# Comprehensive Study of Autonomic Function in a Population with Primary Sjögren's Syndrome. No Evidence of Autonomic Involvement

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*ABSTRACT*. ***Objective.*** Autonomic neuropathy is associated with increased mortality. Autonomic nervous system disorders have been described in patients with primary Sjögren's syndrome (SS), but the results in controlled studies have been contradictory, varying from normal to sympathetic or parasympathetic dysfunction. Since the earlier studies employed varying methodologies, which may have led to the discrepancy, we conducted a comprehensive study on autonomic function in patients with primary SS and compared our findings to healthy, carefully matched population based controls.

***Methods***. A conventional cardiovascular reflex test battery (Valsalva maneuver, deep breathing test, active orthostatic test) and measurements of baroreflex sensitivity with phenylephrine and 24 hour heart rate variability were performed on 30 patients with primary SS and 30 healthy age and sex matched population based controls.

***Results***. There were no significant differences between the SS patients and the healthy controls in any of the tests.

***Conclusions.*** The prevalence of autonomic dysfunction is not increased in patients with primary SS compared to the general population. (J Rheumatol 2003;30:74–9)

*Key Indexing Terms:*
AUTONOMIC NERVOUS SYSTEM FUNCTION
HEART RATE VARIABILITY
CARDIOVASCULAR REFLEX TESTS
BAROREFLEX SENSITIVITY

Sjögren's syndrome (SS) is a chronic autoimmune exocrinopathy of unknown etiology. It is clinically characterized by dryness of the eyes and the mouth and various extraglandular manifestations, such as neurological symptoms, in about one-third of the patients. Peripheral nervous system (PNS) affliction is well documented in 10% to 35% of the patients[1,2], but central nervous system involvement is a matter of debate[3]. Autonomic nervous system (ANS) dysfunction has been described in case reports, usually in connection with PNS symptoms[2,4-7], but its prevalence is unknown. The results of the few small controlled studies performed with various methods have been contradictory, varying from normal to sympathetic or parasympathetic dysfunction[8-12].

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*Submitted March 25, 2002; revision accepted July 15, 2002.*

ANS function has become a matter of interest in SS recently. Since it is known that lymphocyte infiltration and destruction of the salivary gland have poor correlation with saliva excretion[13,14] and that ANS modulates the secretion of exocrine glands[15], it has been speculated whether autonomic impairment might have a role in the pathophysiology of SS. It has been thought that there may be malfunction at some level of the reflex arch modulating saliva excretion, possibly involving the afferent nerve, central nervous system, efferent nerve, or muscarinic (M3) receptors in the exocrine gland[16,17]. Sera of SS patients have been shown to contain antibodies against M3 receptors in murine models[18].

Clinically, the methods most often used to assess autonomic function are cardiovascular reflex tests and measurement of heart rate variability (HRV) from Holter recordings. Conventional cardiovascular reflex tests and baroreflex sensitivity (BRS) express the function of ANS in provoked situations, while 24 hour HRV represents mainly the tonic autonomic balance[19,20]. HRV analysis began to replace conventional reflex tests in research in the 1980s because of its better sensitivity[21,22] and reproducibility[23,24]. It also allows better quantitative and qualitative evaluation of the components of the sympathovagal modulation of cardiovascular function and includes no placebo effect on the results[19,21].

Because of the discrepancy in the results of previous studies, we decided to evaluate the cardiovascular ANS function in patients with primary SS compared to healthy controls by using both cardiovascular reflex tests and measurement of 24

hour HRV and to investigate whether the results are dependent on the method used.

## MATERIALS AND METHODS

Thirty consecutive female outpatients with primary SS in the Division of Rheumatology of Oulu University Hospital were invited to participate in the study in the autumn of 2000. All patients fulfilled the European classification criteria for primary SS[25,26] and had either antibodies to Ro/SSA or La/SSB or a focus score ≥ 1.0 in minor salivary gland biopsy, to ensure the accuracy of the diagnosis. All the invited patients agreed to participate.

