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Heart Rate Variability in Patients with Sjögren's Syndrome

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Abstract: Heart rate variability (HRV) gives information about sympathetic–parasympathetic autonomic balance. Our purpose was to determine whether HRV is abnormal in patients with Sjögren's syndrome. In 16 patients with Sjögren's syndrome and 30 matched controls, a short time analysis of HRV was performed for both the frequency and the time domain. In the time domain, patients tended to display a slower heart rate, greater R-R variability and higher standard deviation of the mean (SDNN) than did healthy subjects, but the differences were not statistically significant. In the frequency domain the spectral measures of HRV showed a slight reduction of LF and an increase of HF; as a result, the ratio between high and low frequencies, representative of sympathovagal modulation, was significantly reduced. Our data suggest an increase in the parasympathetic control of heart rate in patients with Sjögren's syndrome. This predominance in vagal tone could exert a protective and antiarrhythmic role in patients with primary Sjögren's syndrome, and may be relevant with reference to the lower incidence of sudden death in this disorder compared to other major autoimmune diseases.

Keywords: Autonomic disease; Heart rate variability; Sjögren's syndrome

Introduction

Primary Sjögren's syndrome is one of the most common systemic autoimmune diseases. It affects mainly the exocrine glands, but one-third of patients have non-exocrine organ manifestations, such as arthralgias, interstitial nephritis, Raynaud's phenomenon and lymphomas. Nervous system involvement can also be found, including symptoms of peripheral neuropathy. In contrast, autonomic neuropathy associated with Sjögren's syndrome is poorly characterised and the assessment of the prevalence of alterations in cardiovascular autonomic innervation and tone has been, to date, the subject of only one study and few case reports [1,2]. In these studies, provocative autonomic testing, such as measurement of heart rate and blood pressure changes during Valsalva manoeuvres, showed signs of autonomic disturbances mainly affecting the parasympathetic nerves.

Recent studies have demonstrated the correlation of various parameters of heart rate variability (HRV) with parasympathetic and sympathetic activity directed to the heart [3]. Compared to traditional tests, HRV analysis is a practical, reproducible and non-invasive method to detect early autonomic impairment, also allowing better quantitative and qualitative evaluation of the sympathovagal modulation of cardiovascular function [4,5].

The aim of this study was to assess the presence and severity of autonomic impairment by evaluating HRV in a series of randomly selected patients with primary Sjögren's syndrome.

Materials and Methods

The initial study population consisted of 18 women with a mean age of 54 years. These were all of the patients with Sjögren's syndrome who were consecutively seen at Reggio Emilia Hospital (a secondary referral center) from June 1996 to December 1998. All patients were classified as having primary Sjögren's syndrome by the criteria established by Vitali et al. [6]. All patients had objective keratoconjunctivitis sicca, xerostomia, and

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biopsy specimens from the minor salivary gland that were class 3 or higher [7]. No patients met the criteria for any other connective tissue disease. Thirty-six female blood donors volunteered to serve as controls and were matched with the patients' ages.

No patients had clinical evidence of peripheral neuropathy, clinical signs of autonomic dysfunction, history of diabetes mellitus, or myocardial infarction. Two patients with Sjögren's syndrome were excluded from the analyses because they used ß-adrenoreceptor antagonists and nifedipine; their matched controls were excluded as well. At the time of the enrollment all patients were non-smokers and none of them was receiving corticosteroids. Two control subjects were excluded because they were smokers. No patients or controls admitted to more than 6 units of alcohol per week. Therefore, the final group consisted of 16 patients with Sjögren's syndrome (mean age 52.3 yrs, SD 8.5) and 30 healthy controls (mean age 51.4 yrs, SD 10.3).

Even if our patients did not have clinical signs of cardiovascular disease 2D and Doppler echocardiography was performed in all of the 16 pSS patients.

Immunologic Evaluation

We tested patients for autoantibodies , including antinuclear antibodies, by using kidney and Hep-2 substrates. The presence of antibodies to Ro (SS-A), La (SS-B) and IgG and IgM anticardiolipin antibodies was determined by using enzyme-linked immunosorbent assay [8]. Rheumatoid factor was detected in serum samples by using a rheumatoid arthritis latex test.

Heart Rate Variability Measurement

A standard ambulatory Holter recording system (Marquette 8500 series) was used. All recordings were carried out for 1 hour between 8:30 and 11:30 am; patients had fasted overnight and were kept in the recumbent position throughout the short duration of the registration. The subjects were asked to remain awake and relaxed, but the depth and rate of breathing were not controlled. Only time series comprising 256-s consecutive R-R intervals without ectopic beats or artefacts were selected. A dedicated software was used to calculate HRV indices (Holter analysis system, software version 5.7, Marquette, Kettering USA).

In all patients and controls a computer analysis of the following HRV parameters was performed:

1. Time domain:
   - Average NN interval (ms): Average of all normal R-R intervals over the entire recording
   - PNN50: the percentage of intervals that differed from adjacent interval by > 50 ms
   - SDNN (ms): standard deviation of the R-R interval average.

Time domain variables, derived from the sequence of R-R intervals, were automatically calculated by the software.

