mechanisms may also be relevant to the time of development of the disease. Possibly a greater or different type of maternal immune tolerance is required during a male compared with a female pregnancy.⁴ An increased immune tolerance during male pregnancies might then further the establishment and development of breast cancer in women liable to the disease.

In our study breast cancer was diagnosed before the age of 50 in 26 of the 42 women (62%) who had given birth to more than one boy (fig 2). The corresponding figures for mothers of one boy were 13 out of 47 (28%) and for those of only girls four out of 33 (12%). In most mothers of two or more boys screening for breast cancer over the age of 50 may therefore be too late, whereas in mothers of only girls early screening procedures may be less important. Information on the composition of the progeny in a larger group of patients than the present might therefore have some bearing on the optimal age for the start of screening procedures.

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Treatment of vasospastic disease with prostaglandin E₁

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Summary and conclusions

Prostaglandin E₁, a vasodilator and potent inhibitor of platelet aggregation, was administered to 26 patients with severe vasospastic disease of the hands. Patients tolerated infusions well and reported appreciable symptomatic improvement. Five of eight ischaemic ulcers healed in six weeks. Non-invasive studies of blood flow were used to observe haemodynamic changes during and after infusions. The Doppler-derived radial artery pulsatility index fell from 8.8 ± 0.6 to 4.6 ± 0.5 (mean $\pm$ SEM), indicating hand vasodilatation. This fall was maintained 24 hours after infusion (5.9 ± 0.9), but the index had returned to normal values at two weeks. The amplitude of finger pulse volume recordings increased (5.6 ± 0.7 mm to 23.8 ± 3.4 mm) and was raised two and six weeks after infusion (13.5 ± 2.1 mm). Hand temperature measured by infrared radiometry also increased ($27.4 \pm 0.7^\circ\text{C}$ to $31.2 \pm 1.2^\circ\text{C}$). Intensity of digital vasospasm induced by cold water challenge was not objectively affected by prostaglandin E₁ despite an increased finger temperature after infusion. Nevertheless, patients reported less frequent and severe attacks.

Prostaglandin E₁ given by central venous infusion is a safe new vasoactive agent that can produce appreciable symptomatic improvement by increasing digital perfusion, which may last for several weeks after treatment. Further study will define its mode of action and its place in the management of peripheral vascular disease.

Introduction

Vascular disease in the hands and feet produces a wide range of ischaemic changes varying from transient attacks of vasospasm to ulceration and gangrene.¹ Digital vasospasm, first described by Maurice Raynaud in 1862,² is now defined as episodic attacks of vasoconstriction of the small arteries in response to cold or emotional stimuli.³ They may occur alone (Raynaud's disease) or in association with various diseases including connective tissue disorders, arteriosclerosis obliterans (Buerger's disease), and atherosclerosis. The basic abnormality is probably in the peripheral vessels,^{4,5} but patients may also have reduced fibrinolytic activity, raised plasma fibrinogen concentration, and increased blood viscosity.⁶⁻⁸ Thus the typical symptoms and signs of Raynaud's phenomenon are secondary to the intermittent obstruction of digital vessels^{4,9} arising from these rheological or vessel-wall abnormalities.

Management of patients suffering from severe Raynaud's phenomenon with or without trophic skin changes remains controversial. Vasodilators, sympathectomy, plasma exchange, and fibrinolytic enhancement are used with varying effect.^{6,10-13} Recently it has been suggested that prostaglandins may have a role in the management of peripheral vascular disease.¹⁴⁻¹⁹ We describe the use of intravenous prostaglandin E₁, a vasodilator and inhibitor of platelet aggregation,^{20,21} to treat severe digital ischaemia of varying aetiology. We used non-invasive measurements of limb blood flow to quantify the clinical effects.

