# EXTENDED REPORT

# Spectral analysis of heart rate and blood pressure variability in primary Sjögren's syndrome

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Accepted 15 August 2001
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**Background:** Autonomic dysfunction has been described in primary Sjögren's syndrome (SS).
**Objective:** To investigate the circulatory autonomic regulation in patients with primary SS by power spectral analysis of heart rate and blood pressure variability.
**Methods:** Forty three (42 female) patients with primary SS, mean age 52 years (range 23–80), with a mean disease duration of eight years (range 1–30) and 30 (15 female) healthy controls, mean age 43 years (range 21–68) were studied. In each patient blood pressure, heart rate, and respiration were measured continuously during supine rest and orthostatic challenge (60° head-up tilt). Power spectral analysis was performed to determine possible differences in short term sympathetic and parasympathetic autonomic regulation between patients and controls. Furthermore, spectral parameters were studied in relation to illness severity and disease duration of the patients with primary SS.
**Results:** After controlling for differences in age, heart rate variability of the mid-frequency band and the variation coefficient of systolic blood pressure were significantly lower in patients with primary SS than in controls during supine rest. During 60° tilt patients with primary SS showed a significantly higher mean heart rate, mean systolic blood pressure, and variation coefficient of diastolic blood pressure, and a significantly lower baroreflex index than controls. After controlling for age, no differences were found either in heart rate variability, blood pressure results, and baroreflex sensitivity during supine rest and tilt between the subgroups divided according to disease duration, Schirmer test results, or between the subgroups with different fatigue scores. No differences were found in spectral data between the groups with and without positive antinuclear antibody serology.
**Conclusion:** For the group no differences in sympathetic and parasympathetic cardiac control were seen between patients with primary SS and controls, as assessed by spectral techniques, although some cardiovascular differences were found, particularly during orthostatic challenge.

Primary Sjögren's syndrome (SS) is a systemic autoimmune disorder, with characteristics of both organ-specific (lachrymal and salivary glands) and generalised autoimmune disease. The two main features are hyposalivation and diminished tear fluid, although other symptoms may be present if other exocrine glands are affected.

Neurological symptoms from central and peripheral nervous system involvement are well known in primary SS, but their incidence is not clearly defined. Depending on the study group, peripheral complications have been reported in 10–50% of patients. Recently, several case reports and two studies of disturbances of the autonomic nervous system in patients with primary SS were published.[1–9] In both studies the circulatory autonomic function was evaluated by deep breathing and tilt table tests.[1 9] Parasympathetic disturbances were found in a subgroup of patients with primary SS. In other systemic diseases, such as diabetes mellitus, reduction of heart rate (HR) variability seems to precede the clinical expression of autonomic neuropathy.[10 11] Spectral analysis of HR variability is a sensitive, non-invasive tool to detect early disturbances of the autonomic nervous system.

We applied this technique in a group of patients with primary SS and compared the findings with those obtained in healthy controls.

## PATIENTS AND METHODS

### Patients
Two groups of subjects were studied:

### Group 1
Forty three patients (42 female) with primary SS, aged 23–80 years (mean 52) with a disease duration varying between 1 and 30 years (mean eight years), were recruited from the Department of Rheumatology, Medisch Centrum Rijnmond Zuid, Rotterdam. All patients fulfilled the European criteria for primary SS.[12]

### Group 2
Thirty volunteers (15 female), aged 21–68 years (mean 43) served as healthy controls; they were recruited from hospital and university employees, they were all healthy as established from their medical history based on an interview, and none had been taking drugs for at least four weeks at the time of the study.

None of the patients or controls had concomitant conditions, such as neurological disease, amyloidosis, renal failure, diabetes mellitus, myocardial infarction, sustained ventricular tachycardia, or cardiac arrest, all known to interfere with the autonomic nervous system. None of the patients showed abnormalities in heart rhythm. None of the patients or healthy volunteers used drugs interfering with the function of the autonomic nervous system (calcium channel blockers, β blockers, angiotensin converting enzyme inhibitors, antidepressive drugs, antiepileptic drugs).

Administration of non-steroidal anti-inflammatory drugs, used by 55% of the patients, was discontinued one week before the autonomic function tests.

