values well in excess of those expected,[13 14] leading to the suggestion that either circulating erythropoietin is inactive or an inhibitor is present. The effects of differing types of renal disease and of haemodialysis are unknown, and our patients represented an unusual opportunity to examine the interrelations of haemoglobin concentration, erythropoietin concentration, and renal function without these complicating factors. All test sera stimulated the erythropoietic activity of the culture system, but the extent of stimulation might possibly have been limited by the presence of uraemic toxins. This is unlikely, however, because few patients were more than mildly uraemic. All except three had serum urea concentrations below 16·0 mmol/l (96 mg/100 ml) and serum creatinine concentrations below 220 μmol/l (2·5 mg/100 ml), values that are not usually associated with uraemic complications in people without sickle-cell disease. Thus glomerular function as measured by creatinine clearance appears to be closely related to capacity to produce erythropoietin.

Progressive renal failure is common in older patients with sickle-cell disease[1] and is one of the commonest causes of death in those aged over 30.[15] The mechanism is poorly understood but is reflected histologically in progressive glomerular damage and cortical scarring, and functionally in reduced production of erythropoietin and falling haemoglobin concentration. The common clinical presentation is of worsening anaemia together with heart failure that further compromises renal function. Survival may be prolonged by chronic transfusion, but since the fall in haemoglobin concentration appears to be determined predominantly by low erythropoietin concentrations it might be amenable to treatment with bone-marrow stimulants such as steroids or prostaglandins.

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Effects of prostaglandin E_1 on microvascular haemodynamics in progressive systemic sclerosis

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Abstract

The effects of prostaglandin E_1 infusion on nailfold capillary haemodynamics were studied in eight patients with Raynaud's phenomenon secondary to progressive systemic sclerosis. Using a modified Landis microinjection technique the mean (±SEM) transcapillary pressure gradient was increased during and six weeks after infusion by 13·9±3·2 cm H_2O ($p<0·05$) and 5·5±2·5 cm H_2O ($p<0·05$) respectively. Capillary red cell velocity measured in two patients by video television microscopy also increased during and after infusion with prostaglandin E_1. Six patients claimed subjective benefit and in three their ulcers healed. These findings support the observed beneficial effect of prostaglandin E_1 and suggest that it improves the nutritive capillary circulation by lowering precapillary resistance.

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Introduction

The vascular abnormalities found in progressive systemic sclerosis constitute a prominent feature of the disease and mainly affect the microvascular circulation.[1] This association has led some workers to conclude that a microangiopathy might represent the underlying cause of the disease.[2] Raynaud's phenomenon is a common and often early feature of the condition and the characteristic attacks of digital exsanguination may result in painful ischaemic ulceration, occasionally leading to gangrene that requires amputation.

Objective assessment of treatment efficacy for Raynaud's phenomenon associated with progressive systemic sclerosis has proved difficult, partly owing to the specialised nature of the circulation in the hand. Conventional assessment using radiometry, thermography, or plethysmography cannot distinguish

between shunted flow, which serves an important thermoregulatory function in the hand, and nutritional capillary flow.[3]

Several studies have suggested that prostaglandin E_1, a potent vasodilator, may benefit patients with Raynaud's phenomenon.[4-6] The aim of the present study was to determine by direct microvascular techniques whether prostaglandin E_1 improved the nutritive capillary circulation to the hand.

Patients and methods

Eight patients (seven women and one man) with a definite clinical diagnosis of progressive systemic sclerosis were studied. Their mean age was 40·4 years (range 30-74 years) and the mean duration of disease nine years (range 3-22 years). In three patients painful ischaemic digital ulceration was present, and all patients had frequent and disabling attacks of Raynaud's phenomenon. The patients were admitted to hospital for an infusion of prostaglandin E_1 given over 72 hours. Informed consent was obtained before each infusion, which was given through a central venous catheter. One ml (500 μg) of a cooled (4°C) solution of prostaglandin E_1 (Upjohn Ltd) was added to 9 ml of sterile bacteriostatic water with benzyl alcohol 0·9 w/v for injection and infused in 0·15 mol/l saline at a dose of up to 10 ng/kg/min.

Patients were studied after 30 minutes equilibration in a constant room temperature maintained at 24 ± 0·5°C. Measurements were made before, during, and at one and six weeks after infusion. Finger nailfold capillaries were studied using a stereoscopic microscope at magnifications of × 100-160. Capillary pressure was measured using the Landis microinjection technique,[7] as modified and described by Tooke,[8] in which the arterial and venous limbs of individual capillary loops are cannulated with a micropipette. The transmitted pressure was measured with a water manometer. Capillary pressure gradient was calculated as the mean arterial limb pressure minus the mean venous limb pressure.

