Autonomic neuropathy in systemic sclerosis

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SUMMARY Autonomic function assessed by tests of cardiovascular reflexes was studied in 25 patients with systemic sclerosis and 10 patients with primary Raynaud's phenomenon. A comparison was made with 13 normal healthy subjects. Significant abnormalities in the cardiovascular reflexes were found in systemic sclerosis, both in the CREST (calcinosis, Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly, telangiectasia) variant and also in those patients with diffuse involvement. There was sympathetic and parasympathetic dysfunction. These findings suggest that autonomic neuropathy is a feature of systemic sclerosis.

Key words: primary Raynaud's phenomenon.

Neuropathic features such as trigeminal neuralgia, peripheral neuropathy, and subacute combined degeneration of the cord as a consequence of vitamin B_{12} malabsorption are well recognised in systemic sclerosis (SS).[1-4] Degeneration and regeneration of small nerve fibres have been found in both involved and clinically uninvolved skin of patients with SS.[5] Certain features of SS, such as microcirculatory impairment, abnormal oesophageal motility, and gastrointestinal dysfunction, are compatible with autonomic dysfunction. Disorders of the sympathetic nervous system have been implicated by several authors.[6][7] Pathological changes involving the autonomic nerves have been reported, and these changes may precede clinical involvement of the skin by scleroderma.[8] After an initial study of autonomic neuropathy in patients with SS,[9] we have extended this to a much larger group of patients with SS, including those with diffuse disease. We have compared our findings in patients with SS with those in control subjects and patients with primary Raynaud's phenomenon.

Patients and methods

PATIENTS
We studied 25 patients with SS as defined by the American Rheumatism Association.[10] Five had diffuse disease (proximal scleroderma with major organ involvement) and 20 had CREST (calcinosis, Raynaud's phenomenon, oesophageal dysmotility,

sclerodactyly, and telangiectasia) or incomplete CREST variant. Patients with the CREST variant had to have at least three of the five characteristics to be included in the study. Patients were recruited prospectively. They were compared with 10 patients with primary Raynaud's phenomenon. These patients had a history of at least three years' duration of biphasic or triphasic colour changes with numbness or paraesthesiae, or both, in response to cold, with no clinical or immunological evidence of connective tissue disease. Thirteen normal subjects acted as controls. Table 1 shows the demographic details of the patient and control groups. All patients with CREST were examined for evidence of cardiac or respiratory disease. A standard 12 lead electrocardiogram was performed on the patients before testing. Patients with incomplete fist formation, clinical detected cardiac disease (hypertension, cardiac murmur, displaced apex beat, or cardiac failure) were excluded. Patients with

Table 1 *Demographic and clinical features of the patients and control groups*

	Sex (M/F)	Age (years)		Disease duration (years)
		Mean	Range	Mean
Systemic sclerosis— diffuse CREST variant (n=25)	5/20	52	28–77	10
Primary Raynaud's phenomenon (n=10)	0/10	42	17–70	20
Control subjects (n=13)	6/7	39	21–70	—

abnormal electrocardiograms or those receiving antihypertensive treatment were also excluded from the study. All patients and controls were studied in a temperature and humidity (19·5–20·5°C, 40–50%) controlled clinical measurement room after a 20 minute equilibration time.

AUTONOMIC TESTS

Five tests of cardiovascular reflexes were employed. Efferent sympathetic dysfunction was assessed by measuring the postural fall in systolic blood pressure on standing from a supine position. A fall of 30 mmHg or more is abnormal, 11–29 mmHg is borderline, and 10 or less is regarded as normal. Sympathetic function was further assessed by measuring the rise in diastolic blood pressure on sustained hand grip. A hand dynamometer was employed. Maximal voluntary contraction was first determined. The subjects maintained hand grip at 30% of maximal voluntary contraction for as long as possible up to five minutes. An increase in diastolic blood pressure of 16 mmHg or more is normal, 11–15 mmHg is borderline, and 10 mmHg or less is abnormal.

