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Prostaglandin E_1 vasospastic disease and thermography

V KYLE, G PARR, R SALISBURY,* P PAGE THOMAS, AND B HAZLEMAN

From the Rheumatology Research Unit, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ

SUMMARY This is the first study to show a quantitative thermographic difference between patients with Raynaud's syndrome and normal controls after cold stress testing. An improved thermographic response to cold stress testing after treatment of Raynaud's syndrome with PGE_1 has also been shown for the first time. Discriminant analysis of the change in temperature of a finger after cold stress, and the mean thermal gradient along the finger during rewarming, clearly separated patients from controls. After treatment with PGE_1 the patients' discriminant values moved into the normal range. Symptomatic improvement after PGE_1 correlated well with thermographic improvement, and both persisted for up to 12 weeks.

Key words: Raynaud's syndrome, cold stress testing, thermal gradient, scleroderma.

Digital vasospasm (Raynaud's syndrome) is a painful disabling condition which may lead to ulceration and gangrene. Most forms of treatment have been ineffective, but recently infusions of prostacyclin and prostaglandin E_1 (PGE_1), potent vasodilators and inhibitors of platelet aggregation, have been shown to relieve symptoms.[1–3] A major difficulty in assessing treatment has been the lack of reproducible non-invasive objective tests to demonstrate the difference between patients with Raynaud's phenomenon and normal controls. Methods such as photoelectric plethysmography,[4] xenon clearance,[5] venous occlusion plethysmography,[6] digital artery pressure, and ultrasonic flow detection[7] have not distinguished controls from patients nor correlated with the severity of vasospasm.

We have shown[8] that cold stress testing with thermographic assessment differentiated controls from patients with Raynaud's phenomenon. The normal response to cold stress testing by immersing the hand in cold water is rapid rewarming of the hand, the fingertips being the hottest area of the digits. Sufferers from Raynaud's disease, in contrast, fail to rewarm, and their fingertips are the coldest area of the digits. Typical thermographs of a normal control (Fig. 1) and patient with Raynaud's disease (Fig. 2) 10 minutes after cold stress show these changes, with the thermal gradient along the digit running in opposite directions.

The aim of this study was to quantify the difference in cold stress test responses in patients

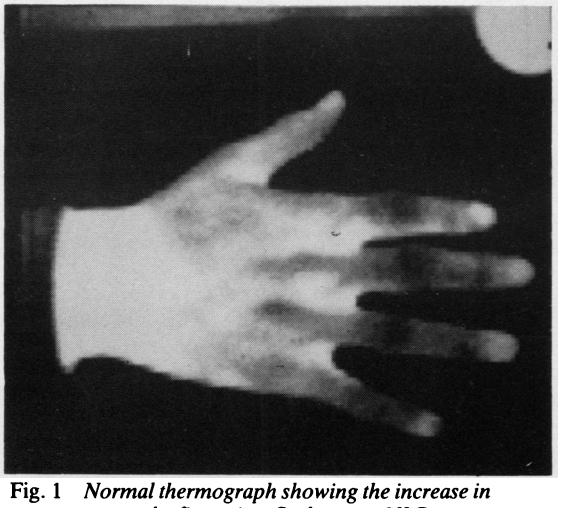

Fig. 1 *Normal thermograph showing the increase in temperature at the fingertips. Scale range 10°C; black→white=cold→hot. Blackbody radiator (top, right)=31°C.*

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*Now at: Department of Rheumatology, The Hope Hospital, Salford.
Correspondence to Dr V Kyle.

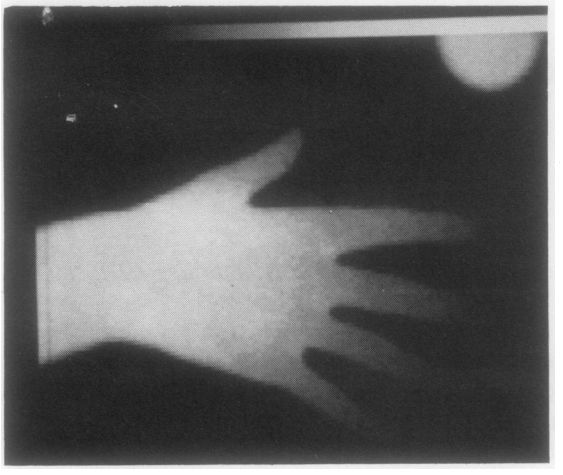

Fig. 2 *Thermograph of a patient with Raynaud's syndrome, showing the temperature decreasing towards the fingertips. Temperature scale as in Fig. 1.*

