Autonomic and Orthostatic Dysfunction in Primary Sjögren's Syndrome

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ABSTRACT. ***Objective.*** Exocrine function always is and autonomic nervous function may be impaired in primary Sjögren's syndrome (pSS). Since autonomic nervous signaling is a prerequisite for exocrine secretion we wanted to assess autonomic nervous function in pSS and relate it to diagnostic measures of exocrine function.

Methods. Autonomic nervous function was determined in 46 patients with pSS using the deep breathing test [expiration/inspiration (E/I) ratio], orthostatic test [acceleration index (AI), orthostatic systolic and diastolic blood pressure response (lSBP ratio and lDBP ratio)], and finger skin blood flow test [vasoconstrictory (VAC) score]. The results were corrected for age and expressed as z-scores by comparison with 3 control groups (E/I ratio and AI, n = 56; lSBP ratio and lDBP ratio, n = 238; and VAC score, n = 80). Exocrine gland function was determined in patients with pSS using the objective functional Schirmer-I test and rose-bengal staining (van Bijsterveld score) for the lacrimal glands and unstimulated whole sialometry for the salivary glands.

Results. The E/I ratio and orthostatic systolic and diastolic blood pressures were significantly decreased and the VAC score was significantly increased in patients with pSS compared to controls, indicating both parasympathetic and sympathetic dysfunction. Autonomic and exocrine function measures were found to associate poorly.

Conclusion. Patients with pSS showed signs of both parasympathetic and sympathetic dysfunction. However, an association between cardiovascular autonomic and exocrine function in pSS was not detected. (First Release July 15 2007; J Rheumatol 2007;34:1869–74)

Key Indexing Terms:
AUTONOMIC NERVOUS DYSFUNCTION PRIMARY SJÖGREN'S SYNDROME

Primary Sjögren's syndrome (pSS) is an autoimmune disease affecting the exocrine glands, giving rise to hypofunction, especially of the lacrimal and salivary glands. Many non-exocrine organs may also be involved in the disease, including the nervous system. Signs of peripheral neuropathy have been found in about 20% of patients with pSS[1,2] and several case reports suggest autonomic nervous system (ANS) involvement in pSS as well, manifested by orthostatic hypotension[3-5], urinary retention[5], and Adie's syndrome[6]. Exocrine secretion is controlled by the ANS, where liquid secretion mainly is parasympathetically and protein secretion mainly sympathetically modulated[7]. Since the degree of exocrine gland destruction and exocrine function in pSS correlate poorly[8], other possible mechanisms behind the diminished exocrine secretion, including disturbed nervous signaling to the exocrine glands, have been proposed[8]. Using autonomic reflex tests, it has been shown that patients with pSS show signs of impaired parasympathetic and sympathetic nervous function[9-13]. Studies of autonomic function in pSS using current methods measuring heart rate variability (HRV) and baroreflex sensitivity have yielded contradictory results, with 2 studies on short-term HRV showing divergent results[13,14] and one study reporting no abnormalities in 24 h HRV and baroreflex sensitivity[15]. Different immunological mechanisms have been suggested for the observed autonomic dysfunction in pSS: anti-muscarine-3-receptor antibodies[16,17], cytokines interfering with nervous signaling[18,19], and inflammation of autonomic nerves or ganglia[20,21].

Due to use of different criteria sets for pSS in the different studies on ANS involvement in pSS, it is difficult to compare results. The American-European Consensus Criteria (AECC)[22] were applied in only 2 of the studies[13,15]. According to the AECC, some evidence of autoimmunity, i.e., anti-SSA/anti-SSB seropositivity and/or a positive lip biopsy (focus score ≥ 1) is mandatory for diagnosis of pSS. If immunological mechanisms affect ANS functioning[16-21], increased ANS involvement would be expected in patients with pSS diagnosed according to the AECC compared to older criteria sets[23,24] where signs of autoimmunity were not a prerequisite for diagnosis.