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**Abbreviations:** ANA, antinuclear antibody; BRS, baroreflex sensitivity; DBP, diastolic blood pressure; HR, heart rate; IBI, interbeat interval; MFI, Multidimensional Fatigue Inventory; SBP, systolic blood pressure; SS, Sjögren's syndrome

Written informed consent was obtained from all subjects. The study was approved by the medical ethical committee of the University Hospital Rotterdam-Dijkzigt.

## Methods
### Cardiovascular function tests
The ECG showed a normal sinus rhythm in all subjects. The studies were performed between 8 00 and 12 00 am. After arrival in the cardiovascular laboratory, the radial or brachial artery of the non-dominant arm was cannulated with a 22 gauge cannula (after local anaesthesia with 1% lidocaine (lignocaine) solution) for direct, continuous blood pressure measurement. In the group of healthy volunteers, blood pressure was measured by the Finapres method.[13] Heart rate was continuously measured by three precordial leads. The respiratory signal was derived from the ECG signal. After instrumentation, the patients rested on a motor driven tilt table before the registration was started. After a stabilisation period of 30 minutes, 15 minutes were recorded while the subjects were in the supine position. Then the subjects were 60° head-up tilted and the recordings were continued for another 15 minutes. The cardiovascular recordings of the second five minute periods during supine rest and head-up tilting were used for further analysis (representing the stabilised situation).

### Recordings and analysis
The ECG, blood pressure, and respiratory signals were recorded continuously on a multichannel FM-type analogue recorder (Racal Store 14DS, Sarasota, Florida, USA), for offline computer analysis. All the signals were digitised at a sample frequency of 1024 Hz by an analogue-digital converter (Advantech PC-LabCard) and stored in a personal computer. R-R intervals in the ECG were detected with an accuracy of 1 ms and transposed to HR series. Systolic and diastolic blood pressure (SBP, DBP) were defined for each R-R interval of the ECG with an accuracy of 0.1 mm Hg.

Time series of interbeat interval (IBI), SBP, and DBP were scrutinised for stationarity, artefacts, and frequency of occurrence of supraventricular extra beats. If more than 5% of a time segment needed correction the segment was discarded from analysis. Consecutive five minute periods (three five minute periods of supine rest and three five minute periods of head-up tilt) of HR, SBP, and DBP time series were subjected to a discrete Fourier transform, based on non-equidistant sampling of the R wave incidences (CARSPAN programme, Groningen, The Netherlands[14]), to yield power spectra of the rhythmic oscillations over a frequency range of 0.02–0.50 Hz, with a resolution of 0.01 Hz. For each time segment, the power was calculated for the total band (0.02–0.50 Hz), low frequency band (0.02–0.06 Hz), mid-frequency band (0.07–0.14 Hz), and high frequency band (0.15–0.50 Hz), in addition to mean HR, SBP, and DBP, and variation coefficients of HR, SBP, and DBP. Only data on mid- and high frequency band power of HR and mid-frequency band power of SBP are presented in order to reduce the number of variables.

Spectral power for each selected frequency band was expressed in relative terms—that is, as a fraction of the mean value of the considered signal (squared modulation index). If this measure is computed for the whole spectrum (0.01–0.50 Hz) it is directly comparable with the squared variation coefficient.

The spectral power data were transformed to natural logarithmic values (ln) because of skewness of the distributions. As an index of baroreflex sensitivity (BRS), we computed for each time segment the modulus in the mid-frequency band between the SBP values and the R-R interval times, based on those frequency points within the 0.07–0.14 Hz range with a coherence between the two signals of ≥0.35.[16] For each time segment, samples of the respiratory signal were obtained at each incidence of the R wave. Subsequently, these respiratory time series were subjected to

spectral analysis, in a similar way to that described above, and the dominant peak in the spectrum was assessed.[15–18]

### Measurement of tear production (Schirmer test)
Standardised paper strips (IOLAB Pharmaceuticals) were placed in the lower eyelids of the unanaesthetised eyes. The wetting of the strips in millimetres five minutes after placement was averaged for both eyes and used as a measurement of tear production. Patients were stratified according to the Schirmer test results in two groups: group 1 (n=23): Schirmer test ≤5 mm/5 min, group 2 (n=17): Schirmer test >5 mm/5 min.

