2 variations (2UV or 2LV; all symbols were different from the previous one. The percentage of the patterns 0 V and 2UV or 2LV were calculated as a predominance of sympathetic and parasympathetic cardiac autonomic modulation, respectively. In addition, the conditional entropy measures were analyzed as another nonlinear evaluation. The conditional entropy (CE) and regulatory indexes (RO) were used to access complexity of RR dynamics. The entropy is the inverse of regularity and either CE or RO indexes seems associate to sympathetic modulation [13].

2.3. Statistical analysis

The Shapiro-Wilk test was used to evaluate the normality of the samples. To compare the HRV index between the groups Unpaired *t*-test was used ($\alpha < 0.05$). For the comparisons between SSc subsets (dcSSc, lcSSc and EaSSc) and healthy controls we used the ANOVA one-way for independent measures and Tukey post-hoc test. For descriptive analysis, means and standard deviation were used. The sample size was calculated for an average statistical power > 0.80 for the main outcome variable (HFnu; obtained statistical power = 0.95). The software used were the GraphPad Prism version 6.0 (GraphPad Software Inc., USA) and the G-Power 3.1.9.2 (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany).

3. Results

3.1. Clinical data

SSc subsets were homogeneous for age, body mass index, systolic and diastolic blood pressure. About lung function, TLC as well as FVC were lower in dcSSc compared to lcSSc and EaSSc patients; DLCO did not significantly differ among SSc subsets. In relation to echocardiography markers, we did not found any differences between dcSSc, lcSSc and EaSSc. Regarding signs and symptoms of heart failure and previous ischemic events, one patient presented previous history of ischemic cardiomyopathy, three had mild atrial dilatation, and no other features indicative of heart failure have been found beyond these enrolled patients. According to the biochemical analysis, Erythrocyte Sedimentation Rate (ESR), C reactive Protein (CRP), γ-globulin, glucose, creatinine were homogeneous among the three SSc subsets. Other clinical features and the prevalence of autoantibodies are listed in Table 1.

3.2. HRV at rest and during orthostatic stress in SSc patients and HC

Table 2 shows a comparison of HRV at rest between all SSc patients and age-matched healthy controls. Considering the spectral analysis, total power and HFnu were lower in SSc than HC group. On the other hand, LFnu and LF/HF were higher in SSc than HC. Symbolic analysis revealed that SSc patients had lower 2LV and 2UV% and higher 0 V% if compared to HC. Finally, entropy analysis showed lower CE values and the regulatory index (RO) was higher in SSc.

Table 1
Clinical features of SSc patients.

