

Sympathetic Dysfunction in Patients with Primary Sjögren's Syndrome

THOMAS MANDL, SIV V. BORNMYR, JAN CASTENFORS, LENNART T.H. JACOBSSON, ROLF MANTHORPE, and PER WOLLMER

ABSTRACT. Objective. To investigate autonomic nervous system function in patients with primary Sjögren's syndrome (SS) and relate the findings to clinical variables.

Methods. Autonomic nervous system function was determined in 30 patients with primary SS using the finger skin blood flow test [vasoconstrictory (VAC) index], deep-breathing test [expiration/inspiration (E/I) ratio], and the tilt table (orthostatic) test [acceleration index (AI), brake index (BI), and orthostatic blood pressure]. The results were compared with age matched control materials (finger skin blood flow test, n = 80, and deep-breathing and tilt table tests, n = 56).

Results. The VAC index was found to be significantly increased and the E/I ratio significantly decreased in patients compared to controls, indicating both a sympathetic and a parasympathetic dysfunction. Further, the patients, especially the anti-SSA and anti-SSB antibody seropositives, were found to have an abnormal blood pressure reaction to tilt compared to controls. No correlations were found between autonomic nerve function variables measured and the clinical ophthalmologic or the oral tests, performed at the time of diagnosis.

Conclusion. Patients with primary SS show signs of both sympathetic and parasympathetic dysfunction. Further, immunological mechanisms seem to influence blood pressure in patients with primary SS. (J Rheumatol 2001;28:296–301)

Key Indexing Terms:

AUTONOMIC DYSFUNCTION

PRIMARY SJÖGREN'S SYNDROME

Primary Sjögren's syndrome (pSS) is an autoimmune systemic disease affecting the exocrine glands¹ giving rise to hypofunction especially of the lacrimal and salivary glands. The disease may also involve many non-exocrine organs including the nervous system². Signs of autonomic dysfunction may, for example, be detected in patients with pSS, possibly reflecting injury to the autonomic nervous system (ANS)³. In a previous study, ANS function in patients with pSS was evaluated by deep-breathing and tilt table (orthostatic) tests⁴. A significantly reduced expiration/inspiration (E/I) ratio was found in patients compared to healthy controls⁴, reflecting an impaired parasympathetic function⁵. The involvement of the sympathetic nervous system, however, was more difficult to evaluate since no sensitive test specifically evaluating the sympathetic nervous system was available at that time.

We investigated the frequency of sympathetic nervous system involvement in pSS using the finger skin blood flow

test (vasoconstriction index), a new more sensitive test for detecting sympathetic nervous dysfunction in the skin circulation⁶, and related the findings to those of other autonomic nervous function tests, as well as to established ophthalmologic, oral, and immunological tests performed when diagnosing the disease.

MATERIALS AND METHODS

Patients and controls. Thirty patients (age 18–59 years, median age 48; 27 women) with pSS were investigated by finger skin blood flow, deep-breathing, and tilt table tests. All patients were diagnosed according to the objective Copenhagen classification criteria for pSS⁷, i.e., at least 2 of 3 objective ophthalmologic as well as at least 2 of 3 objective oral tests had to show abnormal results. The patients also fulfilled the validated European criteria for SS⁸.

Anti-SSA antibodies were detected in 9 patients and anti-SSB antibodies in 8 patients. Presence of anti-SSA and anti-SSB antibodies was not tested in 3 patients. Fourteen of the pSS patients were nonsmokers, 9 were former smokers, and 7 were current smokers. Two patients could not be investigated by the tilt table test due to a feeling of panic when they were strapped on the tilt table. Further characteristics of the patients are presented in Table 1.

The control group for the finger skin blood flow test consisted of 80 healthy subjects (age 19–81 years, median age 43, 37 women) all of whom were nonsmokers, who had no history of vascular disease and were not taking medication⁶. The deep-breathing and orthostatic test controls consisted of 56 healthy individuals (age 16–59 yrs, median age 40, 22 women), all of whom had passed a health examination without signs of cardiovascular disease, respiratory disorders, or diabetes mellitus⁹.

Since ANS function tends to deteriorate with advancing age, the different autonomic nervous function variables measured [VAC index,

From the Sjögren's Syndrome Research Centre, Department of Rheumatology and Department of Clinical Physiology, Malmö University Hospital, Malmö, Sweden.