### Measurement of fatigue score (Multidimensional Fatigue Inventory)
All patients completed the Multidimensional Fatigue Inventory (MFI), a self reporting scale, designed to objectivise fatigue and covering the following dimensions: general fatigue, physical fatigue, mental fatigue, reduced activity, and reduced motivation. The methods and results of using this questionnaire in patients with primary SS have been described elsewhere.[19] Patients were stratified according to the results of the fatigue inventory in two groups: group 1 (n=22), MFI score ≤65; group 2 (n=18), MFI score >65.

### Statistics
The patients with primary SS were stratified in two groups according to disease duration (group 1 (n=22), ≤5 years; group 2 (n=18), >5 years), in two groups according to fatigue and Schirmer test results as mentioned before, and in two groups according to the presence of antinuclear antibody (ANA). Spectral data were averaged to mean values for each supine and tilt period. The SPSS 9.0 statistical package was used to analyse differences between subgroups. Differences between patients and controls were evaluated by analysis of variance, always with age as covariate. Differences between subgroups of patients in the Schirmer test and disease duration were also evaluated by analysis of variance, with age as a covariate. A p value of <0.05 was considered to indicate a significant difference.

## RESULTS
### Demographic characters
Table 1 shows demographic data of the patients with primary SS.

### Orthostatic challenge in patients with SS
Orthostatic challenge in the patients with primary SS induced the following significant effects (table 2B): an increase in HR (a decrease in IBI), an increase in the mid-frequency band log power of HR, a decrease in the high frequency band log power of HR, an increase in SBP, an increase in the variation coefficient SBP, an increase in the mid-frequency band log power of SBP, an increase in DBP, an increase in the variation coefficient DBP, and a decrease in the BRS index of the mid-frequency band.

**Table 1** Demographic data of 43 patients with primary Sjögren's syndrome

|  | No | Min | Max | Mean | SD |
|---|---|---|---|---|---|
| Age (years) | 43 | 23 | 80 | 51.8 | 14.1 |
| Disease duration (years) | 40 | 1 | 30 | 7.9 | 8.1 |
| Schirmer (mm/5 minutes) | 40 | 0 | 35 | 8.7 | 10.1 |
| ESR (mm/1st h) | 41 | 11 | 110 | 37.8 | 25.1 |
| Fatigue index | 40 | 21 | 89 | 60.6 | 18.0 |

ESR, Erythrocyte sedimentation rate; Fatigue index, total score of Multidimensional Fatigue Inventory, a higher score indicates a higher level of fatigue (range 20–100).

**Table 2** Spectral data of 42 patients with primary SS and 30 healthy controls during supine rest and orthostatic challenge. All values are presented as mean (SD)

| 2A | Supine rest | | | 60 degree tilt | | |
|---|---|---|---|---|---|---|
| | Patients | Controls | p Value | Patients | Controls | p Value |
| IBI | 852 (131) | 906 (115) | NS | 747 (105) | 795 (117) | <0.05 |
| HR | 70 | 66 | NS | 80 | 76 | <0.05 |
| CVHR | 4.71 (2.4) | 5.16 (1.7) | NS | 5.15 (2.5) | 4.88 (1.5) | NS |
| MFB HR | 5.57 (1.2) | 6.35 (0.9) | <0.05 | 6.08 (1.1) | 6.38 (1.0) | NS |
| HFB HR | 6.05 (1.5) | 6.16 (0.7) | NS | 5.43 (1.3) | 5.53 (0.8) | NS |
| SBP | 134 (21.6) | 123 (15.6) | NS | 142 (21.8) | 124 (17.3) | <0.01 |
| CVSBP | 3.52 (1.3) | 4.84 (2.3) | <0.01 | 5.10 (2.0) | 5.26 (1.5) | NS |
| MFB SBP | 4.89 (0.8) | 5.19 (0.8) | NS | 6.27 (0.7) | 6.14 (0.9) | NS |
| DBP | 66 (8.9) | 69 (10.8) | NS | 75 (12.o) | 76 (10.8) | NS |
| CVDBP | 4.32 (1.5) | 4.19 (1.5) | NS | 6.37 (3.0) | 4.33 (1.0) | <0.01 |
| BRS MFB | 8.93 (5.0) | 12.69 (8.7) | NS | 4.40 (2.1) | 6.79 (2.8) | <0.01 |