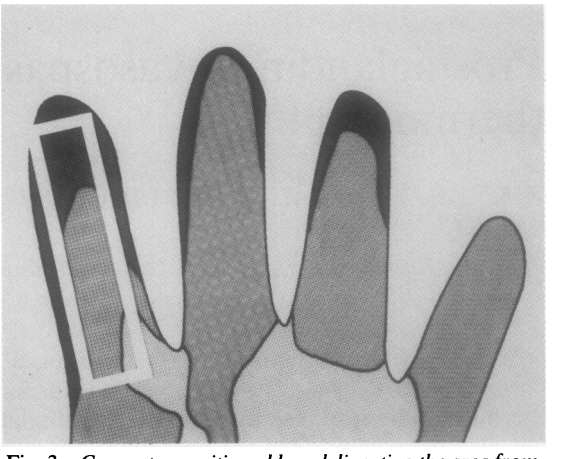

Fig. 3 *Computer-positioned box delineating the area from which mean temperature and thermal gradient were calculated.*

and normal controls, and to see whether these values changed after treatment with PGE_1 infusion. A further aim was to study the clinical response and any concomitant changes in the stress test responses.

Materials and methods

COLD STRESS TEST

Cold stress tests were carried out on 22 controls and on all patients being treated. The response was recorded thermographically with AGA 680M equipment in a room kept at 20°C±1°C. After a 15-minute equilibration period the right hand was immersed in water at 37°C for 3 minutes to allow warming, then immersed in water at 20°C for 1 minute. Thermographs were taken of both hands on entry, after equilibration, immediately after the cold stress to the right hand, and then at 5-minute intervals for 20 minutes. The thermographic data were obtained by means of an interfaced Apple II microcomputer which allowed calculation of the mean temperature within a defined area and the temperature gradient in that area. Readings were taken from an area of interest superimposed over the right index finger by means of the computer (Fig. 3). The mean temperature difference (Δt) in this area 10 minutes after the cold stress was calculated, together with the mean temperature gradient (g) down the finger during the rewarming period. This procedure was carried out on all patients on each assessment. Principal component analysis of Δt and g was used to calculate the function which separated controls and patients, and a discriminant function value thus calculated which expressed quantitatively the thermographic response to the cold stress test.

PATIENTS

Eleven PGE_1 infusions were given to 10 patients. All had severe Raynaud's syndrome (duration 2–20 years, mean 5·6) and six had had ulcerated or gangrenous lesions on their fingers for 2–6 months. These lesions had not responded to conservative treatment with rest, dressings and, where appropriate, antibiotics. One patient had two infusions, the second given six months after the first because of the development of digital ulcers. The underlying diagnoses were: systemic sclerosis 6, SLE 1, dermatomyositis 1, unknown 2. Eight were women, and the patients' ages ranged from 26 to 73 years (mean 48).

A full clinical assessment was carried out before treatment, and follow-up assessments were done at about fortnightly intervals for up to 14 weeks. On each visit the patients completed a visual analogue scale for pain in their hands, graded the frequency of Raynaud's attacks as none/less frequent/same/more frequent, and recorded the temperature of their hands as much warmer/warmer/same/colder. A cold stress test was carried out, the appearance of the fingers and any ischaemic areas were assessed by a single observer, and side effects or any changes in drug therapy were noted.

PGE_1 INFUSIONS

0·5 ml Prostaglandin E_1 (Upjohn) was mixed with 10 ml of supplied diluent, then further diluted to 30 ml with normal saline. This was infused for 72 hours with a fixed-rate low-volume infusion pump in a

central venous line inserted by the subclavian route. The initial dose was 6 ng/kg/min, and this was increased to 10 ng/kg/min over the first six hours. The dose was gradually reduced over the last 12 hours.

Results

BEFORE TREATMENT

Subjective: All patients described their hands as cold before treatment and experienced at least one Raynaud's attack per day.

Thermography

Using the computer-derived readings we plotted the temperature difference in the index finger 10 minutes after the cold stress against the mean gradient down the finger during the 20 minutes rewarming period. Fig. 4 shows these points for the 22 controls and 11 patients, with clear separation of the patients from controls. Principal component analysis of Δt and g was carried out, and the discriminant function obtained was superimposed on the graph (Fig. 4). Only one patient's result was in the control range. The discriminant values thus obtained are shown in a linear scale in Fig. 5. Control discriminant values were all positive, all but one patient had negative values, with 0 representing points on the discriminant function curve in Fig. 4.