The control group consisted of 30 age (± 2 yrs) and sex matched healthy normotensive individuals selected from among a random population sample from the register of the Social Insurance Institution, which covers all the inhabitants of the Oulu district. Originally, they were participating in a cross-sectional population study comparing metabolic abnormalities and HRV of normotensive and hypertensive subjects[27,28] or in a study on age related changes of autonomic function[29]. All patients and controls gave their informed consent. The study protocol was approved by the Ethical Committee of the University of Oulu.

*Subject characteristics*. All patients and controls were physically examined and their medical histories were checked. The mean age of the patients was 52 ± 11 years (range 28–68) and that of the controls 52 ± 11 years (range 26–68). Twenty-two patients (73%) had antibodies to Ro/SSA and 15 of them to La/SSB. Twenty-two had focus scores ≥ 1.0 in the minor salivary gland biopsies (mean 2.3 ± 1.2) taken at the time of the diagnosis. No biopsy had been taken in the 6 cases diagnosed in the 1980s or earlier. Seventeen patients (57%) had hypergammaglobulinemia (mean 21 ± 8 g/l, range 9–35) and elevated serum sedimentation rates (mean 33 ± 23 mm/h, range 1–111). Disease duration was 12 ± 7 years (range 1–31).

Twenty-four of the patients (80%) had a history of previously diagnosed extraglandular disorder probably associated with SS: atrophic gastritis (n = 6), esophagitis (n = 8), microscopic colitis (n = 3), pancreatitis (n = 1), celiac disease (n = 1), primary biliary cirrhosis (n = 1), thyroiditis (n = 8), idiopathic thrombocytopenic purpura (n = 4), leukopenia (n = 9), benign lymphadenopathy (n = 3), paraproteinemia (n = 1), myositis (n = 2), pleuritis (n = 1), and skin vasculitis (n = 2). Two patients had given birth to a child with a total congenital heart block. Previously diagnosed neurological disorders were: epilepsy (n = 1), myelopathy (n = 1), carpal tunnel syndrome (n = 7), trigeminal neuralgia (n = 1), sensory polyneuropathy (n = 1), and Morton's metatarsalgia (n = 1).

Two patients were current smokers, and 7 were taking corticosteroids (for 1 to 7 years, dose 2.5 to 10 mg daily). Two patients had coronary heart disease and 4 hypertension. Three of these patients used beta blockers and 4 angiotensin converting enzyme (ACE) inhibitors. The patients had no other disease known to affect the ANS, such as diabetes or other rheumatic disease. The controls were healthy individuals. One of them was a current smoker.

*Methods*. Cardiovascular reflex tests (Valsalva maneuver, deep breathing test, active orthostatic test, BRS test with phenylephrine) and 24 hour Holter recordings were performed on all the patients and controls in autumn 2000. Reflex tests were performed in the cardiological laboratory of Oulu University Hospital under standard conditions, as described[30,31]. Briefly, reflex tests were performed between 9:00 and 12:00 AM, the room temperature was kept stable at 20 to 22°C, a light breakfast was allowed more than 2 hours before the tests; coffee, tea, tobacco, and alcohol were not allowed in the 12 hours before measurements. During the tests, noninvasive arterial blood pressure was measured on a beat-to-beat basis by using the Finapres finger-cuff method. The R–R intervals were obtained from surface electrocardiography (ECG) and led into an analog-to-digital converter. All data acquisition and analysis were accomplished with a menu-driven software package (CAFTS, Medikro OY, Finland) and all data editing was checked manually.

*Valsalva maneuver*. The Valsalva maneuver was performed in a sitting position by blowing into a rubber tube connected to an anaeroid manometer and maintaining a pressure of 40 mm Hg for 15 seconds, as described[30-32]. The test was repeated 3 times. The result is expressed as a Valsalva ratio, which is the ratio of the longest R–R interval after the blow to the shortest R–R interval during the blow. The Valsalva ratio expresses mainly parasympathetic function[30].

*Deep breathing test*. Six cycles of maximal inspiration (I) and expiration (E) at a rate of 6 breaths per minute were performed in a sitting position[30,33]. Difference (deep breathing difference, DBD) and ratio (E/I index) between the shortest and longest R–R interval during each respiration cycle were measured and the mean values were calculated. The deep breathing test is considered to detect parasympathetic dysfunction[30].