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Our aims were (1) to assess the prevalence and degree of ANS involvement in a cohort of patients with pSS according to the AECC; and (2) to relate autonomic nervous function to exocrine measures performed when diagnosing pSS.

MATERIALS AND METHODS

Forty-six patients fulfilling the AECC for pSS (median age 54 yrs, range 24–60 yrs, 43 women) were recruited from the outpatient clinic at the Department of Rheumatology, Malmö University Hospital. No patient had any other disease known to affect autonomic nervous function or was currently treated with any drugs affecting autonomic nervous function (anticholinergic drugs, beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin-2-receptor blockers) or with disease modifying antirheumatic drugs. Two patients were treated with pilocarpine 5 mg qid and one with prednisolone 5 mg daily, in whom treatment was discontinued 1 week prior to testing. Two patients could not be investigated by the tilt-table test due to feeling of panic when being strapped on the tilt table, one patient could not perform the finger skin blood flow test due to pain in the hand when exposed to cold, and one patient did not perform the unstimulated whole sialometry. Further patient characteristics are shown in Table 1.

The control group for the deep breathing test and orthostatic heart rate test consisted of 56 healthy individuals (median age 40 yrs, range 16–59 yrs, 22 women), all of whom had passed a health examination without signs of cardiovascular disease, respiratory disorders, or diabetes mellitus[25]. The orthostatic blood pressure reaction test controls consisted of 238 healthy nondiabetic individuals (median age 60 yrs, range 16–96 yrs, 106 women)[26]. Finally, the finger skin blood flow test consisted of 80 healthy subjects (median age 43 yrs, range 19–81 yrs, 37 women), all of whom were nonsmokers, had no history of vascular disease, and were not taking any medication[27].

Table 1. Characteristics of the patients with primary Sjögren's syndrome (pSS). Results are presented as median (interquartile range) or % abnormal results. Ocular measures are presented as sum of both eyes.

Characteristic	Patients with pSS, n = 46
Age, yrs	55 (38-58)
Male/female	3/43
Disease duration, yrs	11 (6–15)
Schirmer-I test, mm/5 min	5 (1–10)
Van Bijsterveld score (0–18)	10 (6–14)
Unstimulated whole sialometry, ml/15 min	0.4 (0.0–1.0)
Anti-SSA antibody seropositives, %	80
Anti-SSB antibody seropositives, %	41
ANA seropositives, %	74
RF seropositives, %	83
IgG, g/l	18.7 (15.5–22.6)
C3, g/l	1.20 (1.13–1.38)
C4, g/l	0.21 (0.20–0.29)
Lip biopsy focus score ≥ 1, %	87
Non-exocrine symptoms, %	76
Arthralgia in joints of hands	63
Raynaud's phenomenon	28
Arthritis in joints of hands	20
Peripheral neuropathy	20
Vasculitis-purpura	4
Renal disease	2
Liver disease	0
Interstitial lung disease	0
Myositis	0
Current smokers/nonsmokers	7/39

ANA: antinuclear antibodies; RF: rheumatoid factor.

The patients were investigated by 3 different autonomic nervous function tests, the deep breathing test, the orthostatic heart rate and blood pressure test, and the finger skin blood flow test.

Our study was approved by the ethics committee at Lund University (LU 576-01). All participants gave written informed consent.

Deep breathing test. After supine rest for 15 min, the subject's heart rate was monitored by electrocardiogram (ECG) for 4 min and, once constant, 6 maximal expirations and inspirations were performed during a 1-min period. An expiration/inspiration (E/I) ratio was calculated as the mean of the longest R-R intervals during the expirations divided by the mean of the shortest R-R intervals during the inspirations[28]. The E/I ratio mainly reflects parasympathetic nervous function[28,29].

