

INCREASED $^{133}\text{XENON}$ WASHOUT FROM CUTANEOUS TISSUE IN GENERALIZED SCLERODERMA INDICATES INCREASED BLOOD FLOW

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Abstract. Blood flow in cutaneous tissue of the dorsum of the hand was measured by the local $^{133}\text{Xenon}$ washout technique in 18 normal persons and in 26 patients suffering from generalized scleroderma of the acrosclerosis type. Flow values calculated from the accepted blood-tissue solubility coefficient (λ) were 8.6 ± 0.4 S.E.M. ml/100 g $\times$ min in normals and 14.5 ± 1.1 ml/100 g $\times$ min in sclerodermic skin (i.e. increased by 69%). The difference was significant ($p < 0.001$). Blood flow values in sclerodermic skin were directly proportional to the degree of dermal sclerosis. As λ in sclerodermic skin is probably decreased due to a decreased fat content, it may not be correct to interpret these results as evidence of increased blood flow. A "worst case" was constructed in calculation of λ using zero fat content for sclerodermic skin. Flow value was now 12.3 ± 1.1 S.E.M. ml/100 g $\times$ min for sclerodermic skin, an increase of 43% compared with normal skin. It is probably only justified to use this "worst case λ " in the group of severely involved cases of scleroderma. In these patients it yielded a flow value of 17.8 ± 3.1 ($N=6$) which, when compared with the flow value for normal skin, indicates an increase by 100% of the blood flow in severely involved sclerodermic skin.

Generalized scleroderma (GS) is a disease of the mesenchymal tissues characterized primarily by fibrosis and vascular changes (2, 11).

The involvement of small blood vessels seems to play an important role in the pathogenesis. This is suggested by the frequent presence of Raynaud's phenomenon, the finding of a marked reduction in the number of dermal capillaries, the thickening and hyalinization of arteriolar walls, intimal proliferation of small size arteries, and, eventually, cutaneous necrosis (3, 22).

Blood flow in the skin in GS has not previously been measured quantitatively. The plethysmographic technique which usually yields results within the normal range in GS (19) can give only a rough evaluation of the cutaneous blood flow (28). Washout measurements based on the use of Na^{131}I have also provided results within the normal range in involved sclerodermic skin (4) but are not consid-

ered to give a measure of the blood flow, since, in addition to being determined by the blood flow in the tissue, the rate of washout is influenced by the capillary permeability (15).

In contrast to Na^{131}I , the transcapillary exchange of $^{133}\text{Xenon}$ is limited only by the blood flow at all flow rates (15). This tracer has been used previously in physiological studies of cutaneous blood flow in GS (16). However, the method has not been used in attempts to measure cutaneous blood flow quantitatively, which was the purpose of the present study.

MATERIALS AND METHODS

Patient population and experimental conditions

Experiments were conducted in 18 normal persons aged 23-80 and in 26 scleroderma (acrosclerosis) patients aged 30-75. Vasoactive treatment if any, was stopped at least one week prior to the experiment. A normal haemoglobin concentration was required. Dermal sclerosis on the dorsum of the hand in the patients was graded by an independent observer into 3 groups: "Slight", "moderate" and "severe". A history of Raynaud's phenomenon was found in 21 of the 26 patients (81%).

Air temperature was kept at $21 \pm 1.0^\circ\text{C}$ during the experiments. The subjects were dressed normally and had no subjective sensation of heat or cold; nor were they sweating. Cutaneous temperature on the dorsum of the hand in normals ranged from 30 to 35 (mean 33.2) and in patients from 29.9 to 35.0°C (mean 32.6).