T. Mandl, MD, Sjögren's Syndrome Research Centre; S.V. Bornmyr, PhD; J. Castenfors, MD, PhD, Department of Clinical Physiology; L.T.H. Jacobsson, MD, PhD; R. Manthorpe, MD, PhD, Sjögren's Syndrome Research Centre; P. Wollmer, MD, PhD, Department of Clinical Physiology.

Address reprint requests to Dr. T. Mandl, Solbergag. 11, S-553 33 Jönköping, Sweden.

Submitted March 27, 2000 revision accepted August 2, 2000.

Table 1. Clinical characteristics of the 30 patients (27 women) with primary SS. The characteristics are presented as median, interquartile range (IQR) and/or percentage, of patients with abnormal results, of the whole patient group.

	Median	IQR	Abnormal Results/ Seropositivity (%)
Age (yrs)	48.0	20.3	—
Disease duration (yrs)	10.0	7.3	—
Breakup time (s)*	6.0	10.3	93**
Schirmer I test (mm/5 min)*	3.5	8.3	100**
Van Bijsterveld score*	11.0	6.5	80**
Unstimulated whole sialometry (ml/15 min)	0.4	0.9	97**
Stimulated whole sialometry (ml/5 min)	2.8	5.4	60**
Salivary gland scintigraphy	—	—	50**
Lower lip biopsy focus score > 1	—	—	53**
Anti-SSA antibody seropositivity	—	—	30**
Anti-SSB antibody seropositivity	—	—	27**

*Combined value (sum of right and left eye).

**See Methods regarding cutoff values for abnormality.

acceleration index (AI), brake index (BI), and expiration/inspiration (E/I ratio)] were age corrected and expressed as z scores.

Exclusion criteria. Patients over 60 years of age were excluded since the deep-breathing and orthostatic test control material only included subjects under 60 years of age. Sex was not matched, since sex does not seem to have any significant influence on the autonomic nervous function variables measured^{6,9}. Patients with comorbidity for type I and II diabetes mellitus, rheumatoid arthritis, Crohn's disease, and ulcerative colitis were excluded since these diseases are known to affect the autonomic nervous function as well¹⁰⁻¹⁵. Patients treated with beta-blockers or calcium channel blockers were also excluded to avoid pharmacological influences on the variables measured. Further, no patient was treated with diuretics, nitrates, or angiotensin converting enzyme inhibitors.

Diagnostic tests, serological tests, and questions. The diagnostic ophthalmologic and oral tests were performed when diagnosing the disease. To fulfill the Copenhagen classification criteria for SS, at least 2 of 3 objective ophthalmologic tests, as well as at least 2 of 3 objective oral tests, had to show pathological results. The ophthalmologic tests^{16,17} and cutoff values used were the following: Schirmer I test, abnormal if ≤ 10 mm/5 min (in both eyes); breakup time (BUT), abnormal if ≤ 10 s (in both eyes); rose bengal staining, abnormal if van Bijsterveld's score ≥ 4 (in both eyes). Oral tests¹⁸ and cutoff values used were: unstimulated whole sialometry (UWS), abnormal if ≤ 1.5 ml/15 min; salivary gland scintigraphy, abnormal if diminished uptake and/or spontaneous secretion and/or abnormal secretion to citrus stimulation; lower lip biopsy, abnormal if focus score > 1. Anti-SSA and anti-SSB antibodies were analyzed by immunodiffusion. If inconclusive results were obtained, an ELISA test was used. Patients were considered seropositive if antibodies were detected with either method. Symptoms of Raynaud's phenomena (RP), i.e., intermittent 3 color change (white to blue to red) of the fingers and/or toes, and the smoking habits of the patients were requested.

Finger skin blood flow test. The subjects were in a semi-recumbent position with their left hand on an aluminum holder situated at heart level, and with the middle (third) finger placed in a groove of the holder. The temperature of the aluminum holder was kept stable at 40°C by a Peltier element. The finger skin blood flow was measured 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 monitored every minute for 6 min, during rest at the 40°C heating (h) procedure. The subject then immersed the right (contralateral) hand and forearm in a water bath, which was kept stable at a temperature of 15°C, and kept the forearm there for 3 min. A

scan of the left middle finger was made every 30 s, both 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 contralateral cooling procedure (LDI_h), a vasoconstriction (VAC) index could be calculated ($VAC \text{ index} = LDI_c/LDI_h$)⁶. This test measures the reflex vasoconstrictor response to cooling of the contralateral hand and forearm and was shown to be a sensitive test for sympathetic nervous function in the skin, as described⁶.