Three further tests based on heart rate variation reflected the integrity of cardiac parasympathetic nerve supply. These are performed with continuous electrocardiographic tracing. The R-R interval is measured at the 15th beat and at the 30th beat after standing from a supine position. The 30:15 ratio is calculated. An abnormal value is 1·00 or less, the normal ratio is greater than 1·04. Heart variation was also recorded during deep breathing. In normal subjects there is a difference in heart rate of 15 beats/minute or more between inspiration and expiration. A standardised Valsalva manoeuvre was performed with a modified sphygmomanometer. An electrocardiograph was recorded for 15 seconds during the manoeuvre and for one minute after. The Valsalva ratio was calculated by measuring the longest R-R interval after the manoeuvre and the shortest R-R interval during the manoeuvre. A ratio of 1·10 or less is abnormal, 1·11–1·20 is borderline, and 1·21 or more is normal. These tests are well recognised, practical, reproducible, and non-invasive tests of autonomic function.[11] [12]

STATISTICAL METHODS

Spearman correlations between autonomic test values and age were significantly negative, showing that autonomic function deteriorates with age. Fig. 1 shows the effect of age on the Valsalva manoeuvre. Significance levels for the comparisons between normal controls, patients with primary Raynaud's
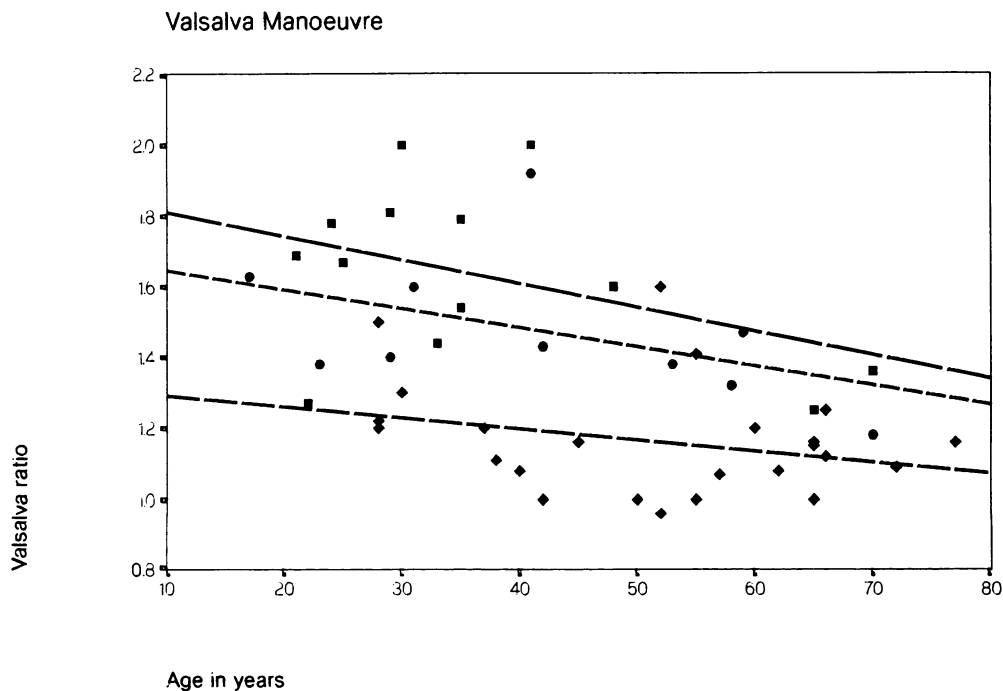

Valsalva Manoeuvre

Fig. 1 *Deterioration of autonomic function with age.* – – – –, ● *Raynaud's: RSQ=0·214;* — — —, ◆ *sclerosis: RSQ=0·084;* —— ——, ■ *normal: RSQ=0·177.*

phenomenon and those with SS were therefore obtained by performing an analysis of covariance. In this technique values for the three groups were corrected for age before comparison. This correction was necessary because the three groups of patients were not completely age matched. The change in autonomic function due to this, however, was much greater than any deterioration due to age.

Results

Table 2 shows the means and standard deviation for each autonomic function test for each group. In the subjects with SS there was borderline postural hypotension only in two patients. All the other autonomic function tests were significantly abnormal. The rise in diastolic blood pressure with sustained hand grip was abnormal in 13 patients, five were borderline, and seven were normal. Heart rate variation on standing as measured by the 30:15 ratio was abnormal in 17 patients and eight patients were within normal limits. The Valsalva ratio was abnormal in 11 patients and borderline in eight patients. Heart rate variation on deep breathing was abnormal in 21 patients. Eighty per cent of patients had at least three abnormal tests. The degree of autonomic failure did not correlate with sex or disease duration. All five patients with diffuse SS had deficient autonomic responses. Of the 20 patients with the CREST variant, two patients had only one abnormal test.