Application of tracer and measurement of washout

$^{133}\text{Xenon}$ washout was measured on the dorsum of the hand after local application of tracer. 1) By means of the epicutaneous atraumatic application of gaseous radioactive isotopes (26, 27) an area 6 cm in diameter was labelled with $^{133}\text{Xenon}$ with a specific activity of 20 mCi/ml. Diffusion processes were allowed to take place for 3 min. Epicutaneous application was used in 12 normals and in 18 patients. 2) Intracutaneous injections of 0.01 ml $^{133}\text{Xenon}$ dissolved in isotonic saline (specific activity 3 mCi/ml) was administered in 16 normals and 15 patients. In this way, $^{133}\text{Xenon}$ washout was measured after both epicutaneous and intracutaneous application of tracer in

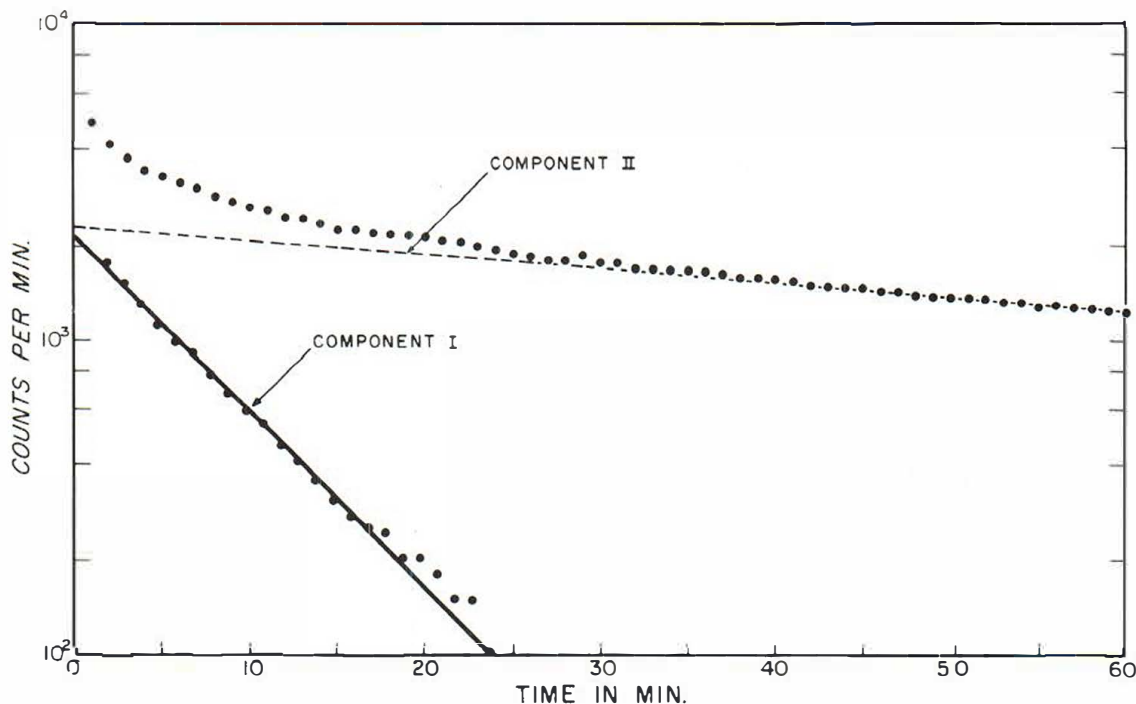


Fig. 1. $^{133}\text{Xenon}$ washout curve after epicutaneous application to a normal person. The principles of the biexponential resolution are shown. Component II represents

washout from subcutaneous tissue. Component I represents the cutaneous washout. The washout constant of component I is used in the calculation of blood flow.

12 normals and in 7 patients. A total of 30 experiments were carried out in normals and 33 in the patients.

A NaI (TI) scintillation detector was placed 5 cm above the radioactive field which was placed at heart level. The pulses from the detector were fed into a printing gamma-spectrometer (Meditronic, Copenhagen). Counting was started immediately after termination of labelling and the activity was printed out at 1-min intervals. The count figures were corrected for background activity and plotted versus time in a semilogarithmic diagram. In each experiment, counting proceeded for one hour.