Deep-breathing test. After having been in a supine position 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 minute period. An E/I ratio was calculated as the mean of the longest R-R intervals during each expiration divided by the mean of the shortest R-R intervals during each inspiration⁵. According to previous studies, this test chiefly reflects parasympathetic nervous function⁵.

Orthostatic test. The subject was strapped on a tilt table in a 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 the tilting maneuver. Systolic and diastolic blood pressures were measured before as well as 1 and 8 min after tilting.

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), as well as the longest R-R interval, during the time in erect position, after B (C) were determined. From the values above, an AI, defined as $[(A - B)/A \times 100]$ and a BI, defined as $[(C - B)/A \times 100]$, were calculated^{10,11}. Some studies suggest that the AI is influenced by both the parasympathetic and sympathetic nervous system, while the BI mainly should be influenced by the latter^{19,20}.

All ANS function tests were performed in the morning under standard conditions, i.e., the temperature conditions were kept stable and the patients were not allowed to eat, drink coffee, or smoke later than 2 h prior to the testing procedure. All autonomic nervous function tests on each patient were performed within a year. However, 90% (27/30) of the patients were investigated by all tests within a week.

Statistical analysis. The ANS function variables (VAC index, E/I ratio, AI, and BI) of each patient were all age corrected by comparing each value with an age matched control material and expressing it as a z score.

Mann-Whitney U test was used for comparisons. For correlations the Spearman rank correlation test was used. P values < 0.05 were considered significant. Results are presented as median (interquartile range).

RESULTS

Patients with pSS were found to have a significantly higher VAC index compared to controls [0.59 (2.67) vs 0.09 (1.26); $p < 0.05$] (Figure 1). Twenty-three percent (7/30) of the

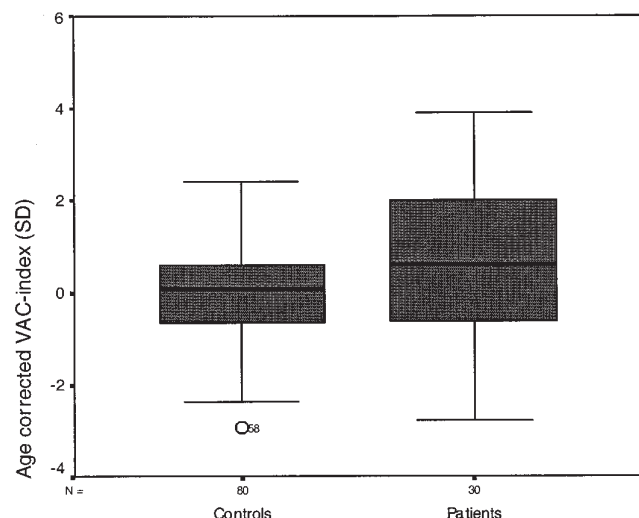


Figure 1. Distribution of the age corrected vasoconstrictory (VAC) index in controls and patients with primary Sjögren's syndrome. The VAC index was found to be significantly higher in patients versus controls ($p < 0.05$). The horizontal line in the middle of the box represents the median value and the height of the box the interquartile range. The horizontal bars above and below the box define the range.

patients were found to have an age corrected VAC index > 2 standard deviations (SD), demonstrating a reduced ability for vasoconstriction on cooling of the contralateral hand indicative of sympathetic neuropathy in the skin circulation.

Further, the expiration/inspiration ratio was found to be significantly lower in patients with pSS compared to controls [-0.75 (1.27) vs -0.25 (1.21); $p < 0.05$], indicating parasympathetic dysfunction. However, no patient was found to have age corrected E/I ratio < 2 SD.

The acceleration index and brake index did not significantly differ between patients and controls. However, 13% (4/30) of the patients were found to have an age corrected AI < 2 SD and 3% (1/30) of patients were found to have an age corrected BI < 2 SD (Table 2).

The systolic blood pressures 1 and 8 min after tilt were found to be significantly lower in patients compared to controls, while the systolic blood pressure at rest did not significantly differ (Table 2). Further, the systolic and diastolic blood pressure reaction to tilt significantly differed between patients and controls. The latter maintained or increased their blood pressures during tilt, while the former showed a smaller increase in diastolic blood pressure 8 min after tilt and a decrease in systolic blood pressure 1 and 8 min after tilt (Table 2).

