Autonomic nervous system dysfunction in sclerodermic and primary Raynaud’s phenomenon

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ABSTRACT

Our aim was to investigate the sympathetic hyperactivity of systemic sclerosis that may lead to greater morbidity and mortality from cardiovascular events. We analysed the sympathetic (low-frequency) and vagal (high-frequency) components of heart rate variability, in supine and upright positions, in 10 patients with systemic sclerosis, 12 patients with primary Raynaud’s phenomenon and 14 controls. We also analysed lung function in order to evaluate a possible link between heart rate variability and ventilation parameters. Heart rate variability was reduced in the supine position in subjects with systemic sclerosis both in comparison with primary Raynaud’s phenomenon (total power: $1103 \pm 156$ versus $3302 \pm 486$ ms$^2$, $P < 0.004$) and control subjects ($3148 \pm 422$ ms$^2$, $P < 0.002$). Low-frequency power was higher in patients with systemic sclerosis than in the controls ($54.5 \pm 4.5$ versus $42.5 \pm 3.5$ normalized units, $P < 0.01$). During tilt, the change in heart rate was $> 44\%$ in controls, $> 24\%$ in subjects with primary Raynaud’s phenomenon, and only $17\%$ in the patients with systemic sclerosis ($P < 0.01$ versus controls). In patients with systemic sclerosis we found a significant correlation between high-frequency power and the indices of lung function (residual volume: $r^2 = 0.5143$, $P < 0.01$; total lung capacity: $r^2 = 0.5142$, $P < 0.01$, vital capacity: $r^2 = 0.3789$, $P < 0.05$). Heart rate variability was reduced and sympathetic output increased in patients with systemic sclerosis. Subjects with primary Raynaud’s phenomenon were characterized by normal heart rate variability and by some degree of sympathetic hyperactivity. During tilting, subjects with systemic sclerosis maintained an unmodified heart rate variability, thus suggesting an impaired baroceptor modulation of the autonomic control. The negative correlation between high-frequency power and indices of respiratory insufficiency in patients with systemic sclerosis suggests that the pulmonary structure plays an important role in the modulation of heart rate variability.

INTRODUCTION

In recent years many reports have pointed out an impairment of the sympatho-vagal balance in patients with scleroderma [1–3]. The main feature of this impairment is a significant prevalence of the sympathetic component demonstrated both through indirect methods (variations in blood pressure on movement from supine to upright position, deep breathing, Valsalva manoeuvre), and through assessment of circulating catecholamine levels [4,5]. More recently, researchers have focused on the study of the sympatho-vagal balance by means of...
A recent study by Ferri et al. [6] showed that patients suffering from progressive systemic sclerosis present a faster heart rate than control subjects; they also present an impaired modulation of the autonomic tone which leads to reduced variability in heart rate. These findings emerged during the analysis of ambulatory 24-h electrocardiographic recordings. The particular algorithm employed for the spectral analysis permits a differentiation between the so-called high-frequency (HF) oscillations which identify the influence of the vagal activity on cardiac frequency [8] from those at low frequency (LF) which mainly depend on baroreceptor modulation of the sympathetic nervous system [9]. Moreover, this type of recording, by virtue of its length, permits analyses which take into consideration components with a longer and more defined period, such as very-low frequency (VLF) and ultra-low frequency (ULF), whose meaning is not yet clear [10].

A different analytical approach, which takes ‘short term’ recordings into account, provides us with information which can be more easily evaluated. Prolonged recording necessarily requires the use of procedures of averaging which involve an attenuation of the resulting message [11]. In particular, it could be difficult to assess the importance of the need for the trace to be stationary since the length of the period of observation is inversely proportional to this.