Orthostatic heart rate and blood pressure test. The subject was strapped on a tilt table in the supine position for 10 min, and then, within 2 s, tilted to an erect position in which he/she remained for 8 min. The heart rate was monitored by ECG during the entire procedure beginning 1 min before tilt. Systolic and diastolic blood pressures were measured before and every minute after tilt. A mean of the R-R intervals before tilt (A) was calculated and the shortest R-R interval during the first minute after tilting (B) was determined. From the values above, an acceleration index, defined as [(A – B)/A × 100], was calculated[30,31]. The acceleration index seems to be influenced by both the parasympathetic and sympathetic nervous system[32,33]. The systolic and diastolic blood pressures before tilt (SBPrest and DBPrest) as well as the lowest systolic and diastolic blood pressures during the first 8 min after tilt (lSBP and lDBP) were determined. From these, orthostatic SBP and DBP ratios were calculated (lSBP ratio = lSBP/SBPrest and lDBP ratio = lDBP/DBPrest). In addition, the relative orthostatic SBP and DBP changes (%) in response to tilt were determined.

Finger skin blood flow test. The subject was seated in a semirecumbent position with the left hand on an aluminum holder situated at heart level, with the middle finger placed in a groove of the holder. The temperature of the aluminium holder was kept stable at 40°C by a Peltier element. The finger skin blood flow was monitored by a laser Doppler imaging (LDI) instrument, scanning an area of 2 × 2 cm of the distal phalanx of the middle finger. The finger skin blood flow was then monitored every minute for 6 min, during rest at the 40°C heating (h) procedure. The subject then immersed the contralateral hand and forearm into a water bath, kept at a stable temperature of 15°C, and kept the forearm there for 3 min. A scan of the left middle finger was made every 30 s during immersion and afterwards for a further 3 min. Hence, the finger skin blood flow of the left hand was being monitored during this contralateral cooling (c) procedure. By dividing the lowest finger skin blood flow value during the first minute of contralateral cooling (LDI_c) by the mean of the 2 last measurements of finger skin blood flow at rest, before the cooling procedure (LDI_h), a vasoconstriction (VAC) score could be calculated (VAC score = LDI_c/LDI_h). This has been shown to be a sensitive test for sympathetic nervous function in the skin[34].

Since ANS function usually deteriorates with advancing age, the autonomic nervous function variables were age-corrected and expressed as z-scores by comparison with 3 control groups. The z-scores of patients with pSS were then compared with z-scores of controls to detect differences between the groups. Since sex does not seem to significantly affect the autonomic variables measured in the tests used in our study[25,27], data were not matched for sex. All autonomic nervous function tests were performed in the morning under standard conditions, i.e., the temperature conditions were kept stable and patients were not allowed to eat, drink coffee, or smoke later than 2 h prior to testing.

Exocrine tests and questions. The function of lacrimal and salivary glands in patients with pSS was evaluated by Schirmer-I test, rose bengal staining/van Bijsterveld score, and unstimulated whole sialometry (UWS). Ocular measures were expressed as sum of both eyes. All autonomic nervous function and exocrine tests, on each patient, were performed closely in time [median 1 month apart (interquartile range 0–2)]. Moreover, patients were asked for smoking habits and for presence of Raynaud's phenomenon, i.e., an intermittent 2–3 color change [white – (blue) – red] of the fingers and/or toes. The

patients' journals were reviewed for other signs of non-exocrine symptoms (arthralgia/arthritis in the joints of the hands, symptoms of peripheral neuropathy, i.e., paresthesias in the extremities, vasculitis, renal disease, liver disease, interstitial lung disease, and myositis).

Statistics. Due to a skewed distribution of the autonomic nervous function test measures, nonparametric tests were used. For comparison between groups the Mann-Whitney U-test was used. P values < 0.05 were considered statistically significant. If not stated otherwise, values are presented as median (IQR) or percentage with abnormal results.

RESULTS

The E/I ratio was significantly decreased and the VAC score significantly increased in patients with pSS compared with controls, indicating parasympathetic and sympathetic dysfunction (Table 2). Four percent (2/46) and 9% (4/45) of patients had an E/I ratio ≤ –2 standard deviation (SD) and a VAC score ≥ 2 SD, as a sign of significant parasympathetic and sympathetic neuropathy, respectively. Although the acceleration index did not significantly differ between patients with pSS and controls, 7% (3/44) had an acceleration index ≤ –2 SD.