Patients seropositive for anti-SSA and anti-SSB antibodies were found to have significantly lower systolic blood pressures 1 as well as 8 min after tilt compared to seronegatives (Table 3). The anti-SSA and anti-SSB antibody seropositive patients were also found to have significantly lower systolic blood pressures at rest, as well as 1 min and

Table 2. Distribution of the vasoconstrictory (VAC) index, expiration/inspiration (E/I) ratio, acceleration (AI), and brake index (BI), as well as systolic and diastolic blood pressure (bp) at rest, 1 and 8 min after tilt, in patients with primary SS ($n = 30$) and controls ($n = 80$ for VAC index and $n = 56$ for the other tests). The VAC index, E/I ratio, AI, and BI were all age corrected and are presented as z scores (SD). All values are presented as median (interquartile range (IQR)).

Test	Patients Median (IQR)	Controls Median (IQR)	p
VAC index (SD)	0.59 (2.67)	0.09 (1.26)	< 0.05
E/I ratio (SD)	-0.75 (1.27)	-0.25 (1.21)	< 0.05
AI (SD)	-0.38 (2.07)	0.03 (1.32)	NS
BI (SD)	-0.17 (1.98)	0.00 (1.01)	NS
Systolic bp at rest (mm Hg)	120 (23)	125 (20)	NS
Systolic bp 1 min (mm Hg)	115 (25)	125 (15)	< 0.05
Systolic bp 8 min (mm Hg)	115 (25)	125 (20)	< 0.01
Systolic bp change at rest → 1 min (mm Hg)	0 (9)	0 (10)	< 0.05
Systolic bp change at rest → 8 min (mm Hg)	-5 (10)	5 (10)	< 0.01
Diastolic bp at rest (mm Hg)	80 (18)	78 (15)	NS
Diastolic bp 1 min (mm Hg)	85 (19)	83 (10)	NS
Diastolic bp 8 min (mm Hg)	80 (15)	85 (15)	NS
Diastolic bp change at rest → 1 min (mm Hg)	5 (9)	5 (10)	NS
Diastolic bp change at rest → 8 min (mm Hg)	5 (5)	10 (5)	< 0.01

Table 3. Distribution of the systolic and diastolic blood pressures (bp) at rest and 1 and 8 min after tilt, as well as the systolic and diastolic blood pressure change to tilt, 1 and 8 min after tilt in patients seropositive (SSA+) and seronegative (SSA-) for anti-SSA antibodies and controls. Values were identical for anti-SSB seropositive and seronegative patients versus controls, respectively. All values are presented as median value (interquartile range).

	Patients SSA+ (n = 9)	Patients SSA- (n = 18)	Controls (n = 56)	p SSA+ vs SSA-	p SSA+ vs Controls	p SSA- vs Controls
Systolic bp at rest (mm Hg)	115 (10)	123 (23)	125 (20)	NS	< 0.05	NS
Systolic bp 1 min (mm Hg)	105 (15)	123 (30)	125 (15)	< 0.05	< 0.01	NS
Systolic bp 8 min (mm Hg)	110 (15)	120 (30)	125 (20)	< 0.05	< 0.001	NS
Systolic bp change at rest → 1 min (mm Hg)	-5 (10)	0 (11)	0 (10)	NS	NS	NS
Systolic bp change at rest → 8 min (mm Hg)	-5 (0)	-5 (20)	5 (10)	NS	< 0.05	< 0.05
Diastolic bp at rest (mm Hg)	80 (15)	83 (18)	78 (15)	NS	NS	NS
Diastolic bp 1 min (mm Hg)	85 (15)	88 (21)	83 (10)	NS	NS	NS
Diastolic bp 8 min (mm Hg)	80 (10)	90 (25)	85 (15)	NS	NS	NS
Diastolic bp change at rest → 1 min (mm Hg)	5 (5)	5 (10)	5 (10)	NS	NS	NS
Diastolic bp change at rest → 8 min (mm Hg)	0 (5)	5 (8)	10 (5)	NS	< 0.01	NS

8 min after tilt compared to controls. Furthermore, the systolic and diastolic blood pressure change to tilt significantly differed between seropositive patients and controls, where the latter increased their blood pressures during the first 8 min after tilt, while the former showed a decrease in systolic blood pressure and an inability to increase diastolic blood pressure (Table 3).