	All SSc	dcSSc	lcSSc	EaSSc	p-value
Personal Characteristics					
N	69	18	39	12	–
Age (years)	58 ± 12	58 ± 12	59 ± 12	54 ± 8	0.32
Gender (M/F)	18/51	7/11	9/30	2/10	–
Weight (kg)	68.00 ± 11.45	72.20 ± 19.28	65.17 ± 6.17	67.00 ± 2.4	0.62
Height (m)	1.63 ± 0.11	1.70 ± 0.14	1.57 ± 0.05	1.62 ± 0.04	0.09
BMI (kg/m^2)	25.60 ± 3.93	24.90 ± 6.53	26.39 ± 2.77	25.30 ± 0.55	0.83
SBP (mmHg)	119 ± 12	122 ± 18	118 ± 18	120 ± 10	0.53
DBP (mmHg)	73 ± 7	75 ± 7	72 ± 8	76 ± 6	0.23
SSc duration (years)	11 ± 8	14 ± 10	12 ± 7	7 ± 6[a]	0.04
PAH (n/%)	13/19%	4/22%	9/23%	0/0	–
Controlled hypertension (n/%)	14/20%	3/17%	6/18%	2/16%	–
Antibodies					
Anti-Scl-70 +	20/29%	8/44%	11/28%	1/8%	–
ACA +	31/45%	2/11%	21/54%	8/67%	–
Spirometry					
TLC (l; %)	4.94 ± 1.53 (96 ± 22%)	1.78 ± 0.53 (90 ± 28%)	4.93 ± 1.53[a] (90 ± 22%)	5.59 ± 1.30[a] (104 ± 16%)	< 0.001
FVC (l; %)	3.00 ± 1.07 (101 ± 25%)	2.64 ± 1.01 (92 ± 28%)	2.88 ± 0.99 (92 ± 25%)	3.85 ± 0.99[a,b] (115 ± 18%)	0.01
FEV_1 (l; %)	2.33 ± 0.87 (96 ± 21%)	2.22 ± 1.03 (89 ± 25%)	2.25 ± 0.68 (87 ± 21%)	2.91 ± 0.68[b] (108 ± 15%)	0.01
DLCO SB (ml/mmHg/min; %)	16.26 ± 24.70 (68 ± 24%)	10.94 ± 6.12 (59 ± 25%)	17.84 ± 31.13 (62 ± 19%)	18.27 ± 11.59 (79 ± 24%)	0.70
DLCO SB/VA (ml/mmHg/min/L; %)	4.80 ± 9.85 (68 ± 25%)	9.38 ± 20.45 (73 ± 32%)	3.32 ± 1.58 (79 ± 19%)	3.83 ± 1.05 (86 ± 27%)	0.21
Echocardiography					
LVEF (%)	63 ± 6	61 ± 6	64 ± 5	63 ± 4	0.20
TPSE (mm)	22 ± 4	21 ± 3	21 ± 4	24 ± 5	0.18
PAPs (mmHg)	34 ± 14	35 ± 17	35 ± 14	28 ± 5	0.31
Biochemical					
PCR (mg/dL)	0.95 ± 2.53	0.54 ± 0.36	0.71 ± 1.52	0.66 ± 0.94	0.64
ESR (mm/h)	21.29 ± 11.90	24.20 ± 15.41	24.64 ± 9.71	14.58 ± 8.70	0.20
γ-globulin (g/dL)	16.53 ± 5.72	16.52 ± 2.34	16.58 ± 7.02	16.40 ± 5.82	0.98
Creatinine (mg/dL)	0.83 ± 0.23	0.74 ± 0.33	0.85 ± 0.18	0.81 ± 0.18	0.40
Glucose (mg/dL)	88.39 ± 9.77	85.00 ± 11.78	87.20 ± 9.34	94.00 ± 3.00	0.43

SSc: systemic sclerosis; lcSSc: limited cutaneous SSc; dcSSc: diffuse cutaneous SSc; EaSSc: Early SSc; SBP: systolic blood pressure; DBP: Diastolic blood pressure; BMI: Body mass index PAH: pulmonary arterial hypertension confirmed by right heart catheterization. Anti-Scl-70 +: Anti-topoisomerase I; ACA +: Anti-centromere antibodies positive; TLC: total lung capacity; FVC: forced vital capacity; FEV1: forced expiratory volume in 1 s; DLCO SB: Diffusing capacity for carbon monoxide; DLCO SB/VA: Diffusing capacity corrected for alveolar volume; LVEF: Left ventricular ejection fraction; TPSE: Tricuspid plane systolic excursion; PAPs: Mean pulmonary artery pressures CRP: C Reactive Protein; ESR: Erythrocyte sedimentation rate; ANOVA one-way for independent measures and Tukey post-hoc test.

[a] Differences from dcSSc.

[b] Differences from lcSSc. $\alpha < 0.05$.

