commonly occur in an attempt to identify an adenoma and at least one normal gland. Virtually all the adenomas are accessible through a cervical incision, and the sternum should not be split at the primary exploration. The surgical task is much facilitated by working with an anaesthetist who is fully aware of the requirements of the operation. There should be a clear airway, controlled ventilation, and normotension. Using these guidelines we find that the operation is well tolerated by these elderly patients, all of whom have had an uneventful post-operative course. There have been no deaths, and the improvement in wellbeing and activity after operation has been striking.

These results encourage us to consider more patients for operation irrespective of age provided that they have symptoms. Hypercalcaemia, however mild, should be investigated, as a preoperative diagnosis of hyperparathyroidism can now usually be made with considerable accuracy. Other reports support our findings that muscle weakness, lethargy, and general malaise respond well to correction of the hyperparathyroidism, but our present findings suggest that improvement in dementia may be more common than other reports indicate.

Although the improvements in our patients were predominantly subjective, they were enough to prevent three of the patients from being admitted for long-term hospital care. The improved mobility also allowed several of them to manage

shopping and other domestic duties. As more and more elderly patients are found to have hyperparathyroidism it will be important to try to devise more objective methods of assessing their response to treatment.

We thank Dr M Waite for permission to include case 11.

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Cutaneous microcirculation in systemic sclerosis and response to intra-arterial reserpine

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Summary and conclusions

The cutaneous microcirculation in the hand was measured in 23 patients with systemic sclerosis, 19 with Raynaud's phenomenon and four without Raynaud's phenomenon, and 20 controls. The patients with Raynaud's phenomenon had a reduced basal blood flow and an exaggerated further reduction on local cold stimulation, though both were normal in patients without Raynaud's phenomenon. Reflex-induced vascular changes by cold stimulation of the contralateral hand showed no differences between the three groups. The blood flows were similar in the affected skin of the anterior chest wall in four patients with systemic sclerosis and peripheral Raynaud's phenomenon and matched controls. In the seven most severely affected patients 1 mg of intra-arterial reserpine produced a prompt improvement in the cutaneous microcirculation which usually lasted one to three weeks but occasionally much longer. By judicious use of repeated injection guided by measurements of the microcirculation it was possible to heal indolent ulcers of the fingers.

The results indicate that vascular changes are common in systemic sclerosis but are not fundamental in the

pathogenesis of the disease. More probably there is a general soft tissue abnormality that usually but not necessarily affects the vessels.

Introduction

The clinical features of systemic sclerosis are due to a combination of fibrosis and induration of tissue, vascular obstruction, and ischaemic atrophy. In particular, Raynaud's phenomenon and widespread vessel changes occur in various organ systems. In patients with severe Raynaud's phenomenon peripheral ischaemia leads to gangrene of the digits. There is debate over whether these vascular changes are fundamental in the pathogenesis of systemic sclerosis and initiate the florid tissue changes or whether there is a generalised tissue abnormality around and including the blood vessel walls which causes vascular obstruction. We compared these hypotheses by measuring the microcirculation within the skin and the changes that occur during exposure to cold in controls and patients with progressive systemic sclerosis with and without Raynaud's phenomenon. In those patients with severe Raynaud's phenomenon and peripheral ischaemia the responses of the microcirculation to intra-arterial reserpine were recorded.

Patients and methods

Twenty controls and 23 patients with systemic sclerosis with typical cutaneous features confirmed by biopsy (19 with and four without Raynaud's phenomenon) were studied. The patients with systemic sclerosis showed varying degrees of visceral changes. In particular, the four without Raynaud's phenomenon all had

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oesophageal lesions, one had calcinosis, and one pulmonary fibrosis. Informed consent was obtained from all.

The cutaneous microcirculation was measured atraumatically in the skin fold between the extended index finger and the abducted thumb by recording the clearance of epicutaneous applied xenon-133^{1,2} under strictly controlled environmental conditions. The subject had not taken vasoactive drugs in the preceding 48 hours, had not smoked or drunk alcohol, coffee, or tea during the preceding four hours, and wore light clothes. Changes in blood flow during standardised local and contralateral hand cooling tests³ were recorded. Four patients with extensive disease affecting the anterior chest wall and with Raynaud's phenomenon that severely affected only their hands underwent further tests: the cutaneous microcirculation in the skin over the manubrium sterni was measured in each patient and the values compared with those of matched controls.