No significant differences were observed in VAC index, E/I ratio, AI, BI, diastolic blood pressure, or systolic blood pressure at rest between anti-SSA, anti-SSB antibody seropositive and seronegative patients.

No correlations were found between the VAC index and the other ANS function variables measured (E/I ratio, AI, and BI) in patients tested within one week, and no correlations were found between the ANS function variables and objective ophthalmological tests (breakup time, Schirmer I test, and rose bengal staining) or the objective oral tests (salivary gland scintigraphy, lower lip biopsy, unstimulated and stimulated whole sialometry) performed at the time of diagnosis, respectively. Furthermore the ANS function variables did not correlate with disease duration.

Only 2 patients had RP (Patient 1: VAC index 2.87, E/I ratio 0.40, AI -1.11, and BI -0.87; and Patient 2: VAC index -0.69, E/I ratio -0.42, AI -1.43, and BI -1.51) and they were not found to differ significantly in autonomic nervous function indices compared with patients without symptoms of RP. As well, comparing smoking, former smoking, and nonsmoking patients with pSS, no significant differences in autonomic nervous function (VAC index, AI, BI, and E/I ratio) were found.

DISCUSSION

In this study, pSS patients were studied for the presence of autonomic dysfunction. The patients were found to have an increased vasoconstrictory index as well as a decreased expiration/inspiration ratio compared to controls, and hence showed signs of both sympathetic and parasympathetic dysfunction. Twenty-three percent of the patients had a VAC index > 2 SD, indicating sympathetic neuropathy. Furthermore, patients, especially the anti-SSA and anti-SSB seropositives, had an abnormal blood pressure reaction to tilt compared to controls.

Autonomic nervous function may be impaired in other chronic diseases such as type I and II diabetes mellitus^{5,10-12}, rheumatoid arthritis¹³, Crohn's disease¹⁴, and ulcerative colitis¹⁵. In type I and II diabetes mellitus and rheumatoid arthritis, involvement of both the sympathetic and parasympathetic nervous system have been described^{5,10-13}. In Crohn's disease and ulcerative colitis, however, a predominantly sympathetic dysfunction was suggested in the former¹⁴ and a parasympathetic dysfunction in the latter¹⁵. Some patients with pSS syndrome may show symptoms due to impaired autonomic nervous function, for example, orthostatism³. Recently we reported an increased frequency of parasympathetic dysfunction in patients with pSS as measured by the deep-breathing test (E/I ratio)⁴. To what degree the sympathetic nervous system was involved, if at all, we were not able to deduce since the tilt table test used only shows more advanced sympathetic dysfunction.

In our study the finger skin blood flow test, a specific sympathetic nervous function test⁶, was used to assess early

subclinical impairment of sympathetic nervous function⁶. It has been shown that patients who have undergone transthoracic endoscopic sympathectomy due to hand hyperhidrosis show almost abolished responses to the cooling procedure in the test⁶. The result of this test was expressed as the VAC index, measuring the degree of reflex vasoconstriction in the skin due to a cooling procedure. An increased VAC index indicates impaired vasoconstriction, in the skin, to the contralateral cooling procedure, and hence impaired function of the sympathetic nervous system in the regulation of skin blood flow.

According to previous studies, Raynaud's phenomenon (RP), which is known to affect some patients with pSS^{21,22}, should not affect the VAC index, since it has been shown that indirect cooling usually does not trigger RP^{23,24}. In studies on patients with progressive systemic sclerosis, on the other hand, it has been reported that indirect cooling might elicit RP^{25,26}. However, this might be due to organic changes in the blood vessels²³, not seen in patients with pSS.

Although it might be expected that smoking would affect vasoreactivity, the VAC index did not differ significantly between smoking, former smoking, and nonsmoking patients. Further, the smoking patients were not allowed to smoke later than 2 hours prior to testing to avoid acute influences on the variables measured.