*Active orthostatic test*. The subjects stood up quickly from a lying position without any help[30,33]. The shortest R–R interval at approximately the 15th beat after standing up and the longest R–R interval at approximately the 30th beat after standing up were determined to obtain the heart rate response to standing (the 30/15 index). The postural change in blood pressure was measured separately for systolic and diastolic pressures as the difference between the pressures in a lying and standing position. The relative overshoot tachycardia response is mediated by the vagus nerve and the blood pressure response by sympathetic nerves[30].

*BRS test with phenylephrine*. BRS can be calculated by measuring the changes in R–R intervals (in ms) against the concomitant changes in blood pressure (in mm Hg). The changes in blood pressure can be achieved with vasoactive agents, such as phenylephrine. The test was performed as described[20,32]. After a period of rest, with a stable heart rate and blood pressure, a bolus of phenylephrine was injected into a peripheral vein. The initial dose was 100 µg; the dose was increased in order to obtain at least 2 acceptable tests with an adequate (> 15 mm Hg) rise in systolic blood pressure. The analysis window included the time from the beat that started the sustained rise in systolic blood pressure to the beat following the peak. Only regression lines with a correlation coefficient > 0.8 and with a blood pressure rise ≥ 15 mm Hg were accepted for analysis. BRS is considered to reflect vagal reactivity[20]. However, sympathetic activity has also been related to BRS[34].

*24 hour heart rate variability.* A 24 hour ambulatory ECG recording was performed during the normal everyday activities. HRV analysis was as described[13,28]. The measures of R–R interval dynamics were calculated for the entire 24 hour recording. The data were edited automatically and manually, carefully eliminating any premature beats and artefacts. All subjects had at least 18 hours of ECG data, with at least 85% consisting of normal sinus beats.

*Heart rate variability measures*. The results of time domain analysis reflect the total amount of HRV[19,35]. The mean and the standard deviation of all R–R intervals were used as time domain measures. Frequency domain analysis yields quantitative information about the overall variance in heart rate resulting from periodic heart rate oscillations at various frequencies[19,36]. Three frequency bands were considered: very low (0.003–0.04 Hz), low (0.04–0.15 Hz), and high (0.15–0.4 Hz) frequency. The low frequency component is modulated by both the sympathetic and the parasympathetic nervous systems and affected by the oscillatory rhythm of the baroreceptor system[19,36]. The high frequency power is mainly parasympathetically mediated and represents primarily respiratory variation[19,36]. The physiological correlates of the very low frequency component are still unknown, but it is thought to be mediated mainly by vagal outflow[19,36].

*Reference values*. Since the results of all the heart rate based reflex tests are strongly age dependent, we used population based, age related reference values[31]. Thus, the lower normal limit for DBD ranged from 2 to 17, for 30/15 index from 0.99 to 1.39, and for the Valsalva ratio from 1.10 to 1.45, depending on the age of the subject. Postural blood pressure changes > 30 mm Hg of systolic or 10 mm Hg of diastolic pressure were considered abnormal[31]. BRS < 3.0 ms/mm Hg was regarded as abnormal[37]. Values < 70 ms for the standard deviation of consecutive R–R intervals were defined as abnormal[38].

Tear and saliva excretions of the patients were measured 1 to 2 years earlier in connection with our previous HRV study[11]. Tear excretion was measured with Schirmer I test (mm/5 min) and saliva flow with 15 min unstimulated sialometry (ml/15 min)[25,26].

*Statistical analysis*. The results are given as means ± standard deviation, with 95% confidence intervals. The values derived from power spectral analysis were statistically analyzed after natural logarithmic transformation because of the skewed distribution of the absolute values[39]. Mann-Whitney U test was used for group comparisons. The associations were analyzed by Spearman's rank correlation. P values < 0.05 were considered as significant.

## RESULTS

There were no significant differences between patients and controls in any of the cardiovascular reflex tests or measures of 24 hour HRV (Table 1, Figure 1). One patient and 2 controls had abnormal results in the deep breathing test and 1 patient and 1 control in the orthostatic test, in which their 30/15 index values were low, but blood pressure responses were normal. There were no other abnormal test results. None of the reflex test results or measures of 24 hour HRV correlated with tear or saliva excretion in the patients.

When the patients receiving corticosteroid treatment (7 patients) or those with cardiovascular disease and medication (6 patients) were excluded, separately, there were still no differences between the groups, and when analyzed by subgroups, no differences emerged compared to other patients or controls.