Seven patients had systemic sclerosis and severe Raynaud's phenomenon with such peripheral ischaemia and ulceration that treatment with intra-arterial reserpine was considered necessary; 1 mg diluted in 2 ml of normal saline was injected slowly over 60 seconds either directly into the brachial artery or into the subclavian artery during arteriography of the arm. All repeat injections were given directly into the brachial artery. The cutaneous microcirculation was measured before and 24 hours after injection and at regular intervals thereafter.

Results and comment

The basal skin blood flow before cooling was slower in the patients with Raynaud's phenomenon than in the controls but was normal in the four patients without Raynaud's phenomenon (fig 1). Local

FIG 1—Mean basal skin blood flows in controls and patients with systemic sclerosis with and without Raynaud's phenomenon.

cooling produced an excessive reduction in the cutaneous microcirculation of patients with Raynaud's phenomenon but not of those without Raynaud's phenomenon (fig 2). The three groups showed no differences in response to the contralateral hand cooling test. Skin blood flow fell by 23.4±(SD)10.4% in controls, 28.2±10.5% in patients with Raynaud's phenomenon, and 26.1 (range 14.8-36.2)% in those without Raynaud's phenomenon. The results from both cooling tests were similar when calculated as absolute rather than proportional changes in blood flow.

One patient had no Raynaud's phenomenon and repeatedly normal values at initial assessment but developed the phenomenon seven months later. Basal skin flow and local cooling then became abnormal and remained so thereafter (table I).

The basal flows in sclerodermatous skin over the manubrium sterni in four patients (4.0, 4.2, 4.8, 6.0 ml/min/100 g) were similar to those of the matched controls (4.6, 4.8, 5.0, 6.4 ml/min/100 g). Unfortunately, this site is not suitable for the local cooling test.

FIG 2—Percentage changes in basal skin flows during local cooling.

TABLE I—Sequential changes in blood flow and sensitivity to cold in a 52-year-old woman with systemic sclerosis since 1973 (affecting skin and oesophagus) who developed Raynaud's phenomenon for the first time in March 1977

Date	Aug 1976	Nov 1976	Feb 1977	March 1977	June 1977
Basal skin flow (ml/min/100 g)	6.3	5.7	6.1	3.9	3.4
Decrease in flow during local cooling (%)	8.6	11.6	9.4	65.4	56.8
Decrease in flow during contralateral cooling (%)	23.8	30.0	27.4	39.2	36.0

The seven patients who received intra-arterial reserpine all showed a large increase in the basal skin blood flow 24 hours after injection (fig 3) with loss of the excessive reduction in blood flow after local cooling and lessening of the relatively normal fall in blood flow on contralateral cooling (fig 4). Three subjects received saline injections during arteriography with no change in the basal flow and cooling responses, but all improved in a comparable fashion to the others after brachial reserpine injections one week later.

The long term responses to intra-arterial reserpine were examined by repeated measurements at the same site. The improvement usually lasted one to three weeks but in one patient lasted five months. Basal

FIG 3—Basal skin blood flows before and 24 hours after intra-arterial injection of 1 mg of reserpine in patients with systemic sclerosis.

skin blood flows and cooling responses usually began to deteriorate before symptoms developed. A repeat injection again improved the peripheral microcirculation. Limited observations suggested that if the reserpine was reinjected as soon as the test became abnormal again ischaemic ulcers healed faster and relapses could be avoided. The results of the injections are shown in table II.

FIG 4—Percentage changes in basal skin flows in response to local and contralateral cold stimulation before and 24 hours after intra-arterial injection of 1 mg of reserpine in patients with systemic sclerosis.