AFTER TREATMENT

Subjective: Nine patients reported reduction or

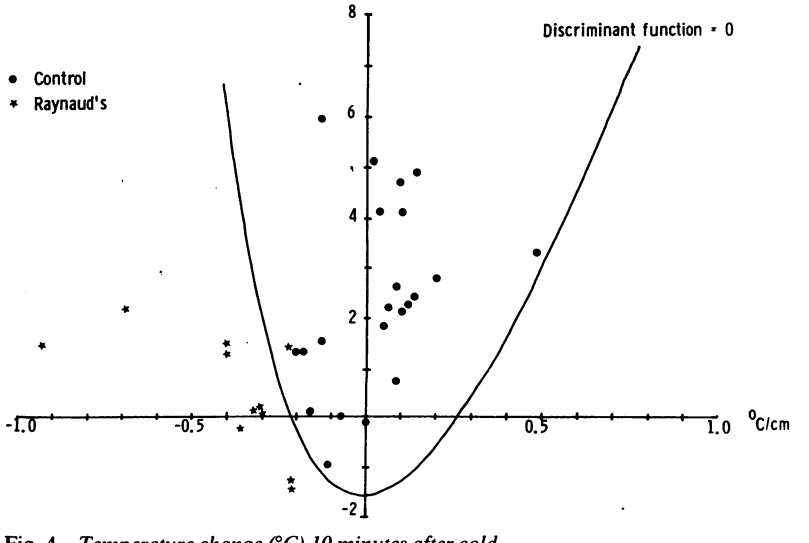

Fig. 4 *Temperature change (°C) 10 minutes after cold stress plotted against mean gradient after cold stress (°C/cm) for patients and controls. The curve of the discriminant function which=0 is superimposed.*

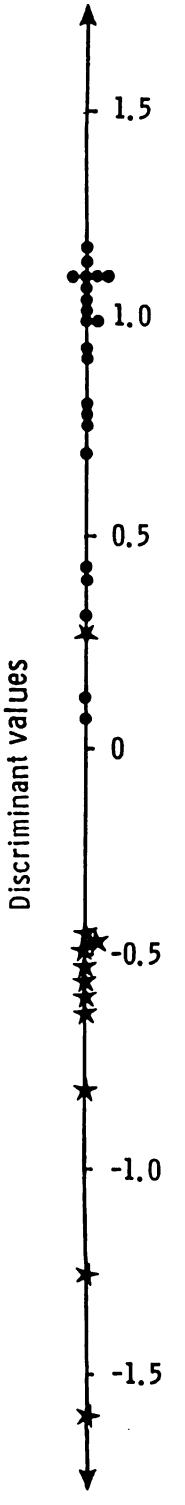

Fig. 5 *Discriminant values (calculated from variables in Fig. 4) for controls (●) and patients before treatment (★).*

abolition of Raynaud's attacks, less pain, and much warmer hands than before treatment. All the ulcers had healed completely six weeks after treatment except for one which crusted but did not heal completely (Figs. 6 and 7). One patient was lost to follow-up at four weeks, but the other eight were followed-up for 6–14 weeks. Six still reported warmer, less painful hands with fewer Raynaud's attacks eight weeks after treatment. Four were still improved at 10 weeks and two at 12 weeks. The mean pain scores are shown in Table 1.