In a study on patients with type I diabetes mellitus, with probably more advanced ANS dysfunction, a correlation between the VAC index and the E/I ratio was found²⁷. In our group of patients with pSS, no significant correlations were found between these variables, which is in agreement with findings in patients with type II diabetes mellitus²⁷. Such lack of correlations in patients with type II diabetes²⁷ and in patients with pSS may be explained by a less pronounced, early impairment of autonomic function in these groups compared to the more advanced and general autonomic dysfunction in type I diabetes. Another possible explanation to the observed increased frequency of abnormalities in tests, reflecting both the sympathetic and parasympathetic nervous function, and the lack of correlation between the two, may be differences in etiological or modifying factors. Possible mechanisms to these autonomic impairments found in patients with pSS include a vasculitis affecting the vasa nervorum, and functional impairment due to immunological or inflammatory mechanisms, which will have to be elucidated in further studies.

During the tilt test, systolic blood pressure 1 and 8 min after tilt were found to be significantly reduced in patients compared to controls, which is in accord with our previous study⁴. On the other hand, diastolic blood pressure at rest, 1, and 8 min after tilt did not differ significantly between the patients and the controls. Furthermore, pSS patients were not able to maintain or increase the blood pressure during tilt in the same manner as healthy controls. According to a previous study, impaired diastolic blood pressure reaction to

tilt is an early sign of sympathetic dysfunction¹¹. The significantly attenuated increase in diastolic blood pressure during the first 8 min after tilt in patients compared to controls might therefore indicate a sympathetic dysfunction, which is in accord with our other findings.

The observed blood pressure differences between the patient group and the controls were chiefly confined to those patients having abnormal levels of anti-SSA and anti-SSB antibodies. This suggests that the seropositive patients represent a subgroup among the pSS patients with deranged orthostatic blood pressures, and that the mechanisms behind the observed differences in blood pressure may be immunologically mediated.

No correlations were found between the VAC index and the objective clinical ophthalmologic and oral tests at the time of diagnosis. Since the ophthalmologic and oral tests were performed before measuring ANS function, i.e., when diagnosing the disease, we cannot rule out the possibility that lacrimal as well as salivary gland function may have changed at the time of the ANS function tests. Additional studies where both the diagnostic tests and ANS function tests would be performed simultaneously should be done to elucidate any possible correlation between exocrine and ANS function.

About one-third (30%) of pSS patients have been reported to have RP^{21,22}, and it has been reported that patients with pSS experiencing RP may have a higher prevalence of peripheral neuropathy²². In addition, it seems as if the sympathetic nervous system is important in provoking RP²⁸ and low arterial blood pressure is known to be of importance for RP due to the low transmural pressure across the arterial wall²⁴. The low systolic blood pressure in pSS patients, at least in the upright position, might be one of the contributing factors to RP. However, in our study only 2 patients (7%) had RP. The attenuated sympathetic skin blood flow vasoconstriction, observed in 23% of the pSS patients, should on the contrary favor a decreased tendency for RP.

Our study indicates that patients with pSS show signs of both sympathetic and parasympathetic dysfunction. Further immunological mechanisms seem to influence the blood pressure in patients with pSS.

REFERENCES

1. Asmussen K, Andersen V, Bendixen G, Schiødt M, Oxholm P. A new model for classification of disease manifestation in primary Sjögren's syndrome: evaluation in a retrospective long-term study. *J Intern Med* 1996;239:475-82.
2. Mellgren SI, Conn DL, Stevens JC, Dyck PJ. Peripheral neuropathy in primary Sjögren's syndrome. *Neurology* 1989;39:390-4.
3. Andonopoulos AP, Ballas C. Autonomic cardiovascular neuropathy in primary Sjögren's syndrome. *Rheumatol Int* 1995;15:127-9.
4. Mandl T, Jacobsson L, Lilja B, Sundkvist G, Manthorpe R. Disturbances of autonomic nervous function in primary Sjögren's syndrome. *Scand J Rheumatol* 1997;26:401-6.
5. Sundkvist G, Almer L-O, Lilja B. Respiratory influence on heart