Further, patients with pSS had significantly reduced lSBP ratio and lDBP ratio compared with controls, representative of an attenuated blood pressure response to tilt (Table 2).

Nine percent (4/44) and 2% (1/44) of patients displayed an lSBP ratio ≤ –2 SD and lDBP ratio ≤ –2 SD, respectively, and 11% (5/44) and 7% (3/44) of patients with pSS had orthostatic systolic and diastolic hypotension, defined as orthostatic systolic blood pressure drop of ≥ 30 mm Hg and orthostatic diastolic blood pressure drop ≥ 10 mm Hg.

When correlating the autonomic nervous function indices only, the acceleration index and lDBP ratio were found to be significantly correlated (r_s = 0.54; p < 0.001). Comparing patients with normal (> –2 SD) and abnormal (≤ –2 SD) lSBP ratio, the latter had higher VAC scores than the former, although the difference was not statistically significant [1.20 (0.64 to 1.67) vs 0.48 (–0.40 to 1.35); p = NS], still implying that the lSBP ratio is also a sympathetic index.

Eighty-four percent (38/45), 74% (34/46), and 59% (27/46) had an abnormal UWS (abnormal ≤ 1.5 ml/15 min), Schirmer-I test (abnormal ≤ 10 mm/5 min), and van Bijsterveld score (abnormal ≥ 8), respectively, when tested. Comparing autonomic nervous function variables between patients with normal and abnormal UWS, a significantly lower lDBP ratio and a tendency toward a lower acceleration index were found in the latter. However, when comparing patients with a normal and abnormal Schirmer-I test, a significantly lower E/I ratio was found in the former (Table 3). Moreover, when comparing the autonomic nervous function indices in patients with and those without anti-SSA and anti-SSB antibodies as well as non-exocrine symptoms (arthralgia/arthritis in the joints of the hand, Raynaud's phenomenon, peripheral neuropathy, vasculitis, renal disease, liver disease, interstitial lung disease, and myositis), no significant differences were found. Finally, current smokers and nonsmokers were not found to differ significantly in autonomic nervous function indices.

DISCUSSION

In our study we found signs of a parasympathetic and a sympathetic dysfunction as well as an impaired orthostatic blood pressure response in patients with pSS. However, autonomic nervous function, as assessed by cardiovascular reflex tests, was poorly associated with exocrine function.

Autonomic nervous dysfunction is a feature in many different chronic diseases such as type I and II diabetes mellitus[30,35], rheumatoid arthritis[36], systemic lupus erythematosus[37], scleroderma[38], and inflammatory bowel disease[39,40]. Patients with primary Sjögren's syndrome may also show symptoms due to impaired autonomic nervous function, especially orthostatic hypotension[3-5]. Most previous studies on autonomic nervous function in pSS have shown signs of ANS disturbances[9-13], and different immunological mechanisms for these findings have been suggested[16-21]. Considering that exocrine gland destruction due to inflammation in pSS often is much less pronounced than the extremely decreased

Table 2. Results of the deep breathing, orthostatic heart rate, finger skin blood flow, and orthostatic blood pressure tests in 46 patients with primary Sjögren's syndrome (pSS) and 3 control groups (E/I ratio and acceleration index, n = 56; vasoconstrictory [VAC] score, n = 80; lSBP and lDBP ratio, orthostatic SBP and DBP change, n = 238). E/I ratio, acceleration index, VAC score, lSBP and lDBP ratio are age-corrected and expressed as z-scores (SD). Orthostatic systolic and diastolic blood pressure (SBP, DBP) changes are expressed as relative blood pressure change to tilt (%). Results are median (interquartile range).