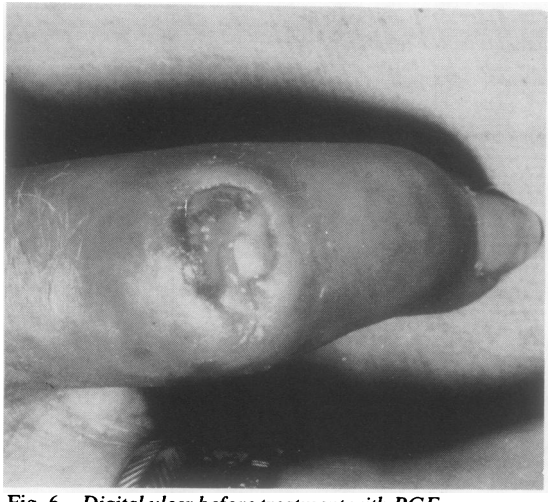

Fig. 6 *Digital ulcer before treatment with PGE_1.*

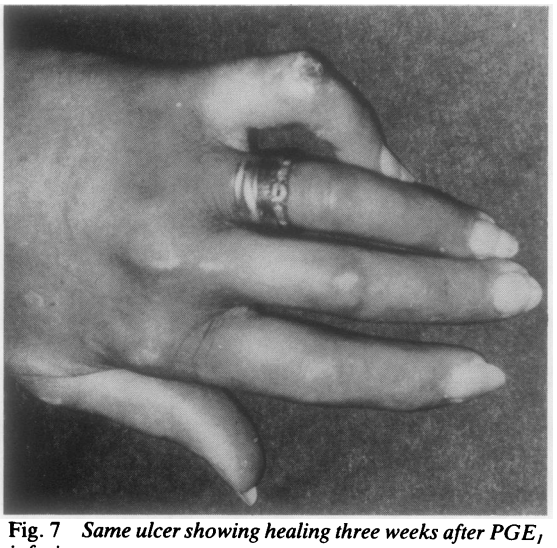

Fig. 7 *Same ulcer showing healing three weeks after PGE_1 infusion.*

Table 1 *Patients' pain scores (mean values) before and after PGE_1 recorded on visual analogue scale*

Time (weeks)	0	2	4	8	12
Pain Score (0–10)	6·7	2	1·6	3·7	6·3

Two patients reported no subjective improvement: one had an exacerbation of dermatomyositis and the other had severe systemic sclerosis.

Thermography

The discriminant function values of 10 of the 11 patients moved close to or within the normal range reflecting a more normal thermal response to cold stress testing. Six remained normal for eight weeks, and four were still in the normal range at 12 weeks. Fig. 8 shows discriminant function values for all patients before treatment and at the point of maximal improvement (0=separating value between controls and patients, as shown in Fig. 3). Fig. 9 shows the mean change in all patients' discriminant values against time; an increase in discriminant value represents movement towards the control range.

The patient with a flare-up of dermatomyositis also improved thermographically but not symptomatically. The patient with severe systemic sclerosis who had no symptomatic improvement showed no thermographic improvement.

Infusions were well tolerated; three patients complained of headache, two of nausea, and one of diarrhoea. Symptoms were relieved in all cases by a temporary reduction in the infusion rate. Several patients had a low grade fever, and pain around the site of insertion of the venous catheter was also reported by a few patients. One patient sustained a pneumothorax during the insertion of the central venous line, but there were no other serious adverse effects either at the time of infusion or on follow-up.

Discussion

A quantitative thermographic difference between controls and patients with Raynaud's phenomenon after cold stress testing has not been shown before. This is also the first time an improved thermographic response to cold stress testing after treatment with PGE_1 has been shown. Discriminant analysis of the change in temperature of a finger after cold stress, and the mean thermal gradient along the finger during rewarming, clearly separated normal controls from patients with Raynaud's disease. After treatment with PGE_1 infusion the patients' discriminant values moved into the normal