Fig. 1 shows the HRV response to orthostatic stress in SSc patients and HC. As to spectral parameters, %ΔLFnu and ΔHFnu were significantly lower in SSc group compared to HC (%ΔLFnu 0.08 ± 0.72 *vs.*1.42 ± 2.10 p = .001; %ΔHFnu 0.12 ± 1.22 *vs.* −0.40 ± 0.51 p = .02, in SSc and HC respectively). The HRV symbolic analysis indices %Δ0 V, %Δ2UV and %Δ2LV were also lower in SSc compared than HC group (%Δ0 V 0.35 ± 1.07 *vs.*1.25 ± 2.33 p = .01; %Δ2UV 0.28 ± 1.05 *vs.* −0.26 ± 0.57 p = .003; %Δ2LV 0.80 ± 2.95 *vs.* −0.23 ± 0.55 p = .04, SSc and HC respectively).

3.3. HRV at rest and during orthostatic stress between SSc subsets

Among SSc subsets, we found a higher LF/HF, LFnu and a lower HFnu at rest in dcSSc, lcSSc subsets compared to HC. However, only dcSSc patients showed a lower total power when compared to HC and EaSSc. Symbolic analysis showed that 2UV% and 2LV% were lower and 0 V% was higher in dcSSc and lcSSc subsets compared to HC. According to the results above, the RR_ce was lower but the RR_ro was higher in dcSSc, lcSSc subsets when compared to HC.

In relation to HRV adjustments from orthostatic stress, the %ΔLFnu and %ΔLF/HF were lower in dcSSc, lcSSc subsets compared to HC. The %Δ0 V, %Δ2UV and %Δ2LV were just lower in lcSSc than HC. The %Δ2UV was also different between EaSSc and lcSSc. For the others HRV indices (%ΔTotal power and %Δ1 V) we did not find any significant differences between SSc subsets and HC. Although SSc subsets showed an impaired HRV if compared to HC, we did not find differences in any HRV index among dcSSc, lcSSc and EaSSc subsets. All these indices are described in Table 3.

4. Discussion

The present study revealed some novel findings: SSc patients have a different autonomic profile at rest and in response to orthostatic stress, compared to healthy subjects. Stratification by disease subset revealed a predominant sympathetic modulation at rest in lcSSc and dcSSc while EaSSc patients have an autonomic profile similar to healthy subjects. Finally, dcSSc and lcSSc patients have a blunted response to orthostatism compared to EaSSc patients and HC.

The presence of an autonomic dysfunction in SSc had been reported since 1982 [20]. Although classical studies already described a cardiovascular autonomic impairment in SSc through autonomic test such as tilt test, Valsalva maneuver, deep breathing and handgrip [20–24], studies focused of HRV assessment in SSc patients are recent [14,15,25].

Table 2
Comparison of HRV indexes at rest between SSc and age-matched healthy control group.

	SSc (n = 69)	HC (n = 36)	p-value
Spectral analysis			
Total power (ms^2)	933 ± 1107[a]	1769 ± 1973	< 0.01
LFnu	57 ± 22[a]	38 ± 22	< 0.001
HFnu	34 ± 19[a]	57 ± 21	< 0.001
LF/HF	3.27 ± 4.23[a]	1.12 ± 1.60	< 0.001
Symbolic analysis			
0 V (%)	36.76 ± 17.74[a]	16.55 ± 9.84	< 0.001
1 V (%)	43.48 ± 9.91[a]	49.60 ± 5.70	< 0.001
2UV (%)	13.39 ± 7.95[a]	21.37 ± 8.55	< 0.001
2LV (%)	6.37 ± 5.22[a]	12.49 ± 6.28	< 0.001
Conditional entropy			
RO	0.36 ± 0.10[a]	0.27 ± 0.08	< 0.001
CE	0.86 ± 0.24[a]	1.10 ± 0.12	< 0.001

HRV: heart rate variability; SSc: systemic sclerosis; HC: age-matched healthy control group; HFnu: high frequency normalized unity; LFnu: low frequency normalized unity; 0 V%: patterns with no variations; 1 V%: patterns with one variation, 2LV%: patterns with two like variations, 2ULV%: patterns with two unlike variations; RO: regulatory index; CE: conditional entropy index; es: effect size. Unpaired test t.