The condition of sympathetic hyperactivity reported in sclerodermic subjects may have unfavourable consequences for their greater morbidity and mortality from cardiovascular events. A prevalence of cardiac involvement in subjects with systemic sclerosis (SSc) developing severe restrictive lung disease has been reported [12]. Moreover, a reduction in HRV after right lung resection or after oesophagectomy has been shown [13], suggesting a link between the pulmonary integrity and the reflex arc influencing vasomotor tone that results from the balance between sympathetic and vagal drive. Therefore, given the possibility of an influence of damaged lung structures on the low-pressure baroreceptor drives, we tried to define a clinical grading of patients with SSc by relating HRV components to lung function parameters. We therefore decided to use a method of short-term spectral analysis to investigate sympato-vagal balance in a group of patients suffering from Raynaud’s phenomenon secondary to scleroderma (SSc) and in subjects with primary Raynaud’s phenomenon (PRP), comparing the results with those found in controls.

**MATERIALS AND METHODS**

**Population studied**

We assessed a group of 10 female subjects [mean age 38 ± 7 (range 25–52) years] affected by secondary Raynaud’s phenomenon from progressive systemic sclerosis diagnosed on the basis of the criteria proposed by the American Rheumatism Association Subcommittee for Scleroderma [14]. Four subjects were affected by the limited cutaneous form of the disease. The mean duration of the disease was 6 ± 3 years (range 2–15 years). All the patients were receiving acetylsalicylic acid (100 mg/day) and transdermal nitroglycerine (5 mg/day except for the day before, and the day of the examination); 7/10 patients were on nifedipine (10 mg twice daily, except for the day before, and the day of the examination), and 5/10 patients were on prednisone (5 mg/day).

The second group consisted of 12 subjects with PRP [10 females and two males, mean age 28 ± 5 (range 19–45) years] diagnosed on the basis of the criteria of Allen and Brown [15]. Finally the control group consisted of 14 healthy subjects [five males and nine females, mean age 31 ± 2 (range 25–36) years]. The male/female ratio and the age range of the groups was slightly different, but the overlap was large enough to reasonably exclude an appreciable bias in the results.

Exclusion criteria were the presence of arterial hypertension, diabetes mellitus, any form of heart disease, including echocardiographic signs of left ventricular hypertrophy [16], and other diseases known to cause alterations in autonomic control. The subjects were either non-smokers or had not used tobacco for more than 3 months, and none was following a regular training programme of physical activity. During the whole period of study, subjects maintained a balanced diet with a daily intake of 180–200 mmol of NaCl. The study was carried out in accordance with the Declaration of Helsinki of the World Medical Association and was approved by the local ethics committee. All subjects gave their informed consent before being recruited to the investigation.

**Biohumoral and instrumental examinations**

The following laboratory tests were carried out in all the patients with either primary or secondary Raynaud’s disease: antinuclear antibody (ANA) and extractable nuclear antigen (ENA) (anti-Scl70, -Sm, -RNP, -SSA, -SSB, -Jo1) antibodies, circulating immune complexes, C1q, C3–C4, latex test, cryoglobulins, plasma protein and immunoglobulin electrophoresis.

An echocardiographic examination of the same subjects was carried out with mono- and bi-dimensional evaluation of the heart walls and of the valve apparatus with subsequent colour Doppler and CW and PW Doppler velocimetric investigation of the transvalve flow with relative spectral analysis (Hewlett-Packard Sonos 1000). Lung function was investigated by chest X-ray and spirometry with evaluation of the usual parameters of
Study protocol
On the day of examination, subjects were requested to eat only a light breakfast, and drinks containing caffeine were prohibited. Taking into account the circadian rhythm of the autonomic tone, all examinations were carried out between 09:00 and 12:00 hours.

Adhesive electrodes were applied to the chest of each subject choosing the position which allowed the best ECG deflection (normally chest lead V5). The software automatically corrected for the maintenance of an isoelectric line to avoid any possible interference due to respiration on ventricular depolarization vector. After 20 min of stabilization in the supine position on an electrically driven tilt table, the ECG recording was started. This was performed in real time using a dedicated program with a sampling frequency of 240/s and a precision of 12 bit/sample (Microlab Diagnostica, Padua, Italy). The chosen frequency of sampling was correct as demonstrated for the normal range of frequencies at rest [10]. No patient suffered from dyspnoea, and all subjects were instructed to breathe regularly and to avoid deep breathing during the test (breathing rate per minute: 16 ± 1).