- rate in diabetes mellitus. *BMJ* 1979;1:924-5.
6. Bornmyr S, Svensson H, Söderström T, Sundkvist G, Wollmer P. Finger skin blood flow in response to indirect cooling in normal subjects and in patients before and after sympathectomy. *Clin Physiol* 1998;18;2:103-7.
 7. Manthorpe R, Oxholm P, Prause JU, Schiødt MT. The Copenhagen Criteria for Sjögren's syndrome. *Scand J Rheumatol* 1986;15 Suppl 61:19-21.
 8. Vitali C, Bombardieri S, Moutsopoulos HM, et al. Assessment of the European classification criteria for Sjögren's syndrome in a series of clinically defined cases: results of a prospective multicentre study. *Ann Rheum Dis* 1996;55:116-21.
 9. Bergström B, Lilja B, Rosberg K, Sundkvist G. Autonomic nerve function tests. Reference values in healthy subjects. *Clin Physiol* 1986;6:523-8.
 10. Bergström B, Lilja B, Österlin S, Sundkvist G. Autonomic neuropathy in type I diabetes: Influence of duration and other diabetic complications. *Acta Med Scand* 1987;222:147-54.
 11. Sundkvist G, Lilja B, Almer L-O. Abnormal diastolic blood pressure and heart rate reactions to tilting in diabetes mellitus. *Diabetologia* 1980;19:433-8.
 12. Bergström B, Lilja B, Österlin S, Sundkvist G. Autonomic neuropathy in non insulin dependent (type II) diabetes mellitus. Possible influence of obesity. *J Intern Med* 1990;227:57-63.
 13. Leden I, Lilja B, Sturfelt G, Sundkvist G. Autonomic nerve function in rheumatoid arthritis of varying severity. *Scand J Rheumatol* 1983;12:166-70.
 14. Lindgren S, Lilja B, Rosen I, Sundkvist G. Disturbed autonomic nerve function in patients with Crohn's disease. *Scand J Gastroenterol* 1991;4:361-6.
 15. Lindgren S, Stewenius J, Sjölund K, Lilja B, Sundkvist G. Autonomic vagal nerve dysfunction in patients with ulcerative colitis. *Scand J Gastroenterol* 1993;7:638-49.
 16. Paschides CA, Kitsios G, Karakostas KX, Psillas C, Moutsopoulos HM. Evaluation of tear break-up time, Schirmer's-I test and rose bengal staining as confirmatory tests for keratoconjunctivitis sicca. *Clin Exp Rheumatol* 1989;7:155-7.
 17. van Bijsterveld OP. Diagnosis and differential diagnosis of keratoconjunctivitis sicca associated with tear gland degeneration. *Clin Exp Rheumatol* 1990;8 Suppl 5:3-6.
 18. Manthorpe R, Axéll T. Xerostomia. *Clin Exp Rheumatol* 1990;8 Suppl 5:7-12.
 19. Bergström B, Mattiasson I, Rosen I, Lilja B, Sundkvist G. Platelet sodium and potassium ATPase activity and noradrenaline efflux rate in relation to autonomic and peripheral nerve function in insulin dependent diabetic patients. *J Intern Med* 1989;225:185-90.
 20. Bergström B, Manhem P, Bramnert M, Lilja B, Sundkvist G. Impaired responses of plasma catecholamines to exercise in diabetic patients with abnormal heart reactions to tilt. *Clin Physiol* 1989;9:259-67.
 21. Skopouli FN, Talal A, Galanopoulou V, Tsampoulas CG, Drosos AA, Moutsopoulos HM. Raynaud's phenomenon in primary Sjögren's syndrome. *J Rheumatol* 1990;17:618-20.
 22. Kraus A, Caballero-Urbe C, Jazez J, Villa AR, Alarcón-Segovia D. Raynaud's phenomenon in primary Sjögren's syndrome. Association with other extraglandular manifestations. *J Rheumatol* 1992;19:1572-4.
 23. Engelhart M, Kristensen JK. Raynaud's phenomenon: blood supply to fingers during indirect cooling, evaluated by laser Doppler flowmetry. *Clin Physiol* 1986;6:481-8.
 24. Coffman JD. Raynaud's phenomenon — An update. *Hypertension* 1991;17:593-602.
 25. Gustavsson R, Mannting F, Kazzam E, Waldenström A, Hällgren R. Cold-induced reversible myocardial ischaemia in systemic sclerosis. *Lancet* 1989;1:475-9.
 26. Lekakis J, Mavrikakis M, Emmanuel M, et al. Cold-induced coronary Raynaud's phenomenon in patients with systemic sclerosis. *Clin Exp Rheumatol* 1998;16:135-40.
 27. Bornmyr S, Castenfors J, Svensson H, Wroblewski M, Sundkvist G, Wollmer P. Detection of autonomic sympathetic dysfunction in diabetic patients — A study using laser Doppler imaging. *Diabetes Care* 1999;22:593-7.
 28. Engelhart M. The effect of sympathetic blockade and cooling in Raynaud's phenomenon. *Clin Physiol* 1990;10:131-6.