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Cardiac autonomic dysfunction precedes the development of fibrosis in patients with systemic sclerosis

SIR, In recent years, clinicians involved in scleroderma research have proposed the identification of a subset of systemic sclerosis (SSc) to be named 'pre-scleroderma', which is characterized by Raynaud's phenomenon plus

TABLE 1. Cardiovascular reflex tests and time-domain indices

Patient	Age (yr)	Deep breathing test	Valsalva ratio	Lying-to-standing test	SDNN (ms)	SDANN (ms)	RMSSD (ms)
CL	16	1.28 (>1.22)	1.54 (>1.23)	1.22 (>1.17)	64 (93–257)	45 (79–241)	15 (21–87)
GG	36	1.38 (>1.16)	1.67 (>1.20)	1.30 (>1.11)	71 (79–219)	49 (67–206)	14 (15–63)

Age-corrected normal values are shown in parentheses [2, 3].

nailfold capillary changes, disease-specific circulating antinuclear autoantibodies (anti-topoisomerase-1, anti-centromere or nucleolar), and digital ischaemic changes [1]. Here, we report two patients with pre-scleroderma in whom cardiac autonomic dysfunction was present.

The two patients (both females, aged 36 and 16 yr) were given the diagnosis of pre-scleroderma because of Raynaud's phenomenon, digital ischaemic changes, antinucleolar antibodies in both patients, anti-DNA topoisomerase I in one and megacapillaries and microhaemorrhages of nailfold capillaroscopy in both.

Neither patient presented either skin sclerosis or skin oedema. However, in order to detect the pre-sclerotic stage, we investigated target internal organs. In particular, each patient underwent heart rate, thoracic computed axial tomography and pulmonary function tests in order to assess lung fibrosis, thallium scintigraphy in order to assess myocardial fibrosis (fixed defect) and oesophageal manometry in order to assess oesophageal fibrosis (i.e. reduced wave amplitude). No alteration was found, including those which are not likely to reflect fibrosis (i.e. reversible perfusion defects, reduced low oesophageal sphincter pressure and isolated reduced diffusing lung capacity for carbon monoxide).

The two patients underwent three classic cardiovascular reflex tests, i.e. the deep breathing test, the Valsalva manoeuvre and the lying-to-standing test [2]. During performance of these tests, heart rate was recorded in each patient by continuous standard 12-lead ECG. In addition, heart rate variability (HRV) was analysed in the time domain [3] by 24-h Holter ECG (ECGH) recording with a two-channel recorder (Cardioline LP 103; Remco-Cardioline, Vignate, Italy). The mean duration of Holter ECG was 1340 (s.d. 80) min. The following domain indices were evaluated: SDNN [standard deviation of all NN (normal-to-normal) intervals]; SDANN (standard deviation of the averages of NN intervals in all 5-min segments of the entire recording); and RMSSD (the square root of the mean of the sum of the squares of differences between adjacent NN intervals). The analysis of HRV was performed between 08.00 and 12.00 a.m.

Table 1 lists the results of the investigations of autonomic neuropathy. Both patients presented increased sympathetic activity.

Autonomic neuropathy is an established feature of SSc and other autoimmune diseases, such as systemic lupus erythematosus and inflammatory bowel disease [4, 5]. Its role in the pathophysiology of some SSc disease manifestations is well defined. In this regard, parasympathetic dysfunction is known to characterize

the early stage of gut wall involvement in SSc [6], while sympathetic derangement is thought to be responsible for the increased heart rate detected in SSc patients [7]. It is therefore quite important to understand whether autonomic neuropathy is a very early feature in SSc patients. Previously, autonomic neuropathy has been investigated in patients with full-blown SSc. Our preliminary results show that sympathetic derangement occurs before SSc is manifest.

The main limitation of our study is the low number of patients investigated and the absence of controls with primary Raynaud's phenomenon. The occurrence of sympathetic derangement in patients with primary Raynaud's phenomenon is supported by some studies [8, 9], but different results have been reported [10].

Our preliminary results await confirmation and need to be compared with HRV in patients with Raynaud's disease. Nevertheless, our study suggests that HRV should be assessed in patients with pre-scleroderma.

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