We used the response to passive orthostatism to assess the autonomic control of haemodynamic changes induced by positional variations. Therefore, after 15 min of recording in the supine position, the bed was inclined to 70° in about 4 s and the ECG recording continued for another 15 min.

The ECG trace was post-processed using a dedicated program (Microlab Diagnostica). The elaboration in the frequency domain was preferred because of the length of the recorded traces which, given the type of protocol, was chosen on the basis of the recommendations of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [10].

Evaluation of the spectral density power of R–R interval variability was carried out using a type ARMA (AutoRegressive-Moving Average) parametric method (see Appendix). This method works better in relation to the background noise than the simpler Auto-Regressive or Moving-Average models, while possessing the same properties (respectively spectral resolution and simplicity of model). The non-parametric method based on the fast Fourier transform algorithm (Welch method or method of the mean of modified periodogram) was used only as a simple control, because of the shortness of the registration traces. A further characteristic that suggested the use of the parametric method was the possibility of performing modal decomposition, by finding the precise frequency of the dominant peaks of the spectrum. The software also permitted the automatic calculation of the best order of the ARMA model using Akaike’s criteria.

The following parameters were calculated: mean length of N–N intervals (reciprocal of the mean frequency in stationary sequences of at least 256 consecutive R–R complexes, ms), total power (variance of N–N intervals in the period considered, ms²), LF (variance in the LF range: 0.03–0.15 Hz, ms²), HF (variance in the HF range: 0.15–0.40 Hz, ms²), LF/HF (ratio between the respective variances). LF and HF were also calculated in normalized units: LF-norm (variance in the LF range in normalized units: LF/(total power – VLF) %) and HF-norm (variance in the HF range in normalized units: HF/(total power – VLF) %). These mathematical calculations demonstrate the controlled and balanced behaviour of the two branches of the autonomic nervous system and permit an evaluation of the changes in each component while excluding the effects of the changes in total power [17]. The central frequency values of each of the considered spectral components (f-LF and f-HF, Hz) were also evaluated. The value of VLF is difficult to interpret in such short-term assessments; we therefore decided not to consider it [10].

Statistical analysis
Results are given as means ± S.E.M. After variance analysis, parametric and non-parametric tests were used for paired and unpaired data. Spearman’s test was used to identify a correlation between HRV and respiratory parameters after the Mantel–Haenszel test for association of linearity. Only P values less than 0.05 were considered significant. SPSS for Windows (version 6.01) software (SPSS Inc., Chicago, IL, U.S.A.) was used for the analysis.

RESULTS
All the subjects with PRP and the controls had normal chest X-ray and spirometric tests. However, the majority of patients (7/10) in the sclerodermic group exhibited alterations in the interstitial bronchopulmonary reticulum and/or tests of respiratory function (Table 1).

ANA and ENA tests were negative in the control group and in subjects with PRP, whereas positive results were found in subjects with the secondary disease (ANA, 10/10; anti-centromere, 4/10; anti-Scl70, 6/10).

Spectral analysis of HRV
Spectral analysis of heart rate (Figure 1) showed that its variability was significantly reduced in the supine position in patients with scleroderma, as demonstrated by the low level of total power, both in comparison with PRP subjects (1103 ± 156 versus 3302 ± 486 ms², P < 0.004) and control subjects (3148 ± 422 ms², P < 0.005). Table 2 illustrates the differences found in the power of the different components of the autonomic control of HRV.
Table 1  Lung function parameters in control subjects and patients suffering from primary (PRP) and secondary (SSc) Raynaud’s phenomenon