	pSS Patients, n = 46	Controls, n = 56/80/238	p
E/I ratio (SD)	–0.50 (–1.29 to 0.32)	–0.25 (–0.62 to 0.60)	0.03
Acceleration index (SD)	–0.08 (–1.11 to 0.37)	0.03 (–0.67 to 0.65)	0.22
VAC score (SD)	0.62 (–0.36 to 1.40)	0.09 (–0.67 to 0.62)	0.02
Orthostatic SBP change (%)	–10.3 (–14.7 to –6.0)	–5.3 (–9.1 to 0.0)	0.00
lSBP ratio (SD)	–0.75 (–1.33 to –0.08)	–0.02 (–0.62 to 0.70)	0.00
Orthostatic DBP change (%)	0.0 (–5.9 to 5.3)	0.0 (0.0 to 7.1)	0.02
lDBP ratio (SD)	–0.38 (–1.04 to 0.14)	0.00 (–0.47 to 0.54)	0.00

NS: not significant.

Table 3. Age-corrected autonomic nerve function measure comparisons between patients with normal and abnormal unstimulated whole sialometry (abnormal ≤ 1.5 ml/15 min), Schirmer-I test (abnormal ≤ 10 mm/5 min), and van Bijsterveld score (abnormal ≥ 8). Ocular tests are presented as sum of both eyes. Results are median (interquartile range).

	Unstimulated Whole Sialometry, ml/15 min			Schirmer-I test, mm/5 min			Van Bijsterveld Score		
	Abnormal ≤ 1.5	Normal > 1.5	p	Abnormal ≤ 10	Normal > 10	p	Abnormal ≥ 8	Normal < 8	p
E/I ratio	–0.48 (–1.30 to 0.40)	–0.49 (–0.69 to 0.07)	0.57	–0.33 (–0.90 to 0.51)	–1.25 (–1.87 to –0.55)	0.01	–0.30 (–1.21 to 0.61)	–0.62 (–1.42 to –0.36)	0.18
AI	–0.50 (–1.34 to 0.30)	0.24 (–0.06 to 1.35)	0.07	–0.07 (–0.82 to 0.35)	–0.77 (–1.68 to 0.53)	0.38	–0.06 (–1.02 to 0.39)	–0.56 (–1.21 to 0.45)	0.76
VAC score	0.62 (–0.39 to 1.56)	0.96 (0.37 to 1.25)	0.83	0.71 (–0.24 to 1.53)	0.46 (–1.17 to 1.01)	0.21	0.58 (–0.28 to 1.11)	0.69 (–0.71 to 1.74)	0.65
lSBP ratio	–0.75 (–1.46 to –0.19)	–0.84 (–1.01 to –0.02)	0.75	–0.77 (–1.33 to –0.15)	–0.63 (–1.68 to –0.08)	0.93	–0.77 (–1.86 to –0.07)	–0.63 (–0.99 to –0.11)	0.55
lDBP ratio	–0.70 (–1.20 to –0.13)	–0.01 (–0.27 to 0.51)	0.03	–0.58 (–1.20 to 0.14)	–0.33 (–0.80 to 0.17)	0.44	–0.38 (–1.34 to 0.22)	–0.51 (–0.98 to –0.09)	0.65

exocrine function implies, another mechanism besides exocrine gland destruction has to explain the exocrine insufficiency in pSS. Lately, much interest has been directed to the anti-M3-receptor antibodies, found in a subgroup of pSS patients[16,17]. These antibodies seem to block parasympathetic nervous signaling to the exocrine glands, which is mainly transmitted via the parasympathetic M3-receptor, thereby depriving the glands of the necessary nervous signal to start liquid secretion. Since the M3-receptor is also found in other tissues, e.g., the bladder and the gastrointestinal system, these antibodies may be involved in other symptoms such as irritable bladder and constipation[41]. Since orthostatic hypotension may be found in patients with pSS, which is usually considered a sign of sympathetic dysfunction[42], the possible presence of anti-M3 antibodies cannot explain all demonstrated disturbances in ANS function. Inflammation of sympathetic ganglia in patients with pSS[21] and cytokines interfering with neural transmission[19] have for example been reported as other mechanisms behind ANS dysfunction in pSS.