In two patients capillary red blood cell velocity was recorded in the same capillaries at each visit using video television microscopy[9] with frame-to-frame analysis of the video record. Capillaries were visualised through intact skin through a drop of glycerol. Lighting was provided by a 100 w mercury vapour lamp with green and heat-absorbing filters. An image of the capillary was obtained using a Silicon Diode video camera mounted on a Leitz Laborlux microscope. The image was relayed by a vertical enhancement unit (Hitachi VE-102) to a Sony Eumatic video recorder. A digital timer in series with a television monitor recorded real time in 1/100th seconds. Red cell velocity was assessed by measuring the distance moved by plasma gaps over a defined length of the capillary. Mean velocity was determined from 20 component estimations over a five-minute period.

Finger temperatures were recorded using adherent thermocouples and an infra-red radiometer (KT41, Heinmann, West Germany). Total finger blood flow was measured using a sensitive electrocardiogram-triggered mercury strain-gauge plethysmograph (Periflow, Janssen Scientific Instruments). Mean values were obtained and analysed using Student's paired *t* test.

Results

Prostaglandin E_1 infusions were well tolerated. Finger swelling occurred in seven patients during the infusion and persisted in five for several days after the immediate infusion period. At six weeks four of the patients reported good clinical improvement with a lessening in the frequency of Raynaud's attacks and a reduction in pain during the recovery phase. In two patients the response was moderate with some improvement in the symptoms of pain, but in two no benefit was recorded.

Previously described microvascular changes in progressive systemic sclerosis were confirmed.[10] Every subject showed large capillary forms (greater than 20 μm diameter), and tortuous bizarre shapes were often seen. Reduced capillary numbers and subcuticular haemorrhages were present in 50%.

The mean arterial limb capillary pressure rose significantly ($p < 0·05$) during the infusion and fell gradually towards the preinfusion value at six weeks. The mean venous limb pressure remained unchanged during the infusion and then rose slightly, but not significantly, in the immediate postinfusion period (fig 1). At six weeks the mean venous pressure fell, but not significantly ($p = 0·2$), below the preinfusion value (fig 1). The transcapillary pressure gradient increased, the difference in pressures being significant at the 5% level, not only during the infusion but also at six weeks after infusion (fig 1). The four patients with the largest increases in transcapillary pressure gradient corresponded to the four patients who reported most clinical benefit.

Mean skin temperature rose in all subjects during infusion and fell slowly over the six-week study period (table I). Significant changes in total finger rest blood flow measured by plethysmography (table I) also occurred during the infusion.

Capillary red cell velocity, which was very low before treatment, showed a pronounced rise during infusion and at six weeks (table II).

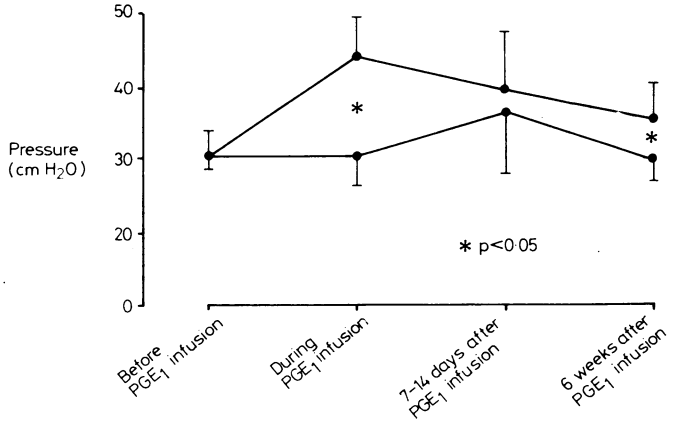

FIG 1—Transcapillary pressure gradient before, during, and after prostaglandin E_1 (PGE_1) infusion. (Mean arterial capillary pressure values above, mean venous capillary pressure values below.)

TABLE I—*Mean results: total rest blood flow and skin temperature* (± *SEM*). (*n* = 8)

	Preinfusion	During infusion	7 Days after infusion	6 Weeks after infusion
Mean rest flow (ml/100 ml tissue/min)	4·0 ± 2·4	9·0* ± 2·3	5·0 ± 1·3	8·6 ± 3·7
Mean nailfold skin temp (°C)	29·3 ± 0·7	30·0 ± 0·5	29·3 ± 0·9	29·2 ± 0·8
Mean finger radiometry (°C)	26·9 ± 1·1	29·2 ± 0·6	28·2 ± 1·6	27·6 ± 1·1

* $p < 0·05$.

TABLE II—*Red blood cell velocity* (μm/sec)

Case No	Preinfusion	During infusion	7 Days after infusion	6 Weeks after infusion
1	70	300	100	200
2	50	1000	160	600

Discussion

Norton and Nardo[1] have suggested a vascular hypothesis in the pathogenesis of systemic sclerosis. Abnormalities of the small blood vessels are common, but large artery changes are rare.[11]

The nailfold capillary abnormalities seen microscopically are striking in progressive systemic sclerosis (fig 2), although similar changes have been described in dermatomyositis and to a lesser extent in systemic lupus erythematosus.[12] These capillary changes were present in all of our unselected group of patients with progressive systemic sclerosis, highlighting the potential value of this technique in diagnosis.