[a] Differences from HC. $\alpha < 0.05$.

The decrease of vagal-mediated HRV at rest, described in recent studies [14,15,25], corroborate the reduction of heart rate and blood pressure responses during vagal-mediated autonomic tests (Valsalva maneuver and deep breathing test), reported in the classical studies [21–24]. In line with previous data, our results showed that a decrease vagal modulation and a predominant sympathetic one in resting conditions (see Table 2) characterize SSc patients.

In addition, HRV nonlinear indexes confirmed the cardiac autonomic impairment in SSc as shown by spectral analysis. It is physiologically interesting because the conditional entropy and regulatory indexes may be related to sympathetic modulation [13]. Symbolic dynamics, conditional entropy and regulatory index are complementary tools to traditional indexes of HRV assessment. These indexes could be more sensitive to detect the physiological patterns, especially in some disease conditions' [12,13].

Our observations of a sympatho-vagal balance shift towards a sympathetic predominance in SSc is in line with a previous study that showed higher concentration of adrenaline and noradrenaline at rest, during active standing and during sustained handgrip in SSc patients compared to HC [26]. As to the response to orthostatic stress, we found that SSc patients showed a blunted autonomic response compared to healthy subjects confirming a previous study in which SSc patients presented a higher sympathovagal balance at rest, but a lower HRV sympathetic modulation in orthostatic position than HC [16].

Some hypotheses have been considered to explain sympatho-vagal dysfunction in SSc disease. The main injury in SSc patients involves microcirculatory systems and induces impairment of pulmonary and cardiac structures [10], which reduces the integrity and numbers of receptors and exerts a general inhibitory influence on cardiovascular control centers [16,26]. Taken together, afferent information's may be interrupted and could lead a sympathetic overactivity at rest [10,26], and a blunted response to sympathetic stimulation [16], as orthostatic standing, in SSc patients.

Previous studies focusing on disease subsets, namely on lcSSc and dcSSc provided conflicting results: some authors [26] did not find any differences while Zlatanovic and colleagues [14] found a lower total power, LF and HF in dcSSc compared to lcSSc. Similarly, we found that dcSSc is characterized by a significant reduction of total variability compared to lcSSc, pointing to an altered global autonomic modulation of the heart.

Intriguingly we also observed that non-fibrotic early scleroderma subjects do not have an altered autonomic dysfunction compared to HCs, while these alterations can be detected only in fibrotic patients. These findings may reflect the different degree of vascular damage, immune system activation and fibrosis described in SSc subsets [19, 27, 28]. We previously observed that vascular dysfunction markers linearly increase from EaSSc to fibrotic subjects [29]. Similarly, epigenetic alterations that may regulate fibrosis development are slightly altered in