Several studies have described autonomic nervous function in pSS, but due to the use of different criteria sets for pSS and sometimes concomitant use of vasoactive medication among study subjects, results become difficult to compare. The widely used AECC for pSS comprise a more homogenous immunological active population of sicca patients as compared with the older European and Copenhagen criteria[23,24].

The strength of our study was the use of the widely accepted AECC for pSS and exclusion of patients taking vasoactive medication as well as the use of large control groups for the autonomic nervous function tests, allowing for age correction of the different indices. Possible concerns with this and all other case-control studies is the choice of controls, which in this study were collected several years ago to serve as reference materials in previous studies on autonomic dysfunction. Although population based controls would be preferable, the controls were mainly recruited among laboratory staff and their friends and relatives. However, the protocol and equipment used when studying patients and controls were identical. Another concern might be the sex difference between patients and controls, with a female preponderance among the former. Since it has been shown that women have a decreased baroreflex sensitivity and HRV[43,44] in comparison to men, it may be argued that the abnormal autonomic nervous function indices in patients with pSS could be explained by sex differences. However, we found no significant sex related differences in the autonomic nervous function indices we used in this study[25,27], a finding supported by another study, which similarly found no sex related differences regarding the heart rate reaction to deep breathing or heart rate and blood pressure reactions to tilt[45]. Repeated measures of the autonomic nervous function indices and calculation of means from several measurements would probably improve reproducibility, which would facilitate assessment of associations between autonomic and exocrine measures. However, this was not done for practical purposes. Finally, the clinical implications of the detected autonomic dysfunction with regard to symptoms and prognosis needs to be further clarified.

We found that the E/I ratio was significantly decreased and the VAC score significantly increased in patients with pSS compared to controls, reminiscent of what we previously have reported[9,10]. The E/I ratio is considered a parasympathetic index, measuring a reflex inhibited by atropine but not by propranolol[29]. The VAC score, on the other hand, has been demonstrated to be a sensitive test of sympathetic function, since the reflex it measures is abolished in patients sympathectomized due to excessive hand sweating[27]. In addition, patients with pSS were not able to maintain orthostatic blood pressures as were healthy controls, which probably explains the orthostatic symptoms experienced by some pSS patients. Patients with pSS thus show signs of both parasympathetic and sympathetic dysfunction.

Autonomic and exocrine function was found to be poorly associated. While patients with an abnormal UWS test had a

significantly lower lDBP ratio and a tendency toward a lower acceleration index, patients with an abnormal Schirmer-I test showed a paradoxically increased E/I ratio, a finding for which we have no explanation. Possible reasons for this lack of association are low reliability in the test procedures for autonomic and exocrine function (although all were performed in a standardized manner) and too little exocrine variability in patients with pSS, with a high proportion having maximal exocrine dysfunction. A relation between autonomic and exocrine function could perhaps be found early in the disease before structural damage to the exocrine glands has occurred. Due to the limited number of patients with pSS in our study, a subanalysis of patients with short disease duration was not possible. Moreover, the autonomic nervous function measures we used mainly measure cardiovascular autonomic nervous function, not necessarily reflecting autonomic nervous function in the exocrine glands. In the context of the anti-M3-receptor antibodies in pSS, these findings may also reflect differences in the presence of muscarine receptor subtypes in the heart (mainly M2-receptors), involved in the cardiovagal reflexes, and in the exocrine glands (mainly anti-muscarine-3-receptors), involved in exocrine secretion. For that reason future studies on patients with pSS using tests measuring exocrine autonomic nervous function, such as the quantitative sudomotor axon reflex test[46], would be of great interest. Development of more widespread and feasible methods for the detection of M3-receptor antibodies than the biological assays used today would also enable correlations of these, with different signs of ANS involvement and clinical measures, including exocrine function.

We found that patients with pSS according to the AECC show signs of both parasympathetic and sympathetic dysfunction as well as an attenuated orthostatic blood pressure response. However, an association between cardiovascular autonomic and exocrine function in pSS was not detected.

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