2. Frequency domain:
   - Total spectral power (ms^2)
   - Low frequency (ms^2) (LF; 0.04–0.15 Hz)
   - High frequency (ms^2) (HF; 0.15–0.40 Hz)

Spectral analysis of R-R intervals was performed by Fast Fourier transform.

Statistical Method

Comparisons of normally distributed continuous variables between the two groups were performed by analysis of variance (ANOVA), and results are presented as mean value ± SD.

Because power spectral density did not follow a normal distribution a non-parametric Kruskal–Wallis test was used to compare the independent groups, and values are presented as medians. A probability value of less than 0.05 was considered statistically significant.

Results

The demographic and clinical data of the 16 study patients with Sjögren's syndrome are summarised in Table 1. Antinuclear antibodies at a titre of 1:320 or more were present in all patients. Ten of the 16 patients had antibodies to Ro, and six of 16 had antibodies to La. Rheumatoid factor was positive in 14 of 16 patients. Four patients were positive for anticardiolipin antibodies, two for IgG alone and two for both IgG and IgM.

The results of the analysis of heart rate variability in our Sjögren's population and in the controls are shown in Table 2.

Patients tended to display a slower heart rate, greater R-R variability and higher SDNN than did healthy subjects, but the differences were not statistically significant.

Spectral measures of heart rate variability showed a slight reduction of LF and a slight increase of HF; as a

Table 1. Clinical and laboratory variables in patients with Sjögren's syndrome

Variable	Patients (n= 16)
Mean age ± SD, yrs	52.3 ± 8.5
Range of duration of disease, yrs	2–9
Erythrocyte sedimentation rate, *n*	
< 60 mm/h	10
> 60 mm/h	6
Antinuclear antibody titre > 1:320, *n*	16
Presence of antibodies to Ro (SSA), *n*	10
Presence of antibodies to La (SSB), *n*	6
Presence of anticardiolipin antibodies, *n*	4
Raynaud's phenomenon, *n*	5
Vasculitis, *n*	2

Table 2. Heart rate variability parameters in patients with Sjögren's syndrome (n = 16) and controls (n = 30). Mean ± SD

	Sjögren's syndrome	Controls	p
NN intervals	800.50± 65	737.57± 37	n.s
SDNN	134.75 ± 40.43	125.07 ± 29.60	n.s.
pNN50	7.50 ± 6.23	5.61 ± 2.56	n.s.
Total power	32.15 ± 4.3	29.8 ± 5.6	n.s
LF	17.20 ± 7.28	20.92 ± 5.25	n.s.
HF	12.26 ± 6.72	9.97 ± 2.00	n.s.
LF/HF	1.47 ± 0.35	2.1 ± 0.24	< 0.01

NN, average of normal R-R intervals over the entire recording; SDNN, standard deviation of the R-R interval average; PNN50, percentage of R-R adjacent intervals differing from each other by more than 50 ms; LF, low frequencies; HF, high frequencies.

result, the ratio between high and low frequency, representative of sympathovagal modulation, was significantly reduced ($p < 0.01$) (Fig. 1). Figure 2 shows the frequency domain analysis of the heart rate variability in a representative healthy subject and in a patient with primitive Sjögren's syndrome.

No differences were seen between patients with positive or negative antibodies to Ro or La, and between patients with or without anticardiolipin antibodies. No correlation was found between the HRV parameters and disease duration, Schirmer test score and ESR.

Discussion

The analysis of heart rate variability is considered a valid method to assess autonomic nervous system fluctuations in normal healthy individuals and in patients with various cardiovascular and non-cardiovascular disorders [5].

There are two approaches to measure HRV: time domain and frequency domain analysis. In the time domain analysis the standard deviation of the mean of R-R intervals (SDDN) represents a general measurement of autonomic nervous system balance, whereas the percen-

