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Influence of Orthostatic Pressure Changes on Blood Flow in Fingers in Generalized Scleroderma

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Abstract. Autoregulation of blood flow, i.e. tendency towards the maintenance of constant blood flow during changes in arterial perfusion pressure head, has previously been demonstrated in human cutaneous and subcutaneous tissue. The response seem to depend on local intrinsic mechanisms, and the study of autoregulation can yield information as to the reactivity of vascular smooth muscle cells to normal metabolic and myogenic stimuli. Nine patients and 6 normals were studied. Blood flow was measured in subcutaneous tissue of fingers by the local ^{133}Xenon washout technique. A decrease in arterial perfusion pressure head was obtained by graded elevation of the arm above heart level. In 5 normals and 7 patients, blood flow was also measured in a subcutaneous vascular bed made passive by injection of a ^{133}Xenon–papaverine mixture. In this paralysed vascular bed, blood flow diminished corresponding to the decrease in perfusion pressure during elevation of the arm, while in the normal vascular bed blood flow remained almost constant. Patients suffering from generalized scleroderma took an intermediate position. This finding is compatible with an intrinsic vascular smooth muscle cell defect in generalized scleroderma.

In previous studies (8, 9, 10) it was suggested that autoregulation of blood flow was absent from cutaneous and subcutaneous tissue of fingers and cutaneous tissue of hands in generalized scleroderma.

Autoregulation of blood flow, i.e. tendency towards the maintenance of constant blood flow during changes in arterial perfusion pressure has been demonstrated in cutaneous and subcutaneous tissue of normal persons (3, 4, 5). The mechanisms responsible for the adjustment of vascular resistance to changes in arterial perfusion pressure are still largely unknown, but most facts seem to favour a metabolic hypothesis, i.e. vasoactive metabolites liberated from the tissues due to decrease in local oxygyn tension (1, 2).

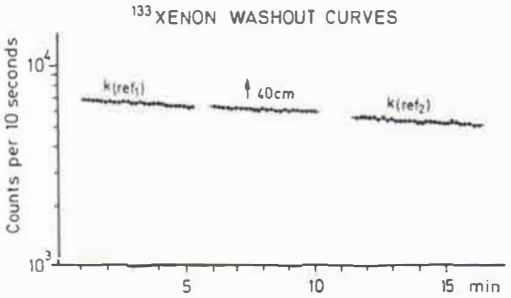

Fig. 1. ^{133}Xenon washout curves illustrationg the triad of measurements.

Autoregulation of blood flow depends on normal functioning of vascular smooth muscle cells. Studies on autoregulation can provide information on the reactivity of vascular smooth mucsle cells to normal metabolic stimuli.

The aim of the present study was to investigate the extent to which the autoregulation of blood flow in fingers is reduced in generalized scleroderma.

METHODS

Blood flow in subcutaneous tissue on the dorsum of the proximal phalanx of the right second finger was estimated by the local ^{133}Xenon washout technique (7, 13). Subcutaneous injection of 0.1 ml ^{133}Xenon dissolved in sterile isotonic saline was performed 30 to 60 minutes before the experiments started in 9 patients and 6 normals. The subjects were seated. A single study consisted of the measurement of ^{133}Xenon washout rate constants (k), (1) with the finger at heart level ($k_{\text{ref. 1}}$); (2) with the finger elevated 20 or 40 cm (k_{test}); and finally (3) with the finger at heart level ($k_{\text{ref. 2}}$)(Fig. 1). In 5 normals and 6 patients, ^{133}Xenon was also administered with an admixture of papaverine (40 mg/ml) to create complete smooth muscle paralysis in the area under study and the sequences were repeated.

The washout rate constant (k) was computed from the logarithmically transformed count rates, corrected for background activity by the least square method.

Relative blood flow during elevation or lowering was computed from the ^{133}Xenon washout rate constants by the formula: $k_{\text{test}}/[k_{\text{ref.1}}+k_{\text{ref.2}}] \cdot \frac{1}{2}$

Statistical tests for significance were performed by using Student's t-test for paired samples and the randomization test for nonpaired samples, 0.05 was chosen as limit of significance.

Patient population and experimental conditions

Informed consent was obtained before each experiment. Patients suffering from generalized scleroderma of the

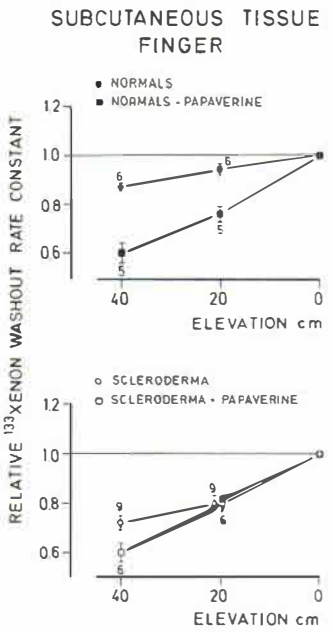

Fig. 2. Blood flow changes during elevation, with or without papaverine injection, in normals and in patients suffering from generalized scleroderma.

acrosclerosis type were investigated. Ages ranged from 26 to 75, disease duration from 2 to 15 years. All had a history of Raynaud's phenomenon and evidence of previous and present ulceration of fingertips. Normal persons aged 35 to 63 years served as controls.