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>PRP</th>
<th>SSc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vital capacity (litres)</td>
<td>3.88 ± 0.09</td>
<td>3.79 ± 0.09</td>
<td>3.12 ± 0.13*</td>
</tr>
<tr>
<td>Total lung capacity (litres)</td>
<td>5.43 ± 0.15</td>
<td>5.34 ± 0.16</td>
<td>4.72 ± 0.21**</td>
</tr>
<tr>
<td>Residual volume (litres)</td>
<td>1.70 ± 0.03</td>
<td>1.65 ± 0.04</td>
<td>1.57 ± 0.09</td>
</tr>
<tr>
<td>Residual volume/total lung capacity (%)</td>
<td>29 ± 0.9</td>
<td>31 ± 0.8</td>
<td>34 ± 1.2*</td>
</tr>
<tr>
<td>Forced vital capacity (litres)</td>
<td>3.65 ± 0.10</td>
<td>3.61 ± 0.10</td>
<td>3.01 ± 0.23**</td>
</tr>
<tr>
<td>Forced expiratory volume in 1.0 s (litres)</td>
<td>3.22 ± 0.07</td>
<td>3.18 ± 0.06</td>
<td>2.38 ± 0.19*</td>
</tr>
<tr>
<td>Diffusing lung capacity for CO (ml·min⁻¹·mmHg)</td>
<td>21.5 ± 0.37</td>
<td>20.8 ± 0.40</td>
<td>15.4 ± 1.6*</td>
</tr>
</tbody>
</table>

Table 2  Heart rate variability parameters during the supine position in control subjects and patients suffering from primary (PRP) and secondary (SSc) Raynaud’s phenomenon

<table>
<thead>
<tr>
<th>Supine position</th>
<th>Controls</th>
<th>PRP</th>
<th>SSc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean N–N (ms)</td>
<td>911 ± 38</td>
<td>903 ± 41</td>
<td>843 ± 31</td>
</tr>
<tr>
<td>Total power (ms²)</td>
<td>3148 ± 422</td>
<td>3302 ± 486</td>
<td>1103 ± 156*</td>
</tr>
<tr>
<td>LF power (ms²)</td>
<td>614 ± 73</td>
<td>654 ± 78</td>
<td>316 ± 50**</td>
</tr>
<tr>
<td>LF (n.u.)</td>
<td>42.5 ± 3.5</td>
<td>43.6 ± 3.7</td>
<td>54.5 ± 4.5**</td>
</tr>
<tr>
<td>f-LF (Hz)</td>
<td>0.085 ± 0.002</td>
<td>0.087 ± 0.001</td>
<td>0.078 ± 0.003</td>
</tr>
<tr>
<td>HF power (ms²)</td>
<td>989 ± 109</td>
<td>954 ± 191</td>
<td>264 ± 61***,†</td>
</tr>
<tr>
<td>HF (n.u.)</td>
<td>57.7 ± 4.5</td>
<td>56.4 ± 5.4</td>
<td>45.5 ± 5.6</td>
</tr>
<tr>
<td>f-HF (Hz)</td>
<td>0.259 ± 0.007</td>
<td>0.247 ± 0.010</td>
<td>0.256 ± 0.007</td>
</tr>
<tr>
<td>LF/HF</td>
<td>1.05 ± 0.25</td>
<td>1.21 ± 0.32</td>
<td>1.69 ± 0.39†</td>
</tr>
</tbody>
</table>

Table 3  Heart rate variability parameters during the upright position in control subjects and patients suffering from primary (PRP) and secondary (SSc) Raynaud’s phenomenon