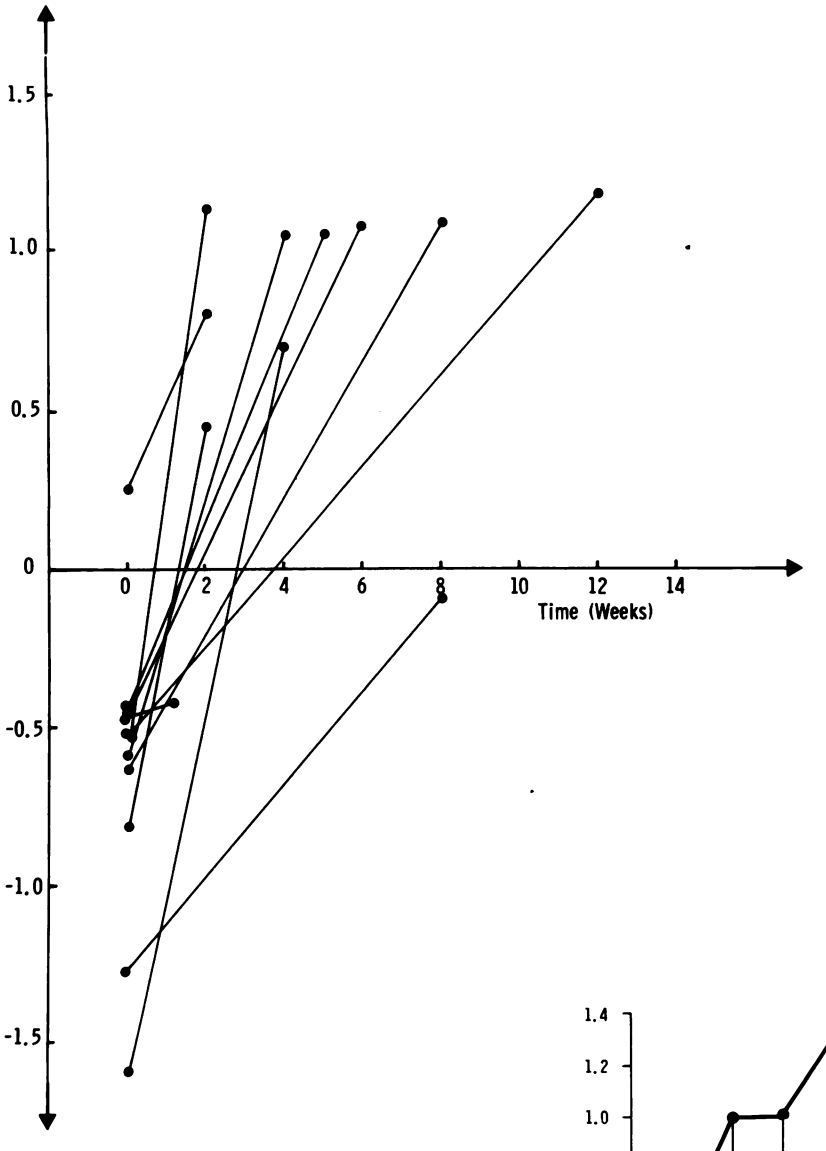

Fig. 8 *Discriminant values for all patients before treatment and at the time of maximal improvement.*

range. Although Martin *et al.*[1] showed thermographically a rise in absolute hand temperature during and two weeks after PGE_1 infusion, they were unable to demonstrate an improved thermographic response to the cold stress testing. However, our methodology differs considerably from theirs. Firstly, we rewarm patients' hands at 37°C for three minutes before the cold stress, as most Raynaud's sufferers cool during the initial 15-minute equilibration period, in contrast to controls, who usually show reactive hyperaemia during this phase. If this is not done, the patients' finger temperature may be below that of the cold stress (20°C), making inter-

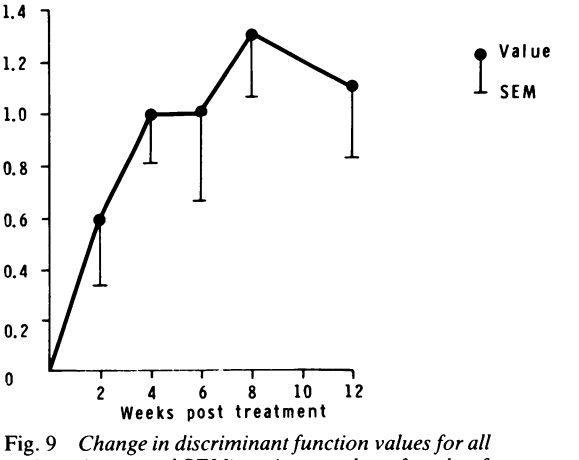

Fig. 9 *Change in discriminant function values for all patients (mean and SEM) against number of weeks after treatment.*

pretation difficult. Secondly, we measure both the change in temperature and also the pattern of heat distribution along the fingers–the thermal gradient. As this pattern of rewarming after cold stress is the main difference between controls and patients, it is important to quantify this rather than simply the mean hand temperature.

Symptomatic improvement correlated well with the quantitative thermographic improvement, and both persisted for up to 12 weeks. The only 'false positive' result occurred when a patient with a flare-up in dermatomyositis did not feel symptomatic improvement despite an improved response to cold stress testing, presumably because any subjective change was masked by her other symptoms. It is unclear why PGE_1 appears to produce improvement for up to 12 weeks when it is rapidly inactivated in the lungs.[9]

Thermographic assessment of cold stress test responses allows visualisation of heat patterns and accurate temperature measurement by non-invasive means under standardised conditions, removing many of the limitations of previously used methods. As quantitative differences between controls and patients with Raynaud's disease can be shown, it appears to be a useful and reliable method of assessing patients and of evaluating therapy. The improved thermographic data obtained after PGE_1 infusions add support to previous reports of the value of PGE_1 in vasospastic diseases. However, as treatment involves inpatient care with the insertion of a central venous line, therapy should be reserved for severe cases.

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