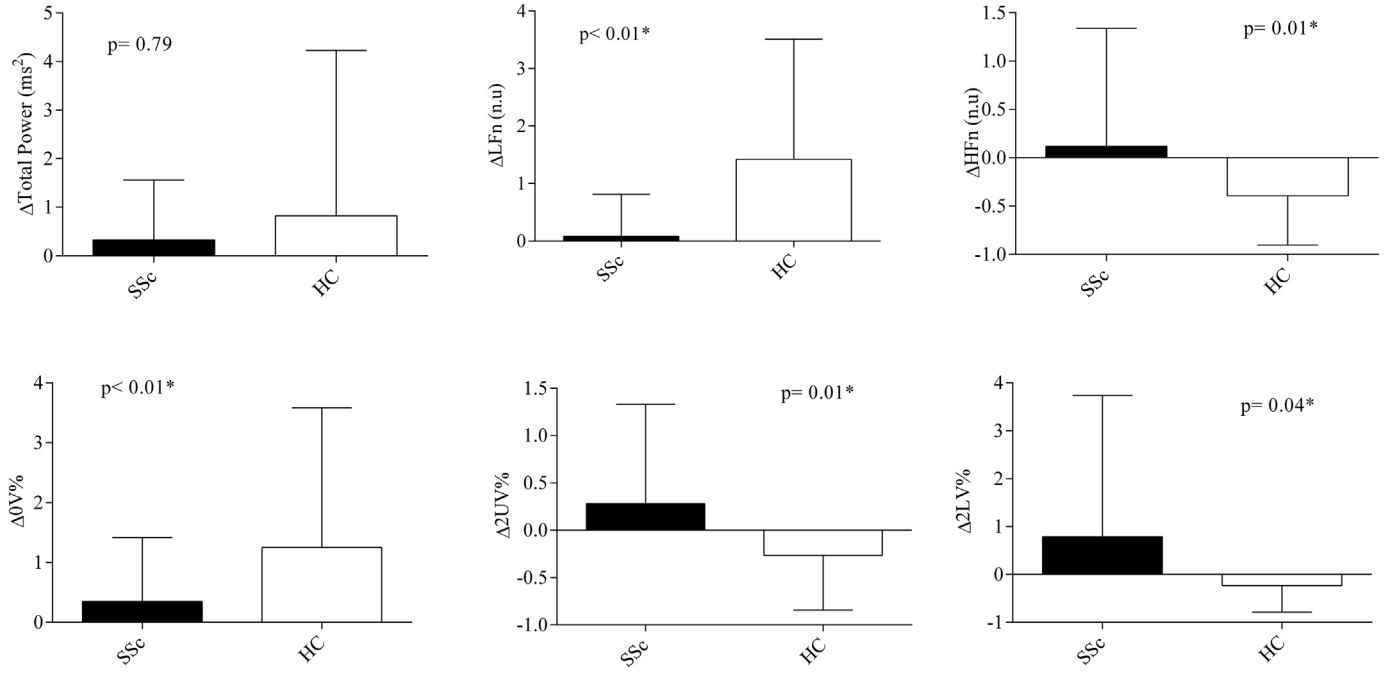

Fig. 1. Comparison of HRV adjustments from supine to orthostatic position between SSc and healthy control individuals. SSc: systemic sclerosis (n = 69); HC: age-matched healthy control group (n = 36); HFnu: high frequency normalized unity; LFnu: low frequency normalized unity; 0 V%: patterns with no variations; 2LV%: patterns with two like variations, 2ULV%: patterns with two unlike variations; ΔORT%: (HRV in SUP position – HRV in ORT position)/HRV in SUP position); Unpaired test t. *differences from HC. $\alpha < 0.05$.

Table 3
Comparison of HRV indexes at rest and HRV adjustments from orthostatic stress between SSc subsets and age-matched healthy control group.