<table>
<thead>
<tr>
<th>Upright position</th>
<th>Controls</th>
<th>PRP</th>
<th>SSc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean N–N (ms)</td>
<td>631 ± 73</td>
<td>725 ± 37</td>
<td>720 ± 24</td>
</tr>
<tr>
<td>Total power (ms²)</td>
<td>2603 ± 485</td>
<td>2200 ± 347</td>
<td>1039 ± 192**</td>
</tr>
<tr>
<td>LF power (ms²)</td>
<td>762 ± 182</td>
<td>702 ± 142</td>
<td>215 ± 39**</td>
</tr>
<tr>
<td>LF (n.u.)</td>
<td>84.2 ± 8.4</td>
<td>72.1 ± 5.3</td>
<td>51.0 ± 5.4**</td>
</tr>
<tr>
<td>f-LF (Hz)</td>
<td>0.074 ± 0.002</td>
<td>0.077 ± 0.002</td>
<td>0.071 ± 0.001</td>
</tr>
<tr>
<td>HF power (ms²)</td>
<td>173 ± 61</td>
<td>215 ± 33</td>
<td>191 ± 33</td>
</tr>
<tr>
<td>HF (n.u.)</td>
<td>16.1 ± 2.1</td>
<td>27.9 ± 3.8</td>
<td>49.1 ± 4.8**</td>
</tr>
<tr>
<td>f-HF (Hz)</td>
<td>0.231 ± 0.007</td>
<td>0.243 ± 0.008†</td>
<td>0.272 ± 0.008*</td>
</tr>
<tr>
<td>LF/HF</td>
<td>7.98 ± 1.64</td>
<td>3.61 ± 0.75†</td>
<td>1.12 ± 0.17**,†</td>
</tr>
</tbody>
</table>

Figure 1  Graphs representing spectral analysis in a control subject (top) and in a patient with SSc (bottom)
OOT, optimal order test; P, order of the chosen model.
When we consider the differences found in the three different groups as normalized units, we can see that the sympathetic output, as shown by the power of the LF component, is higher in the sclerodermic patients when compared with the control subjects (54.5 ± 4.5 versus 42.5 ± 3.5 normalized units, P < 0.01). On the other hand, it is also higher than the values found in subjects with PRP (43.6 ± 3.7 normalized units, P < 0.01).

The HF power presents a significant difference which clearly distinguishes the patients with SSc from the other two groups (Table 2).

During tilting (Table 3), heart rate increased in the patients with SSc, as in the other two groups, but the degree of variation was significantly lower: +44% in the controls, +24% in subjects with PRP, and only +17% in patients with SSc (P < 0.01 versus controls) (Figure 2).

Subjects with PRP showed a significant increase in total power but the change appeared to be smaller than that of the control subjects although the difference is not statistically significant (2200 ± 347 versus 2603 ± 485 ms²).

Upright stimulation caused an increase in LF power in the controls, whereas it caused a reduction in the patients with SSc (Table 3). The response in subjects with PRP was similar to that in control subjects but the increase in LF power was smaller (702 ± 142 versus 762 ± 182 ms²).

Controls and subjects with PRP showed a highly significant reduction of HF power during tilting, whereas patients with SSc did not exhibit substantial changes in this component (Figure 3). However, after normalization, subjects with PRP showed an intermediate behaviour of HF power that was significantly different compared with the control group (27.9 ± 3.8 versus 16.1 ± 2.1, P < 0.03).

As a result of these modifications the analysis of the sympatho-vagal balance, carried out using the LF/HF ratio, demonstrated a prevalence of the sympathetic component in patients with SSc in the supine position. In
The correlation line and 95% confidence intervals are shown. This showed a statistically significant difference only in comparison with control subjects (1.69 ± 0.39 versus 1.05 ± 0.25, \( P < 0.05 \)). The LF/HF ratio increase after upright stimulation appeared to be physiological in the controls (7.98 ± 1.64 versus 1.05 ± 0.25, \( P < 0.002 \)) and also in subjects with PRP (3.61 ± 0.75 versus 1.21 ± 0.32, \( P < 0.001 \)). However, patients with SSc showed substantial stability of the LF/HF ratio after upright stimulation (1.12 ± 0.17 versus 1.69 ± 0.39, \( P \) not significant). The central frequency of the LF component did not show significant differences in the three different groups of subjects in either the supine or upright positions, although upright stimulation caused a significant shift towards VLF in the control and PRP groups, but not in the SSc group. Moreover, there was a significant reduction in the central HF value during orthostatism in the control and PRP groups compared with the SSc group. These variations compared with the supine position were significant within the same group only in the case of the controls.