RESULTS

Results of the experiments are shown in Fig. 2 and Table I. In normal fingers, autoregulation was demonstrated and could be blocked in the papaverine-paralysed vascular bed. In the patients, autoregulation was more or less absent and the results in the papaverine-paralysed vascular bed were very much like the results in the non-paralysed.

Table I. *Statistical comparison between normals and patients*

Scleroderma (S)		Normals (N)	Papaverine (P)
20 cm	S	N	$p<0.01$
40 cm	S	N	$p<0.01$
S	20 cm	20 cm P	$p<0.4$
S	40 cm	40 cm P	$p<0.05$
N	20 cm	20 cm P	$p<0.01$
N	40 cm	40 cm P	$p<0.01$

DISCUSSION

Significance of defective autoregulation

In the patients, blood flow tended to vary quite markedly with the decrease in arterial perfusion pressure head during elevation of the limb, while in normals blood flow was autoregulated and relatively constant. Thus the findings in the patients resemble those in ischemic legs, distal to an arterial occlusion. In ischemic areas with a passive vascular bed, the distal arterial blood pressure is a reflection of the systemic blood pressure and a proximal pressure change also alters the distal blood pressure (and blood flow) (11). This implies a risk of a paradoxical effect of vasoactive drugs, viz. blood flow in passive vascular beds might be decreased by vasodilators and conversely increased by vasoconstrictors (11).

Vasoconstrictor drugs were shown to increase blood flow in ischemic areas of arteriosclerotic legs (6). It has been reported that administration of vasodilators or sympathetic blockade can cause a decrease in distal blood flow in ischemic areas of arteriosclerotic legs (11). This has also been suggested to occur in generalized scleroderma and seems to be dependent on "stealing" of blood flow to less affected areas (12). Thus, in generalized scleroderma, as in arteriosclerotic legs, it is important before embarking on treatment with vasoactive drugs to perform quantitative circulatory studies including measurement at distal perfusion pressure.

ACKNOWLEDGEMENT

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Studies on Gastrointestinal Plasma Protein Loss in Extensive Skin Disease

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Abstract. The gastrointestinal loss of plasma protein was determined in 9 patients with extensive skin disease. $^{51}CrCl_3$ was used as the test substance in 5 patients and [^{131}I]albumin in 4 patients. The fecal isotope excretion was within the normal limits in all patients, though they had hypoalbuminaemia and increased initial disappearance rate of tracer albumin, presumably reflecting an abnormal leakiness of the microvasculature. It is concluded that loss of albumin through the gut does not account for the depressed plasma albumin concentration in these patients.

Key words: Albumin; skin disease; Gastrointestinal protein loss; Microvascular permeability; Transcapillary escape rate of proteins; Hypoalbuminaemia

There is evidence that extensive skin disease may be accompanied by dermatogenic enteropathy[10]. Thus several authors have found malabsorption of fat, D-xylose, iron, vitamin B_{12}, lactose and structural changes of the intestine (1, 3, 9, 10).

It has been postulated that intestinal plasma protein loss follows this involvement of the gut, but experimental evidence is sparse (11).

Protein-losing gastroenteropathy is no remote suggestion as an explanation for the hypoalbuminaemia that is almost always present in patients with extensive skin disease, but dilution or displacement of the intravascular albumin mass, proteinuria, or increased endogenous catabolism might equally well be the cause. However, we have previously found no evidence of dilution and proteinuria (5, 6).

The present study was designed to elucidate whether patients with extensive skin disease and hypoalbuminaemia have an abnormal leakage of plasma protein to the gastrointestinal tract.

METHODS

Nine patients, 4 females and 5 males aged 42–78 (mean 58 years) were examined. The clinical data are given in Table 1. Five patients had erythroderma, due to psoriasis in 4 and of an unknown cause in one (case no. 5).

Routine laboratory values, chest X-ray, ECG and clinical examination revealed no other major disease but the skin disease.

Measurements of gastrointestinal leakage of plasma protein

For technical reasons two methods were applied. In 4 patients a weighed dose of about 20 μCi ^{131}I-labelled albumin (code IK 21 S, Institute for Atomic Energy, Kjeller, Norway) was given intravenously. The thyroid gland was blocked with potassium iodine 100 mg daily (cases 1–4). In another 5 patients a weighed dose of about 50 μCi $^{51}CrCl_3$ (code CJS.2P, Radiochemical Centre, Amersham, England) was given intravenously (cases 5–9). The stools were collected from the time of injection until they became red following oral administration of 1 g carmine 96 h after injection of one of the tracers. The activity of ^{131}I or ^{51}Cr in the stools and in a standard solution of the injected tracer was determined twice in a shielded whole-body counter. The fecal loss of the isotope was expressed as a percentage of the injected dose.

Transcapillary escape rate (TER)

The transcapillary escape rate was calculated from the initial slope of the plasma disappearance curve after injection of [^{131}I]albumin or [^{125}I]albumin (code IT 21 S, Institute for Atomic Energy, Kjeller, Norway). [^{125}I]albumin (code IT 21 S, Institute for Atomic Energy, Kjeller, Norway). [^{125}I]albumin was used in 3 of the cases examined