## DISCUSSION

The previous small controlled studies evaluating ANS function in patients with primary SS have yielded contradictory results[8-12]. We wanted to find out whether the discrepancy was due to the methodological diversity in earlier studies. We made a comprehensive evaluation of ANS function in primary SS patients and healthy population based controls using the conventional cardiovascular reflex test battery (Valsalva maneuver, deep breathing, and orthostatic test), BRS test with phenylephrine, and 24 hour HRV at the same time. We found no signs of autonomic cardiovascular dysfunction in the patients compared to controls in any test, and none of the test results correlated with the patients' tear or saliva excretion. The results are similar to the findings of our study conducted with 24 hour HRV[11]. Conventional reflex tests were used in 3 previous controlled studies with 19 to 32 primary SS patients[8,9,12]. In 2 studies, signs of parasympathetic dysfunction were found[8,9], while one study concluded that the patients had findings suggestive of both parasympathetic and sympathetic dysfunction[12]. Barendregt, *et al* conducted an uncontrolled study of 41 patients with primary SS using conventional reflex tests[40]. They found parasympathetic dysfunction in 15% of the patients, but pupillography, reflecting ocular autonomic function, was normal in all patients[40]. The autonomic dysfunction did not correlate with salivary or lacrimal gland excretion[40]. Tumiati, *et al* evaluated HRV in 16 patients with primary SS and healthy controls from 1 h recordings[10]. Defective sympathetic function was found in the patients compared to the controls[10].

Apart from methodological variations, possible explanations for the discrepancy in the results include differences in the selection of patient populations or control groups. Further, the wide interindividual variation in the autonomic function tests of healthy subjects[23,31,41] may contribute to divergent conclusions in small studies, and publication bias is prone to favor those with "positive" results.

*Methodology*. Conventional cardiovascular reflex tests were developed in the 1970s to diagnose diabetic autonomic neuropathy, and they are still widely used despite their weaknesses[21,30,42]. A battery of 3 to 5 tests should be used because the interpretation of a single test is difficult due to inadequate sensitivity and specificity[21,30,42]. Despite the rigorous standardization of the procedure, there are still many confounding factors, such as the patient's stress, collaboration, and familiarity with the test[21,30,42]. The accuracy of the tests decreases with increas-

*Table 1*. Measures of 24 hour heart rate variability and autonomic reflex tests in patients with primary SS and in controls.

| Variable | Controls | | Patients | | p |
|---|---|---|---|---|---|
| | Mean ± SD | Median | Mean ± SD | Median | |
| 24 hour HRV | | | | | |
| R-R interval, ms | 836 ± 91.6 | 810 | 844 ± 106 | 833 | NS |
| SDNN, ms | 142 ± 37.0 | 144 | 150 ± 34.5 | 150 | NS |
| Ln(HF), $ms^2$ | 5.54 ± 0.80 | 5.56 | 5.57 ± 0.85 | 5.37 | NS |
| Ln(LF), $ms^2$ | 6.40 ± 0.73 | 6.37 | 6.24 ± 0.67 | 6.11 | NS |
| LN(VLF), $ms^2$ | 7.12 ± 0.44 | 7.05 | 7.04 ± 0.43 | 7.03 | NS |
| Reflex tests | | | | | |
| Valsalva ratio | 1.69 ± 0.27 | 1.67 | 1.72 ± 0.37 | 1.65 | NS |
| E/I index | 1.25 ± 0.12 | 1.24 | 1.25 ± 0.17 | 1.20 | NS |
| DBD | 15.8 ± 6.53 | 15.0 | 15.9 ± 9.25 | 15.0 | NS |
| 30/15 index | 1.21 ± 0.14 | 1.20 | 1.20 ± 0.17 | 1.16 | NS |
| SBP change | 12.2 ± 10.9 | 12 | 13.2 ± 11.3 | 10 | NS |
| DBP change | 19.3 ± 10.5 | 18 | 18.9 ± 9.78 | 18 | NS |
| BRS | 11.0 ± 7.71 | 8.75 | 12.0 ± 7.50 | 8.90 | NS |

The probability values are from Mann-Whitney 2 sample tests between controls and patients. SD: standard deviation; HRV: heart rate variability; SDNN: standard deviation of R-R intervals; Ln: natural logarithm; HF: high frequency; LF: low frequency; VLF: very low frequency; DBD: deep breathing difference; SBP: systolic blood pressure; DBP: diastolic blood pressure; BRS: baroreflex sensitivity; NS: nonsignificant.