**HRV and lung function relation**

Correlation analysis between HRV components and ventilation parameters appeared significant only in patients with SSc. Indeed, we found a statistically significant relation of normalized HF power with residual volume (\( r^2 = 0.5143, P < 0.01 \)), total lung capacity (\( r^2 = 0.5142, P < 0.01 \)) and vital capacity (\( r^2 = 0.3789, P < 0.05 \)) (Figure 4). In the same patients LF power showed a correlation with diffusing lung capacity for CO (\( r^2 = 0.6928, P < 0.01 \)), and LF/HF ratio correlated with residual volume (\( r^2 = 0.708, P < 0.01 \)) and with total lung capacity (\( r^2 = 0.628, P < 0.01 \)).

**DISCUSSION**

The variability of R–R interval length is an index of the intensity of the control exercised by the autonomic nervous system on heart rate. The main finding of our study was the reduced variability of heart rate in subjects with scleroderma both in relation to the total power and to the specific power of the various components. This finding can be attributed to a reduced influx of autonomic modulation on the activity of the sinoatrial node linked to a reduced influence of the parasympathetic drive. Various hypotheses have been considered. First, the main lesion in these patients involves the microcirculatory system and induces an impairment of the pulmonary structures, which have an important role as volume receptors [18,19] and exert a general inhibitory influence on the centres involved in cardiovascular control [20]. In this way afferent information may be interrupted and, with a decreasing volume, could lead to a deficiency in sympathetic activation [21]. Moreover, the influx of respiratory rhythm on cardiac frequency, a marker of vagal influence, is fixed. The sclerodermic subjects we studied exhibited a higher cardiac frequency in the supine
position, thus demonstrating sympathetic overactivity and a defect of parasympathetic modulation with reduced HRV. Moreover, after upright stimulation these patients maintained a substantially unmodified total power of HRV, suggesting an impaired baroreceptor modulation of the autonomic control, and the analysis of the sympathovagal balance, carried out using the LF/HF ratio, demonstrated a prevalence of the sympathetic modulation in patients with SSc.

On orthostatic stimulation, when volume is reduced at chest level, we found a physiological sympathetic activation both in the control group and, to a lesser extent, in the subjects with PRP but, conversely, a reduction in sympathetic output in the sclerodermic group. Moreover, the vagal modulation was maintained in the patients with SSc at a significantly higher level than that of the other two groups in which it was markedly inhibited. This behaviour suggests a loss of the control capability of the baroreceptor system which is likely to involve also the low-pressure receptor components. Indeed, it has been shown that reduction of the circulating mass above the diaphragm, which can be obtained using different procedures such as head-up tilting or the application of a negative pressure to the lower part of the body, leads to stimulation of the cardiopulmonary low-pressure receptors with consequent sympathetic vasoconstrictor response [20,21].

The interstitial damage caused by fibrosis, which is typical of the cardiovascular and pulmonary involvement in patients with SSc, could be the cause of alterations which have been found in the autonomic control of circulation in these subjects [22].

The negative correlation observed in sclerodermic subjects between HRV and respiratory parameters suggests that impairment of the respiratory function may well be a cause of the alteration in the autonomic control in these patients. In fact, we found that the indices of restrictive respiratory insufficiency showed a very significant negative correlation with the HF component of HRV, which, as an index of vagal tone, is largely influenced by respiratory modulation of heart rate [8]. Similarly, the evaluation of sympathovagal balance indicated a correlation between LF/HF ratio, residual volume and total lung capacity. There also seems to be an association between the increased sympathetic component and diffusing lung capacity for CO. Overall, these data suggest that normal pulmonary structures play an important role in conditioning the autonomic modulation of HRV. In a different clinical setting, patients with hypoxaemic chronic obstructive pulmonary disease show a significant correlation between parasympathetic autonomic function and $P_{A\text{O}_2}$ [23]. In the same manner, a decreased HRV was recorded in patients with chronic obstructive pulmonary disease [24]. The impairment of normal lung structures (particularly of the parenchymal component) seems to lead to a progressive loss in the vagal function. The sympathetic function seems to be at least partially correlated with the alteration of the interstitial component, as suggested in our study by the relationship with the impairment of CO total lung diffusion.