Patients and methods

We studied 26 patients presenting with severe Raynaud's phenomenon and ischaemic skin changes. Seventeen were women and nine men (age range 33-76 (mean 52) years). Eighteen had progressive systemic sclerosis, six small-vessel-dominant atherosclerosis, and two primary Raynaud's disease. Five patients had already undergone digital amputation, and in eight ischaemic ulceration of the fingers was present. Patients were admitted to hospital for five days, and informed consent was obtained for each infusion, which was given via a central venous cannula over 72 hours. A cooled (4°C) solution

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(1 ml) of prostaglandin E₁ (Upjohn Ltd) containing 0.5 mg was added to 9 ml of sterile benzyl alcohol in water (0.9% w/v) and infused in physiological saline at an initial dose rate of 6 ng/kg/min. This was increased after 12 hours in the absence of side effects to 10 ng/kg/min.

Measurements were made immediately before, during, and 24 hours after the infusion and again two and six weeks later. Patient opinion was recorded using a three-point scale (better, same, worse), as were changes in warmth and cold intolerance of the hands. Pain was assessed on a four-point rating scale and with a 10 cm visual analogue scale. Finger ulceration and ischaemic changes were documented by a single observer and any side effects or adverse reactions noted. Hand and finger perfusion was measured objectively using three independent non-invasive techniques: infrared radiometry (26 patients), Doppler ultrasound (14), and finger plethysmography (14). Measurements were made with the patients supine in a quiet, thermostatically controlled (20 ± 1°C), electrically screened room after a 30-minute equilibration period.

Large conduit arteries were studied by analysis of Doppler-derived blood velocity waveforms, pulse transit time, and ankle systolic pressures; while small vessels were assessed using Doppler signals, finger plethysmography, and radiometry. Doppler signals were analysed using the pulsatility index,²² which quantifies the pulse waveform shape. In the absence of proximal stenosis the pulsatility index falls in response to distal vasodilatation (R Skidmore, PhD thesis, University of Bristol, 1979). The pulsatility index was analysed for 10 consecutive heart beats from the radial artery and an average value obtained. Doppler probes placed on the subclavian and radial arteries were used to record the pulse arrival times, the difference between the two being the pulse transit time.

Digital pulse volume recordings were made with a segmental air plethysmograph (pulse volume recorder, Life Sciences, Greenwich, Connecticut). With a standard volume, changes in cuff pressure reflect change in digital pulse volume.²³ The mean amplitude of pulse volume recordings was calculated from five consecutive waveforms using signals from the proximal phalanges of both index and middle fingers. Hand and finger temperatures were recorded using a KT41 (Heiman Wiesbaden GFR) infrared radiometer, held at a distance of 18 mm over six areas of the dorsum of the fingers and five areas of the dorsum of the hand.²⁴ An average temperature for each area was then calculated. With each radiometric study a standard cold challenge test was performed, one hand in a plastic glove being immersed for one minute in water at 20°C. Measurements were made before and four and 10 minutes afterwards. In five patients the effects of physiological saline via the central venous cannula were recorded before prostaglandin E₁ was added to the infusion. Statistical analysis of data from recordings of pulse volume, radiometry, and Doppler signals was by paired *t* test.

Results

Inflammation around peripheral venepuncture sites in two early cases was corrected by using central venous cannulae in the remainder, and the patients subsequently tolerated the prostaglandin E₁ infusions well. Side effects were minimal but included headaches (five patients), flushing (eight), pain in the shoulder on the side of infusion (one), and mild diarrhoea (one). Symptomatic postural hypotension occurred in

systemic sclerosis, reported no change in their symptoms two weeks after infusion.