In the group with primary Raynaud's phenomenon the results were intermediate between the group with SS and the normals. Two patients had completely normal autonomic testing. Five patients had at least two abnormal tests. In particular, most of the abnormal or borderline tests were seen with hand grip and heart rate variation with breathing. As a group, however, patients with primary Raynaud's phenomenon did not show significant differences from control subjects, and the mean value of each autonomic function test fell within the normal range.

Discussion

Our results show that patients with SS have significantly abnormal autonomic function affecting mainly the parasympathetic pathways. It is recognised that sympathetic innervation may remain intact even in the presence of severe parasympathetic damage.[13][14] Patients with primary Raynaud's phenomenon show minor degrees of autonomic dysfunction. A prospective study is required with repeated autonomic testing to determine whether autonomic dysfunction correlated with duration of the Raynaud's phenomenon.

The aetiology of systemic sclerosis remains unknown. Vasomotor instability with dysfunction, Raynaud's phenomenon, abnormal oesophageal motility, and bowel involvement may all be features of autonomic neuropathy. The precise nature of the autonomic dysfunction is unclear. It is possible that there may be involvement of the vasa nervorum. Cutaneous nerves show degeneration and regeneration both in sclerodermatous and apparently normal skin.[8] Similar changes may affect autonomic nerves, and, indeed, Ormea demonstrated pathological changes in dermal autonomic ganglia, which may precede clinical sclerodermatous involvement.[8] In further work he demonstrated changes in the higher autonomic centres.[15]

These pathological lesions of nerve fibres and ganglia appear to be specific for generalised and localised scleroderma and are not found in pseudo-scleroderma lesions. As apparently normal skin in scleroderma can show abnormal neurohistology it is possible that these neuropathic lesions represent a primary pathogenetic process.[6]

The work of Jablonska and her coworkers measuring skin chronaxy suggested primary injury of the autonomic nervous system at ganglionic and

Table 2 *Results of the autonomic function tests*

Test	SS†	PRP†	Controls	SS v control	SS v PRP	PRP v controls
Sustained hand grip (mmHg); N⩾15†	13·1 (7·8)‡	17·0 (14·9)	23·2 (14·1)	p=0·05 0·1−17·2*	NS	NS
Heart rate on standing (30:15 ratio); N⩾1·04	1·02 (0·08)	1·23 (0·10)	1·23 (0·18)	p=0·005 0·1−0·3*	p=0·045 0·02−0·2*	NS
Valsalva ratio; N⩾1·21	1·16 (0·16)	1·47 (0·20)	1·63 (0·25)	p=0·001 0·3−0·5*	p=0·001 0·1−0·4*	NS
Deep breathing heart rate response (beats/min); N⩾15	7·7 (5·3)	15·3 (5·4)	18·8 (9·0)	p=0·001 4·0−12·8*	p=0·014 1·3−10·4*	NS

*Confidence intervals for the differences.
†SS=systemic sclerosis; PRP=primary Raynaud's phenomenon; N=normal.
‡Values are mean (SD).

higher control levels.[6] Fries demonstrated increased skin resistance to the passage of weak electric current in the digits of patients with SS. This was interpreted as autonomic underactivity, and it was suggested that this may be a compensatory mechanism to increase blood flow to ischaemic areas.[7]

Our results suggest that there may be early autonomic dysfunction in patients with primary Raynaud's phenomenon. This may indicate that autonomic dysfunction is an aetiological factor linked with the development of microvascular disease.

Recently, Sonnex *et al* have demonstrated autonomic neuropathy in a small group of patients with SS. Interestingly, none of their patients had evidence of a peripheral neuropathy.[16] This suggests that the autonomic dysfunction is an isolated neurological lesion, in contrast with the autonomic failure associated with other connective tissue disease, such as rheumatoid arthritis, where usually there is demonstrable peripheral neuropathy.[17] [18]

The abnormal features demonstrated by these tests could be due to primary cardiovascular involvement with fibrous deposition as part of the disease process in the patients with CREST. This appears unlikely because there was no clinical, electrocardiographic, or other evidence of cardiac disease that might have been associated with these abnormal reflex changes. This possibility, however, is prompting further work, currently in progress, directly examining autonomic neurotransmission.

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