The hand is richly supplied with arteriovenous anastomoses under neurogenic control, which subserve body temperature regulation.[13] Conventional methods for measuring blood flow in the extremities do not distinguish between this shunted flow and nutritional capillary flow.[3] Radioisotope clearance studies have

been used to estimate the nutritional fraction of the total blood flow,[14] but the interpretation of these measurements is questionable.[15] In contradistinction we have made direct measurements of pressure and red cell velocity at the capillary level, providing an unambiguous assessment of tissue nutrition.

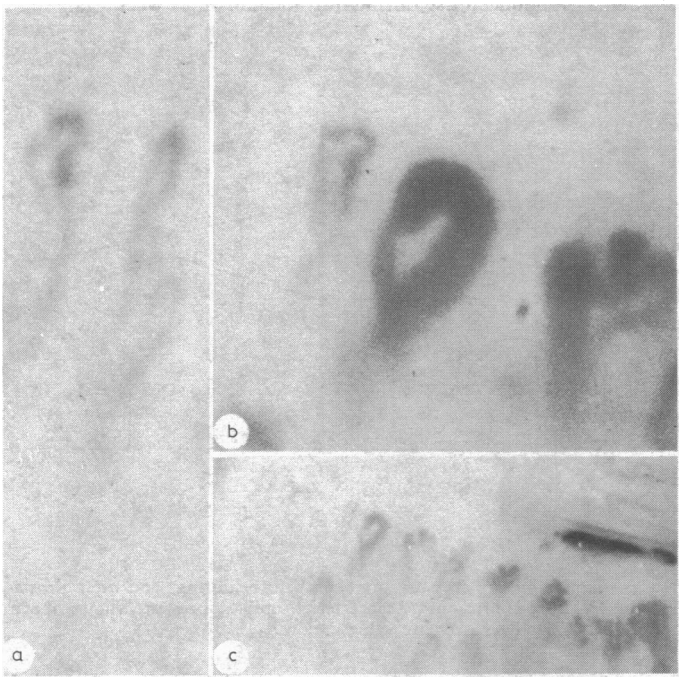

FIG 2—(a) Normal nailfold capillaries (×160); (b) nailfold capillaries in progressive systemic sclerosis showing an enlarged capillary associated with a tortuous bizarre form and a normal sized capillary (×160); (c) abnormal nailfold terminal row capillaries and subcuticular haemorrhage in progressive systemic sclerosis (×40).

Various treatments have been prescribed for patients with Raynaud's phenomenon. Vasodilators have been shown to increase total blood flow,[16] but these agents may shunt blood away from the important nutritional circulation. Short-term benefits have been claimed after treatment with reserpine,[17] fibrinolytic agents,[18] and plasma exchange,[19] but few treatments have produced a long-term improvement.

Prostaglandin E_1 is a naturally occurring potent vasodilator, and several previous studies have reported symptomatic improvements in Raynaud's phenomenon.[4-6] Objective measurements have shown a pronounced relative increase in hand and finger blood flow, not only during the immediate infusion period but for several weeks after. In this study we have shown that prostaglandin E_1 improves the nutritional circulation in patients with progressive systemic sclerosis during and beyond the immediate infusion period. The increased arterial limb capillary pressures presumably reflect precapillary vasodilatation. This increased pressure, acting on abnormal capillaries, would explain the finger oedema that was observed in almost every subject given treatment with prostaglandin E_1.

The mechanism for the long-term effects observed remains obscure. Kyle *et al*,[20] using thermography, have shown that the recovery time after an attack of Raynaud's phenomenon is shortened by treatment with prostaglandin E_1. Infusions of high-dose prostaglandins, by improving cellular nutrition, may increase prostaglandin receptor production on the surface of vascular endothelial cells. This may promote vessel reactivity to endogenous prostaglandins, which would explain the prolonged response reported here and in other studies.[5 6 21]

In conclusion, these direct studies of capillary haemodynamics have shown that prostaglandin E_1 improves the nutritive circulation in patients with Raynaud's phenomenon secondary to progressive systemic sclerosis. Any hypothesis that purports to explain the beneficial action of prostaglandin E_1 must take into account the observed changes in precapillary resistance.

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ONE HUNDRED YEARS AGO Apropos of the ignorant and morbid outbreak of sympathy with the woes of Jumbo which has lately afflicted London, Mr Flower writes to a contemporary that many of the humane folk who went to bid their troublesome pet a last adieu, and do their best to ruin his digestion, were strangely oblivious to the pain that was being suffered by their own carriage-horses. Whilst the humble cab-horses were standing "at ease," with liberty for their heads and necks, most of the carriage-horses were tied up so tightly that they could not lower their heads one inch, and with their lips drawn up most painfully from tight bearing-reins. It is, indeed, singular that the perpetual tossing and turning of their horses' heads to get a little relief from the evident pain and discomfort they suffer, does not induce humane and sensible people to abolish the use of these instruments of daily torture. (*British Medical Journal*, 1882.)