Hand temperature, radial artery pulsatility index, and the amplitude of the recording of finger pulse volume were not affected by infusion of physiological saline in the five patients who received this for 24 hours before prostaglandin E₁ was added. Twenty-four hours after the infusion of prostaglandin E₁ temperature and the amplitude of the pulse volume recording had risen and pulsatility index fallen. The temperature and amplitude of the pulse volume recording remained raised two and six weeks after infusion (table II). Figure 1 shows

TABLE II—Mean ± SEM results of haemodynamic studies

	Before infusion	During infusion	Time after infusion		
			24 hours	2 weeks	6 weeks
Finger temperature (°C)	27.4 ± 0.7	31.3 ± 1.4*	32.1 ± 1.0*	28.8 ± 0.9*	31.2 ± 1.2*
Amplitude of finger pulse volume recording (mm)	5.6 ± 0.7	23.8 ± 3.4*	16.9 ± 2.2*	8.6 ± 1.3*	13.5 ± 2.1*
Radial artery pulsatility index	8.8 ± 0.6	4.6 ± 0.5*	5.9 ± 0.9*	9.5 ± 0.9	6.9 ± 1.0

**p* < 0.01.

FIG 1—Sequential recordings of radial artery Doppler waveforms before and after infusions of prostaglandin E₁, showing vasodilatation with a concurrent fall in pulsatility index.

TABLE I—Subjective results of treatment after two and six weeks

Symptoms	2 weeks		6 weeks	
	Improved	No change	Improved	No change
Overall	21	5	17	9
Hand warmth	21	5	17	9
Hand cold tolerance	19	7	16	10

one patient and resolved quickly when the infusion was stopped. No serious adverse clinical, biochemical, or haematological effects were observed at the time of infusion or on follow-up.

Appreciable symptomatic improvement occurred in all but one patient during infusion, and 21 reported maintained improvement at two weeks (table I). They particularly noted reductions in pain and the severity and frequency of attacks of vasospasm. Pain as measured on the visual analogue scale improved from 7.1 cm to 4.8 cm two weeks after infusion (*p* < 0.05). At six weeks four patients could not detect continued improvement. Five patients, three with severe

typical radial artery Doppler waveforms and the fall in pulsatility index with prostaglandin E₁ treatment. Radial pulsatility index fell with treatment from 8.8 ± 0.6 (mean ± SEM) to 4.6 ± 0.5 (*p* < 0.0001) but had returned to preinfusion values by two weeks. Doppler measurements of arm pulse transit time and ankle and brachial systolic pressures were not affected by prostaglandin E₁. The amplitude of recordings of finger pulse volume rose from 5.6 ± 0.7 to 23.8 ± 3.4 mm (*p* < 0.001) on infusion and remained raised (13.5 ± 2.1 mm) at six weeks (*p* = 0.005). More pronounced changes were seen in some patients (fig 2). Hand and finger temperatures increased in response to prostaglandin E₁ (from 27.4 ± 0.7 to 32.1 ± 1.0°C; *p* < 0.01) and were significantly raised at two and six weeks (*p* = 0.001). Figure 3 shows that parallel rises occurred in temperature and amplitude of pulse volume recording accompanied by a fall in pulsatility index. A standard cold water challenge in 18 patients showed that there was no significant difference (*χ*² test) in the abnormal response before and 24 hours after prostaglandin E₁ infusion (fig 4), despite increased resting finger temperatures. This was confirmed by measuring the amplitude of the pulse volume recordings.

FIG 2—Changes in finger perfusion induced by infusion of prostaglandin E_1 in a patient with arteriosclerosis. Amplitude of pulse volume recording was still raised two weeks after infusion.

FIG 3—Increases in mean finger temperature and amplitude of pulse volume recording with a concurrent fall in radial pulsatility index, confirming that increased hand blood flow is directed into the digits. Finger perfusion is significantly increased six weeks after infusion in the absence of detectable hand vasodilatation (pulsatility index).

Discussion

Blood flow to the hand is significantly reduced in patients with Raynaud's phenomenon.¹⁰ In an effort to increase flow several vasodilators have been prescribed for patients with peripheral vascular insufficiency, and short-lasting benefit has been reported after treatment with reserpine, fibrinolytic agents, and plasma exchange^{6 11-13}; but few workers have claimed prolonged success.