| 2B | Patients | | | Controls | | |
|---|---|---|---|---|---|---|
| | Rest | Tilt | p Value | Rest | Tilt | p Value |
| IBI | 852 (131) | 747 (105) | <0.001 | 906 (115) | 795 (117) | <0.001 |
| HR | 70 | 80 | <0.001 | 66 | 76 | <0.001 |
| CVHR | 4.71 (2.4) | 5.15 (2.5) | NS | 5.16 (1.7) | 4.88 (1.5) | <0.001 |
| MFB HR | 5.57 (1.2) | 6.08 (1.1) | <0.01 | 6.35 (0.9) | 6.38 (1.0) | NS |
| HFB HR | 6.05 (1.5) | 5.43 (1.3) | <0.01 | 6.16 (0.7) | 5.53 (0.8) | <0.001 |
| SBP | 134 (21.6) | 142 (21.8) | <0.001 | 123 (15.6) | 124 (17.3) | NS |
| CVSBP | 3.52 (1.3) | 5.10 (2.0) | <0.001 | 4.84 (2.3) | 5.26 (1.5) | NS |
| MFB SBP | 4.89 (0.8) | 6.27 (0.7) | <0.001 | 5.19 (0.8) | 6.14 (0.9) | <0.001 |
| DBP | 66 (8.9) | 75 (12.0) | <0.001 | 69 (10.8) | 76 (10.8) | <0.001 |
| CVDBP | 4.32 (1.5) | 6.37 (3.0) | <0.001 | 4.19 (1.5) | 4.33 (1.0) | NS |
| BRS MFB | 8.93 (5.0) | 4.40 (2.1) | <0.001 | 12.69 (8.7) | 6.79 (2.8) | <0.001 |

IBI, interbeat interval (ms); HR, heart rate (beats/min); CVHR, variation coefficient heart rate; MFB HR, log power mid-frequency band heart rate; HFB HR, log power high-frequency band heart rate; SBP, systolic blood pressure (mm Hg); CVSBP, variation coefficient systolic blood pressure; MFB SBP, log power mid-frequency band systolic blood pressure; DBP, diastolic blood pressure (mm Hg); CVDBP, variation coefficient diastolic blood pressure; BRS MFB, baroreflex sensitivity index (mid-frequency band); NS, non-significant.

## Orthostatic challenge in healthy controls

Orthostatic challenge in the controls induced the following significant effects (table 2B): an increase in heart rate (a decrease in IBI), a decrease in variation coefficient HR, a decrease in the high frequency band log power of HR, an increase in the mid-frequency band log power of SBP, an increase in DBP, and a decrease in the BRS index of the mid-frequency band.

## Patients with SS versus controls
### Supine rest
After controlling for differences in age between both groups, HR variability of the mid-frequency band and the variation coefficient of SBP were significantly lower in primary SS than in the controls during supine rest (table 2A).

### Orthostatic challenge
After controlling for differences in age, patients with SS showed a significantly lower mean IBI, a significantly higher mean systolic blood pressure, and variation coefficient of diastolic blood pressure, and a significantly lower BRS index during orthostatic challenge than controls (table 2A).

## Patients with SS, according to Schirmer test results
After correction for age, no differences were found in HR variability, BP, and BRS during supine rest and tilt between the patients with and without ocular dryness, according to the Schirmer test results (all p>0.05).

## Patients with SS, according to disease duration
After correction for differences in age between the subgroups, no differences were found in HR variability, BP results, and BRS index in supine rest and during tilt between the two groups with a different disease duration (all p>0.05).

## Patients with SS, according to fatigue score
When stratifying the patients with SS in two groups, according to the results of the fatigue scores, no (age corrected) differences were found in HR variability, BP results, and the BRS index in supine rest and during tilt between those two groups (all p>0.05).

## Patients with SS, according to ANA serology
Twenty nine (67%) of the patients with SS had positive ANA serology. No differences were found in HR variability, BP results, and the BRS index in supine rest and during tilt between the groups with and without positive ANA serology.