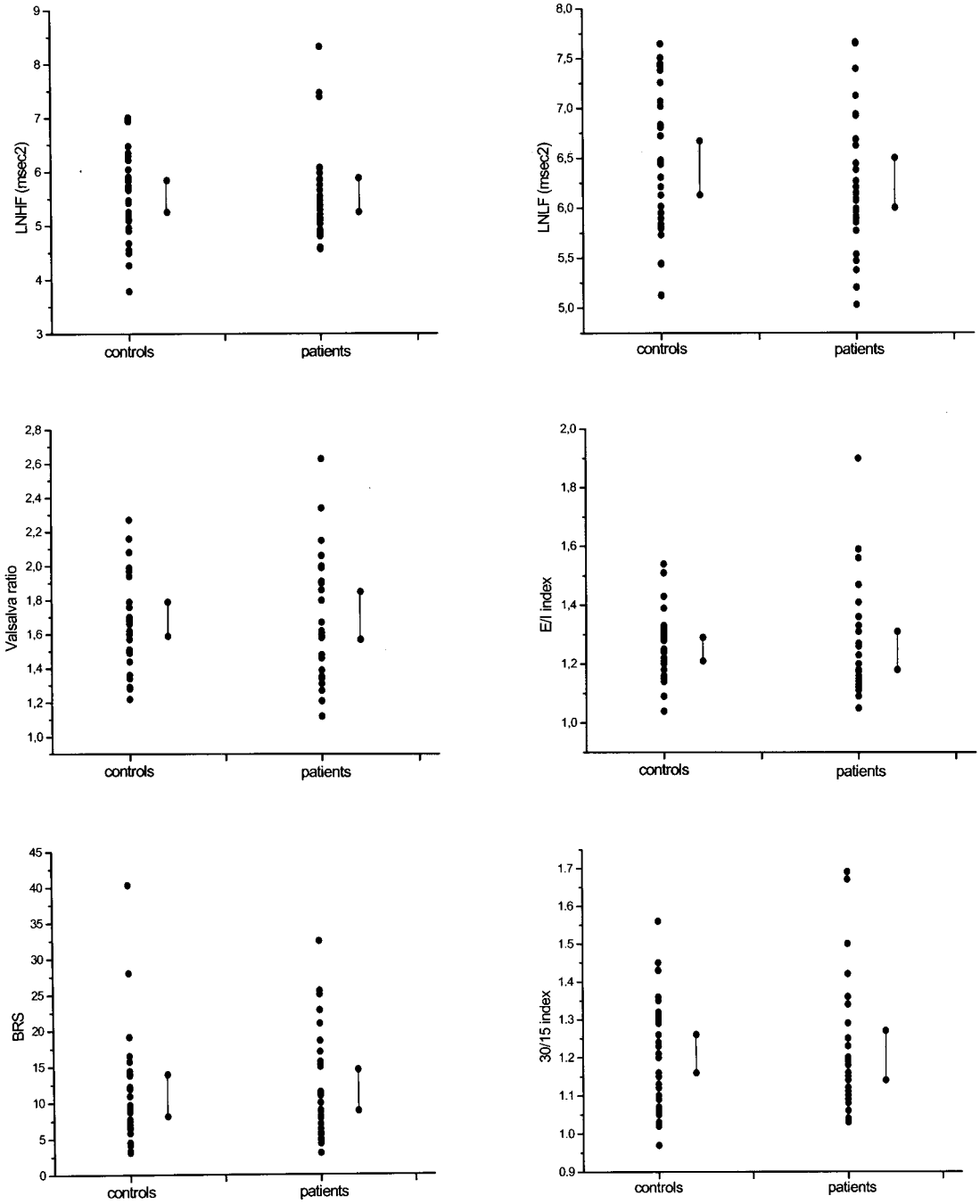


*Figure 1*. Individual values (●) and 95% confidence intervals for the means (●—●) of the frequency domain measures of 24 hour HRV, BRS, Valsalva ratio, E/I index, and 30/15 index. For abbreviations see Table 1.

ing age[43]. In spite of the age related reference values, some of the tests are not feasible in patients older than 50 years[43]. Today, the BRS test with phenylephrine is considered the gold standard among the reflex tests because of its good prognostic value in heart disease patients and more reliable standardization compared to conventional tests[41]. The invasive nature of the test, however, limits its use in larger population series.