TABLE II—Indications for and outcomes of intra-arterial reserpine injections in seven patients with systemic sclerosis

Case No	Indication	Total No of injections	Outcome
1	Ulcer	2	Successful conservative amputation
2	Ulcer	6	Healed in 6 weeks
3	Ulcer	4	Healed in 6 weeks
4	Ulcer	3	Healed in 4 weeks
5	Ulcer	2	Healed in 3 weeks
6	Pain	1	Relieved in 4 hours
7	Pain	1	Relieved in 2 hours

Discussion

Widespread vascular changes are extremely common in progressive systemic sclerosis. Raynaud’s phenomenon is the most obvious clinical feature but it is not always present.⁴ Pathological changes occur in the small arteries and arterioles: the numbers of capillaries fall and those that remain become very dilated. In Raynaud’s phenomenon there is an excessive reduction in peripheral blood flow during exposure to cold. This reduction is caused by narrowed blood vessels, excessive local or reflex-induced constriction of blood vessels in response to a cold stimulus,³ and raised blood viscosity with a disproportionate increase in the cold, which reduces the blood flow.⁵ In systemic sclerosis it is uncertain whether the reduction in peripheral blood flow is responsible for the collagen proliferation and soft tissue changes or whether there is a general soft tissue abnormality that usually affects the blood vessels.^{4 6 7} This distinction is important in developing treatment to fundamentally control the disease.

Clearly a reliable method for measuring the circulation within the skin is required for establishing the physiological basis for the cutaneous changes and for measuring and following the effects of various forms of treatment directed at improving peripheral blood flow. Using the clearance rate of ¹³³Xe after epicutaneous application is an important technological advance in allowing accurate and reproducible measurements in an atraumatic fashion. The local radiation is minimal (less than 3 mrad/s) and well within acceptable limits.

In patients with Raynaud’s phenomenon there was a reduction in the local cutaneous microcirculation compared with controls and an exaggerated further reduction on local exposure to cold. These changes mirror the clinical features. On the other hand, there were patients with typical skin lesions but without Raynaud’s phenomenon who had normal basal flows and responses to local cooling. Moreover, in patients with extensive scleroderma and peripheral Raynaud’s phenomenon the basal flows in the affected chest wall—a site where Raynaud’s phenomenon does not occur—were similar to those of the controls. A single patient with systemic sclerosis but without Raynaud’s phenomenon initially had normal basal skin blood flows and responses to local cooling, but these became abnormal when he developed Raynaud’s phenomenon some seven months later.

These findings suggest that the vascular changes are not fundamental in the pathogenesis of systemic sclerosis. They are common accompaniments of scleroderma, leading to a reduced skin microcirculation and local sensitivity to cold, which are then associated with the development of Raynaud’s phenomenon. This is in keeping with the poor correlation between the extent of skin disease and the severity of small vessel disease,^{6 8} and not with the view that the fundamental lesion lies in and around the small arteries and arterioles.^{4 7} We believe there is a general soft tissue abnormality that usually but not necessarily affects the small blood vessels.

The normal contralateral cooling test suggests that reflex-mediated cold-induced skin vasoconstriction is not important in systemic sclerosis whereas it may be so in other forms of Raynaud’s phenomenon.³ Blocking of these reflex changes is therefore unlikely to be helpful, so accounting for the lack of benefit after sympathectomy for Raynaud’s phenomenon in systemic sclerosis.^{9 10}

After intra-arterial reserpine, the basal blood flow greatly improved and the exaggerated reduction in the microcirculation on exposure to cold disappeared. Although this improvement usually lasted only one to three weeks, it seems a fundamental point that blood flow can be improved, indicating that a significant proportion of the vascular damage is reversible. This reversible element might be amenable to more long-term treatment, lending hope of better control of the microcirculatory manifestations of the disease in the future. By judicious use of intra-arterial reserpine, preferably given when indicated by repeated monitoring of the cutaneous microcirculation, it is possible to heal severe ulceration of the fingers in some patients and prevent and limit loss of digits. Moreover, when surgery is necessary the preliminary injection of reserpine may allow a more limited local procedure to be performed and encourage healing thereafter. Previous studies of the value of intra-arterial reserpine have produced conflicting results.^{11–18} The lack of a suitable method for following the skin blood flow and the limited duration of action of the drug and need for repeated injections made assessment difficult. Our results suggest that reserpine has a definite but limited place in patients with systemic sclerosis and severe Raynaud’s phenomenon.

The mechanism of action of intra-arterial reserpine remains in doubt. It is known to deplete the sympathetic nerve endings of noradrenaline, but this would probably produce only a transitory improvement lasting a few hours. There may well be some other mechanism of action leading to more prolonged improvement in blood flow.

Requests for reprints should be sent to Professor M I V Jayson.