## DISCUSSION
As in other spectral studies, patients and controls responded similarly to the tilt test: mean HR increased (mean IBI decreased), high frequency power decreased, mean SBP mid-frequency power increased, and the BRS index decreased.[20][21] However, in our study, which, as far as we know, is the first evaluation of the autonomic nervous system by spectral analysis in a relatively large group of patients with well defined primary SS, we found significantly higher mean HR and SBP levels and significantly lower values of the modulus between SBP and IBI, as an indicator of the BRS, during tilt in patients with primary SS as compared with healthy controls. Although these findings suggest an altered autonomic function in patients with SS, they were not accompanied by unequivocal changes in HR and BP variability parameters during supine rest or during 60° tilt between patients and controls. The results for BP have to be read carefully, because of the two different methods of measuring BP in the patient and control group.

Further analysis was carried out in the patient group alone. We stratified the primary SS group in two subgroups, according to different disease characteristics, such as disease duration, Schirmer test results, fatigue score, and ANA. When this was done, no differences were found in spectral data between the subgroups with different disease duration and the subgroups with different tear production or between the groups with different fatigue scores or positive or negative ANA serology.

As in our earlier observations,[1] no clear relationships could be shown between the cardiovascular function and tear production, as measured by the Schirmer test. This may suggest, on the one hand, that the production of tear fluid is influenced by the autonomic nervous system in a different way or, on the other hand, one may ask whether the Schirmer test is sufficiently sensitive in a study such as this.

Previously, we found abnormal parasympathetic ocular tests in patients with rheumatoid arthritis and ocular dryness as compared with those without ocular dryness.[22] Possibly, more severe lymphocytic lachrymal gland infiltration in patients with primary SS as compared with those with rheumatoid arthritis might have masked any additive effect of parasympathetic dysfunction on tear production in the present and earlier study.[1]

Although several case reports of autonomic dysfunction, varying from pupillary disturbances to orthostatic hypotension, have been published,[2–7] only a few reports of controlled studies on the cardiovascular autonomic nervous system in primary SS have appeared. These earlier studies showed minor and discrete impairment of the parasympathetic nervous system in subgroups of patients with primary SS.[1 9] A more recent study showed signs of both sympathetic and parasympathetic dysfunction in primary SS, and a possible relation between immunological mechanisms and BP in this group.[23] As in our study, no signs of clinically relevant autonomic disturbances could be shown in patients with primary SS. When we started this study no previous studies had evaluated the autonomic nervous system by spectral analysis in a patient group such as this. Now, two recent studies have evaluated the autonomic function in primary SS by HR variability tests.

One of those studies showed an increased parasympathetic control of HR in patients with primary SS, whereas the other study showed no differences in autonomic function between patients with primary SS and controls.[24 25]

In other connective tissue diseases, such as systemic sclerosis, systemic lupus erythematosus, and fibromyalgia, several reports have been published, in which HR variability testing was performed.

Reduction in HR variability during 24 hours recordings was found in patients with systemic lupus erythematosus in comparison with healthy controls.[26–28] As in our present observations in primary SS, this reduction in HR variability was not related to either disease duration or the use of corticosteroids or disease activity.

In patients with systemic sclerosis, HR variability was analysed on 24 hours electrocardiogram recordings. In 50 patients and 24 healthy controls HR variability was analysed for both frequency and time domain.

Frequency domain analysis showed reduction of low frequency and high frequency values for the patients with systemic sclerosis as compared with controls, whereas analysis in the time domain showed no significant differences in any variable between the groups.[29] Another study by Hermosillo et al in patients with CREST and diffuse scleroderma suggests that patients with CREST have a decreased parasympathetic control of HR, significantly different from those with diffuse disease.[30] Finally, two studies have been published on the autonomic nervous balance in patients with fibromyalgia. In one study, spectral analysis of R-R intervals was done in 19 women with fibromyalgia and 19 age matched controls in supine and standing postures.

The authors found a deranged sympathetic response to orthostatic stress.[31] The second study, by the same investigator showed diminished 24 hours HR variability owing to an increased nocturnal predominance of the low frequency band oscillations consistent with an exaggerated sympathetic modulation of the sinus node. The authors suggest that these findings may explain the sleep disturbances and fatigue that occur in this syndrome.[32]

In conclusion, we found no unequivocal differences for the group in sympathetic and parasympathetic cardiac processes between patients with primary SS and controls, as assessed by spectral techniques, although some cardiovascular differences were found, particularly during orthostatic challenge.

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