Prostaglandin E_1 is a naturally occurring potent vasodilator and inhibitor of platelet aggregation that might be expected to produce some short-term improvement in peripheral blood flow if given in therapeutic doses. When used intravenously high doses are needed to overcome the removal of a large proportion by a single passage through the lungs,^{14 25} which reduces the circulating half life to minutes. With the dose range 6-10 ng/kg/min an immediate rise in hand temperature occurred together with Doppler evidence of increased blood flow, indicating that a therapeutic dose was reaching the systemic arterial circulation.

Infusions of prostaglandin E_1 were well tolerated, and no

serious side effects or adverse reactions were encountered during or after treatment, although there were several minor complaints. Patients reported immediate improvement in symptoms, and in most of the patients with ulcers healing occurred. These subjective results are similar to those reported in previous studies, which include a placebo-controlled study.^{15 17 18}

Our non-invasive studies confirmed subjective impressions, detecting improvement in hand and finger perfusion during and after treatment. Measurements of finger pulse volume recordings varied widely between patients, but this technique was a reliable indicator of changes in finger perfusion in any individual.²⁶ The changes seemed to be confined to small arteries, as there was no detectable change in arm pulse transit time or Doppler ankle systolic pressures. Hand vasodilatation resolved within two

FIG 4—Responses to cold water challenge in 18 patients before and 24 hours after infusion of prostaglandin E_1 . Responses are identical despite raised resting digital temperature after infusion.

weeks, but increased finger perfusion was still detectable at six weeks. This suggests that pharmacological doses of prostaglandin E_1 may also be acting through another mechanism such as platelet disaggregation, or on the vascular endothelium itself. Prostaglandin E_1 was generally free of the effects of other vasodilators, which commonly cause hypotension and shunting of blood away from ischaemic areas.¹¹ This supports the argument that it acts locally on vascular endothelium, which, in atherosclerosis, is depleted of prostaglandins.¹⁶ The reason for the discrepancy between subjective reports of improvement in vasospasm and objective evidence of an unchanged response to standard cold challenge is unclear. Possibly prostaglandin E_1 , producing higher hand temperatures, raises the threshold at which the vasospasm is triggered.

The results of this preliminary study indicate that prostaglandin E_1 given by central venous infusion is a safe and effective method of treating severe vasospastic disease. Further study will define its place in the treatment of peripheral vascular disease, but at present it is best given during episodes of acute ischaemic pain, necrosis, or infection, and during the perioperative period of local surgery to ischaemic tissues.

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Breast-feeding and respiratory syncytial virus infection

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Summary and conclusions

The pattern of breast-feeding in 127 infants admitted to hospital with respiratory syncytial virus infection was compared with that in 503 age-matched controls. Thirty per cent of children with infection had been breast-fed compared with 49% of controls. The approximate relative risk of being admitted to hospital with respiratory syncytial virus infection if not breast-fed was 2.2. Several other factors were also considered, including an assessment of maternal care and home environment; the mother's age, marital state, and smoking habits; the number of siblings; and gestation. Adverse factors were all associated with an increased risk of admission with infection, but breast-feeding still appeared to provide

protection after controlling for these other factors in turn.

These findings provide further support for encouraging mothers to breast-feed their infants and should prompt further studies into the immune status of mothers and into the nature of the protective factors in their breast milk.

Introduction

Infants admitted to hospital with respiratory syncytial virus infection are less likely to have been breast-fed.^{1,2} This may be because breast-feeding is protective. Nevertheless, several adverse social and environmental factors such as overcrowding, large families, and unemployment are associated with respiratory syncytial virus infection,³ and these factors may also be linked with failure to breast-feed. It is therefore not certain whether breast-feeding itself is protective or is only a coincidental finding.

In an attempt to clarify this further we studied various epidemiological factors as well as breast-feeding in a group of children admitted to hospital with respiratory syncytial virus infection and in control children drawn from the general population.

Patients and methods

Children admitted to Tyneside hospitals with respiratory tract infections routinely have nasopharyngeal secretions and nose and throat swabs taken for viral diagnosis. The study included all infants aged 6 months and under in whom respiratory syncytial virus had been

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