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Sauna-induced acceleration in insulin absorption from subcutaneous injection site

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Summary and conclusions

The effect of the Finnish sauna on insulin absorption from a subcutaneous injection site was examined in eight insulin-dependent diabetic patients by measuring externally the disappearance rate of ¹²⁵I-labelled rapid-acting insulin. The sauna (twice for 25 minutes at 85°C) accelerated insulin absorption by 110% as compared with room temperature ($p < 0.01$). After the sauna blood glucose concentrations were 3.0-3.3 mmol/l (54.1-59.5 mg/100 ml) lower than on the control day ($p < 0.05$). The fall in blood glucose values was proportional to the increased rate of insulin absorption ($r = 0.80$; $p < 0.01$).

The hypoglycaemic effect of a sauna in insulin-treated diabetics is clearly at least partly due to enhanced insulin absorption from the injection site. Such an effect might be prevented by taking a snack or reducing the insulin dose.

Introduction

Most Finns take a sauna bath once or twice a week. Anecdotal evidence, however, suggests that insulin-treated diabetics have hypoglycaemic symptoms after a sauna. Apart from factors such as diet and exercise, a major determinant for a fall in the blood glucose concentration in diabetes is insulin availability.¹ Besides the dose and type of insulin used, the rate of insulin delivery from the injection site affects the blood glucose concentration. Thus exercise accelerates insulin absorption from the injection site, resulting in a decline in the blood glucose concentration.²⁻⁴ At rest there are differences in the rate of insulin absorption from various injection sites.^{5,6} Furthermore, changes in blood glucose concentration are proportional to the rate of insulin absorption.^{5,6} Both at rest⁷ and during exercise⁸ variations in blood flow at the injection site may at least partly contribute to the alterations in rate of insulin absorption. Skin blood flow is greatly dependent on environmental temperature.⁹ I therefore decided to see whether a hot Finnish sauna can influence insulin

absorption from injection sites. I also examined the relation between the rate of insulin absorption and changes in the blood glucose concentration.

Patients and methods

I studied eight insulin-dependent diabetic men aged 21-54 years (mean age 34 ± 4 years) who were known to have had diabetes for 1-13 years (mean 6 ± 2 years). They were taking a total of 26-27 U (mean 39 ± 6 U) of intermediate or intermediate plus rapid-acting insulin in one (four patients) or two (four patients) injections daily. Seven had taken insulin from the onset of their disease. One patient, who had been diabetic for 13 years, had been taking insulin for two years, his current dose being 46 U/day. Injection sites were regularly rotated between the leg, arm, abdomen, and buttock. No patient had evidence of lipodystrophy at any injection site, none was obese, and all used a weight-maintaining diet containing about 45% carbohydrate, 35% fat, and 20% protein. Each patient took a sauna once or twice a week. There was no clinical evidence of diabetic neuropathy, nephropathy, or retinopathy and no history of other endocrine disease in any patient. All patients volunteered for the study after its nature and purpose and the possible risks had been explained.

The studies began in the morning after an overnight (12-14 hour) fast, 16-24 hours after the last insulin injection. An indwelling catheter was inserted into an antecubital vein for obtaining samples for blood glucose determinations.¹⁰ Two baseline samples were drawn 15 minutes apart and the mean blood glucose concentration taken as the fasting value. The patients were then given subcutaneous injections in the thigh of 10 U ¹²⁵I-labelled rapid-acting insulin (Actrapid MC) and 6-40 U intermediate-acting insulin (Monotard MC). The radioactive and unlabelled insulins were injected 5-10 cm apart. The total amount of insulin given was 80-90% of the patients' usual morning dose. To prevent ¹²⁵I accumulating in the thyroid the patients were given 0.5 g potassium iodide the night before and for four days after the insulin injection. Immediately after the injections the subjects were given breakfast providing 430 kcal and containing 50% carbohydrate, 30% fat, and 20% protein. A snack of 130 kcal was given 120 minutes after insulin injection. (1000 kcal $\approx$ 4.2 MJ.)

Each subject was studied on two separate days. Throughout the control day the subjects sat in a room at 22°C. On the day of the experiment they entered the sauna 60 minutes after the insulin injections. After 25 minutes at 85°C they left the sauna for five minutes for external counting of radioactivity at the injection site and then returned to the sauna for a further 25 minutes. The order of the control and sauna days was randomised. The total dose of insulin,

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