In subjects with PRP we recorded some degree of sympathetic activation. These data are in agreement with the hypothesis ascribing at least a role to sympathetic hyperactivity in the pathophysiology of vasospastic crises of PRP [25].

In our group of sclerodermic patients, four had the limited cutaneous variant and the presence of anticientomere antibodies. Douvas et al. [26] suggest that these antibodies may influence the sympathovagal balance because they are directed against a protein epitope rich in glutamic acid residues like that found in the calcium channels of the cellular membranes in autonomic fibres. Unlike Hermosillo et al. [27], we did not find a substantial difference in the behaviour of the limited cutaneous subgroup compared with the other patients with the diffuse cutaneous form of the disease. This may be due to the small size of the subgroup or to the fact that our protocol involved suspension of the administration of nifedipine for at least 36 h.

Alternatively the high prevalence of anti-Scl70 antibody in our subjects may play a role in the abnormal autonomic control of HRV. Indeed, anti-Scl70 is correlated with a severe outcome and has a negative prognostic significance, since it seems to be correlated with alterations in the cardiac rhythm in sclerodermic patients [28]. However, we cannot exclude the possibility that the relationship between the presence of Scl-70 and cardiac arrhythmias might be due to the high prevalence of both these elements in SSc, without a clear pathophysiological link between them.

Gender ratio and age class in the control group are slightly different from those of the other two groups. There are known age and gender differences in HRV, especially around the menopause, probably due to hormonal influences. However, it seems difficult to attribute the differences recorded in our study only to gender and age differences.

In conclusion, this study shows that after upright stimulation subjects with PRP are characterized by a normal HRV and usually show only a slight sympathetic hyperactivity. This agrees, at least in part, with the hypothesis attributing importance to an emphasized sympathetic drive in subjects with PRP.

However, HRV is significantly reduced in patients with SSc as demonstrated by the low level of total power, both in comparison with subjects with PRP and with controls. Sympathetic output, as shown by LF power, is higher in patients with SSc when compared with the control subjects, but not significantly different from subjects with PRP. Moreover, during tilting, subjects with SSc maintain a substantially unmodified HRV thus
sugestting an impaired baroreceptor modulation. Of particular interest is the significant negative correlation between HF power and residual volume as well as total lung capacity which suggest a possible pathophysiological explanation of the alteration of autonomic control.

Therefore, taking into account the progressive impairment of lung function in patients with SSc [12], short-term HRV evaluation appears to be an important diagnostic tool in the planned evaluation of sclerodermic patients since it allows an assessment of the autonomic control, and consequently a more complete picture of the pathogenic mechanisms among which cardiac arrhythmias are particularly important.

ACKNOWLEDGEMENT

We thank Dr Mario Olivieri for assistance with lung-function examinations.

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APPENDIX

Parametric methods of spectral estimation based on the elaboration of a model of a linear system that has as output the sequence of samples $x(n)$ and is described by a rational function of the type:

$$H(z) = \frac{B(z)}{A(z)} = \frac{\sum_{k=0}^{q} b_k z^{-k}}{1 + \sum_{k=1}^{p} a_k z^{-k}}$$

where $a_k$ and $b_k$ are the coefficients and $p$ and $q$ represent
respectively the number of poles and the number of zeros. The corresponding equation of differences is:

\[ x(n) = - \sum_{k=1}^{p} a_k x(n-k) + \sum_{k=0}^{q} b_k w(n-k) \]

where \( w(n) \) is the input sequence of the system and \( x(n) \) represents the output sequence. In the evaluation of the power of spectral density, input sequence is not observable. However, if we hypothesize that the output sequence (corresponding to the sample sequence) is stationary, we can assume that the input sequence is an aleatory stationary process [1].

**REFERENCE**