	dcSSc (n = 18)	lcSSc (n = 39)	EaSSc (n = 12)	HC (n = 36)	p-value
Spectral analysis					
Total power (ms^2)					
SUP	439 ± 248	1553 ± 2858	1430 ± 1173[a]	1769 ± 1973[a]	0.04
ΔORT%	0.08 ± 0.68	0.38 ± 1.35	0.31 ± 1.23	0.82 ± 3.40	0.97
LFnu					
SUP	61 ± 20	58 ± 22	54 ± 25	38 ± 22[a,b]	< 0.01
ΔORT%	0.18 ± 0.98	−0.07 ± 0.48	0.45 ± 0.92	1.42 ± 2.09[a,b]	< 0.001
HFnu					
SUP	34 ± 18	32 ± 16	42 ± 25	57 ± 21[a,b]	< 0.001
ΔORT%	−0.05 ± 0.63	0.01 ± 0.69	0.35 ± 1.84	−0.40 ± 0.51	0.09
LF/HF					
SUP	3.01 ± 3.02	3.20 ± 3.40	3.74 ± 5.81	1.12 ± 1.60[a,b]	< 0.001
ΔORT%	0.93 ± 2.71	1.22 ± 3.85	4.54 ± 8.85	9.08 ± 13.92[a,b]	< 0.01
Symbolic analysis					
0 V (%)					
SUP	35.11 ± 22.41	40.12 ± 17.11	30.63 ± 11.86	16.55 ± 9.84[a,b,c]	< 0.001
ΔORT%	0.35 ± 0.74	0.19 ± 0.97	0.79 ± 1.57	1.25 ± 2.33[b]	0.03
1 V (%)					
SUP	43.20 ± 11.88	42.16 ± 10.62	46.50 ± 3.79	49.60 ± 5.70[b]	< 0.01
ΔORT%	0.05 ± 0.43	0.05 ± 0.38	−0.07 ± 0.27	−0.03 ± 0.25	0.52
2UV (%)					
SUP	13.64 ± 9.13	12.63 ± 7.11	15.04 ± 9.02	21.37 ± 8.55[a,b]	< 0.001
ΔORT%	0.19 ± 0.91	0.52 ± 1.18	−0.30 ± 0.28[b]	−0.27 ± 0.58[b]	< 0.01
2LV (%)					
SUP	8.04 ± 6.77	4.65 ± 1.18	7.83 ± 4.77	12.49 ± 6.28[b]	< 0.001
ΔORT%	0.24 ± 1.74	1.37 ± 3.56	−0.38 ± 0.43	−0.10 ± 0.78[b]	0.02
Conditional entropy					
RO	0.39 ± 0.10	0.37 ± 0.11	0.33 ± 0.09	0.27 ± 0.08[a,b]	< 0.001
CE	0.87 ± 0.25	0.84 ± 0.21	0.92 ± 0.12	1.10 ± 0.12[a,b]	< 0.001

SSc: systemic sclerosis; lcSSc: limited cutaneous SSc; dcSSc: diffuse cutaneous SSc; EaSSc: Early SSc; HC: age-matched healthy control group; SUP: supine position; ORT: Orthostatic position HFun: high frequency normalized unity; LFun: low frequency normalized unity; 0 V%: patterns with no variations; 1 V%: patterns with one variation, 2LV%: patterns with two like variations, 2ULV%: patterns with two unlike variations; RO: regulatory index; CE: conditional entropy index. Both RO and CE analysis were performed at rest. ΔORT%: (HRV in SUP position – HRV in ORT position)/HRV in SUP position); ANOVA one-way for independent measures and Tukey post-hoc test.

[a] Differences from dcSSc.
[b] Differences from lcSSc.
[c] differences from EaSSc. $\alpha < 0.05$.

EaSSc and biologically overt in fibrotic SSc [30].

While our data suggest a relationship between autonomic dysfunction and disease severity in SSc, their long-term clinical implications are currently unknown. Due to relatively small sample size of our case-series, and the consequent inability to perform a thorough correlation and covariate analysis, we can consider our findings as exploratory. Further studies are needed to evaluate the disease course of patients with reduced HRV and/or the need to perform additional exams in those subjects (as for instance MRI) that is, to determine the utility of autonomic dysfunction as an early screening tool for early fibrotic/inflammatory cardiac involvement in SSc.

5. Conclusions

Cardiac autonomic modulation evaluated trough HRV linear and non-linear tools, were impaired in SSc compared to aged-matched healthy control. Interestingly, we found alterations of cardiac autonomic control in advanced fibrotic (dcSSc, lcSSc) groups, while EaSSc patients have an autonomic profile similar to controls. These data, suggest that autonomic impairment occurs during the fibro-vascular progression of the disease. Whether these autonomic alterations may be helpful in risk stratification, by the identification of patients at higher risk for instance for cardiovascular complications, warrant further investigations.

Conflict of interest statements

The authors report no relationships that could be construed as a conflict of interest.

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