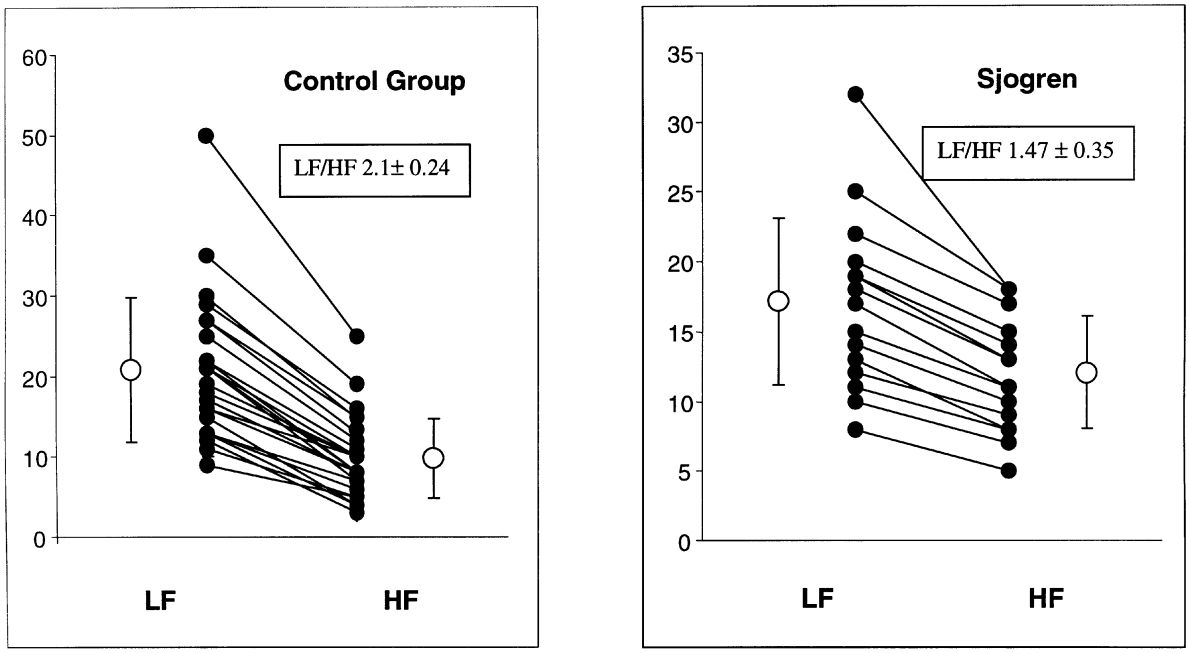

Fig. 1. Individual data points for spectral analysis in patients with pSS and controls.

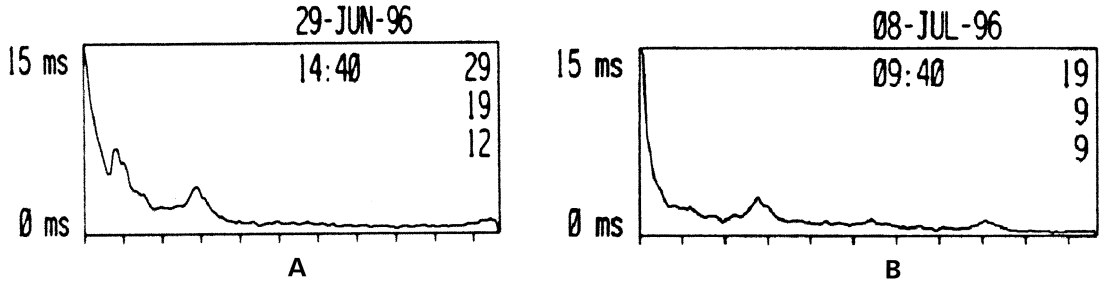

Fig. 2. Frequency domain analysis of the heart rate variability in a representative healthy subject (A) and in a patient with primary Sjögren's syndrome (B).

tage of R-R adjacent intervals differing from each other by more than 50 ms, or pNN50, predominantly reflects parasympathetic activity. In the frequency domain, the spectral analysis of R-R intervals can detect two major components: the so-called high-frequency component (HF) of physiologic heart rate variability (spectral components in the band from 0.15 to 0.5 Hz), and the low-frequency (LF) component (spectral band from 0.05 to 0.15 Hz). The former is modulated predominantly by the parasympathetic nervous system, whereas the second is under the influence of both the parasympathetic and the sympathetic system. The LF/HF ratio can be considered to be a marker of the sympathovagal balance [3,5,9].

Abnormal autonomic function is known to predispose to arrhythmogenesis in both clinical and experimental conditions. The loss of heart rate variability and sympathovagal imbalance (either increased sympathetic or reduced vagal activity) has been shown to be a strong and independent predictor of postinfarction mortality and is of prognostic value in patients with heart failure, and in diabetic autonomic neuropathy. Conversely, a vagal predominance could exert a protective and antifibrillatory effects [9].

In autoimmune diseases such as systemic lupus erythematosus and systemic sclerosis, several studies have shown a significant reduction in heart rate variability [10–13]. In particular, in SLE spectral analysis has revealed a reduction in the high-frequency components, indicating reduced parasympathetic cardiovascular tone. The same has been demonstrated in systemic sclerosis, mainly in the CREST syndrome. In our study we found some differences in heart rate variability in the patients compared to control subjects. Our data show a slight increase in pNN50, SDNN and a significant reduction of LF/HF ratio in the patients with Sjögren's syndrome, suggesting a predominance of the parasympathetic modulation of heart rate. This relative predominance in vagal tone could have a protective and antiarrhythmic role. Indeed, in a recent long-term follow-up study on the cause of death in patients with Sjögren's syndrome, there were neither sudden nor arrhythmia-related deaths [14]. On the other hand, 40%–60% of all deaths in systemic sclerosis are considered to be sudden, and are presumably secondary to ventricular tachycardia or ventricular fibrillation [15]. Sudden deaths also accounted for 8% of total mortality in a recent study carried out in patients with systemic lupus erythematosus [16].

Conclusion

In our patients with pSS there are no indications for an increase in sympathetic control of heart rate as has been observed in other autoimmune diseases. This observation might be of some importance with reference to the differences in the risk of fatal arrhythmias between primary Sjögren's syndrome and the other main autoimmune diseases. However, owing to the small number of cases enrolled in this study, further work will be necessary to confirm our data.

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