The analysis of HRV began to replace cardiovascular reflex tests in cardiological research in the 1980s. In recent years, HRV has also been adopted in the investigation of other diseases because of its better sensitivity[21,22] and reproducibility[23,24] compared to reflex tests. Further, 24 hour HRV has appeared to be a reliable, practical, noninvasive method that is not dependent on the patient's cooperation and does not

involve any placebo effect on the results[19,21]. Conventional reflex tests as well as BRS reveal the function of the regulatory system in provoked situations, while 24 hour HRV represents mainly the tonic autonomic balance during everyday activities[19,20]. Short HRV recordings (1 h) have been shown to correlate with conventional tests[44], but the correlations have been weaker for 24 hour variables[45]. Both autonomic reflex tests and 24 hour HRV have been shown to carry prognostic information in various populations, including patients with diabetes[46], myocardial infarction[41], and the elderly[39]. Our results with no signs of autonomic dysfunction in the patients compared to the controls are in harmony with a recent study showing that patients with primary SS do not have an increased risk of mortality compared to the general population[47].

*Study subjects*. Our series represents primary SS patients of Oulu University Hospital, the referral center of a district of 400,000 inhabitants. It is difficult to compare patients with SS from separate studies because there are no generally accepted criteria for the grading of the severity of disease and various classification criteria are used. Most of our patients had extraglandular manifestations and hypergammaglobulinemia, indicating systemic activity and severity of disease. We used European classification criteria, and either a positive focus score or antibodies to Ro/SSA or La/SSB were required. Seventy-three percent of our patients were Ro/SSA positive compared to about one-third of the patients in other studies[8–10], which may indicate different subgroups of patients in the studies.

Autonomic dysfunction has been described in association with SS, mainly in connection with peripheral sensory polyneuropathy, in as many as 21% to 85% of these patients[2,4]. We had only one patient with sensory polyneuropathy in our series. Her test results were normal.

Recently, a syndrome distinct from classical SS with peripheral polyneuropathy combined with subclinical autonomic neuropathy and isolated sicca syndrome without systemic rheumatic disease has been described[48]. Only a minority of these patients have Ro/SSA or La/SSA antibodies[48].

Unlike the earlier studies, we recruited all the screened patients who fulfilled the primary SS criteria in order to keep the sample representative of all of our patients with primary SS. We had 2 patients with coronary heart disease and 4 with hypertension, both conditions that can reduce HRV[19,28]. Four used beta blockers and 3 ACE inhibitors, which may increase variability[19]. Even when patients with cardiovascular disease and medication were excluded, no significant differences between the groups were found. When the analyses were carried out in subgroups, patients with cardiovascular medication, coronary heart disease, or hypertension did not differ from the others. Since corticosteroid treatment may also influence autonomic function by improving small vessel vasculitis affecting vasa nervosum or decreasing the production of autoantibodies against neurotransmitter receptors, the patients taking corticosteroids were also analyzed in a subgroup. Their results were similar to those of other patients and controls.

Our healthy control group was derived from a random sample of the local general population carefully matched for both age and sex. Neither control subjects nor patients were familiar with the reflex tests in advance. This is important because all these factors can significantly affect the results of autonomic function tests[30,42,49].

In conclusion, as assessed by conventional cardiovascular reflex tests, BRS test, and 24 hour HRV, the autonomic function of our primary SS population did not differ significantly from that of the general population in the same area. While autonomic disorders have definitively been described in some patients with primary SS, our study suggests that significant autonomic neuropathy or dysfunction is rare in primary SS or may only affect some subgroups of patients. To detect minor variations in the function of the autonomic regulatory system, which are possibly restricted to a subgroup of SS patients, larger series of patients with properly matched general population based controls should be studied.

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