Calculations and statistics

The clearance curves obtained were analysed according to the biexponential model proposed by Sejrsen (27). The slow monoexponential tail-part of the curve representing washout from subcutaneous fatty tissue (Component II, Fig. 1) was extrapolated to zero time and subtracted from the initial part of the curve. The new resulting monoexponential Component I (Fig. 1) was used to calculate cutaneous blood flow by the formula $f = k \times \lambda \times 100$ (ml/100 g $\times$ min) (10), where k is the rate constant of Component I ($k = \ln 2 / T_{1/2}$), $T_{1/2}$ is the halftime of Component I. λ denotes the cutaneous tissue to blood partition coefficient for Xenon. In the calculations, a λ -value of 0.7 ml/g was used for cutaneous tissue (27).

When intracutaneous injection of tracer was used, the initial 10 min of the washout curve was discarded to

minimize the influence of the injection trauma (27). Student's *t*-test was used for comparison of paired data and the randomization test for comparison of unpaired data. As limit of significance 0.05 was chosen.

RESULTS

The washout curves were readily resolved into rapid and slow components from which clearance constants for cutaneous and subcutaneous tissue and blood flow in skin were calculated (Fig. 1). Exceptions to this rule were found in 2 patients with severe hidebound sclerosis on the dorsum of the hand. In these patients no slow components were obtained although washout was monitored over three decades (Fig. 2). This result was obtained irrespective of the labelling method. Flow results in these patients were then based on the initial slope of the washout curve. Arterial occlusion applied on the upper arm stopped the washout completely in these two cases (Fig. 2).

Comparison of epicutaneous and intracutaneous tracer application. In 12 normal persons, blood flow values after epicutaneous tracer application

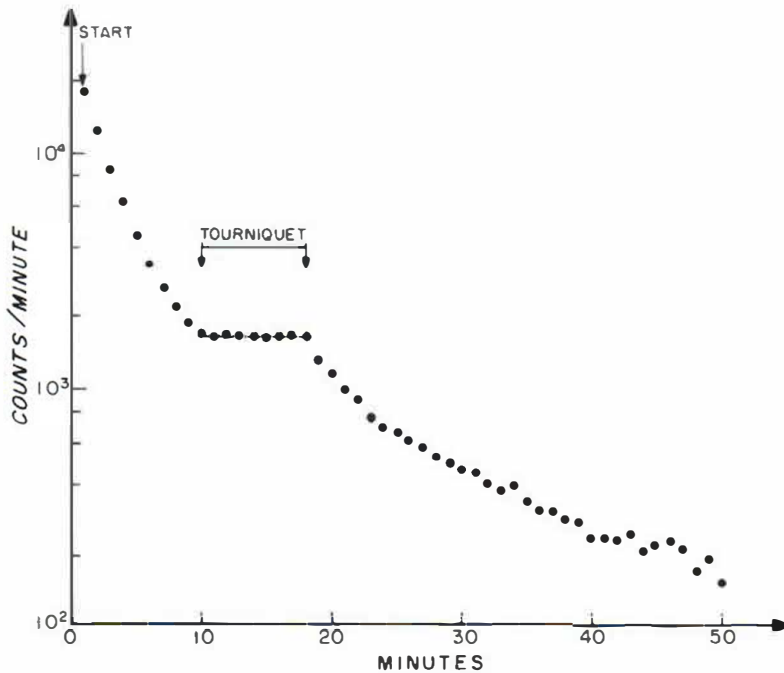


Fig. 2. ¹³³Xenon washout curve obtained from a patient with severe sclerosis on the dorsum of the hand. The result of arterial occlusion (tourniquet) with a cuff inflated to 200 mmHg is a complete cessation of washout. In this patient, the cutaneous washout constant was calculated on the basis of the initial slope washout constant (a straight line was drawn through the initial data points).

was 8.9 ± 0.4 S.E.M. ml/100 g $\times$ min and after intracutaneous application 8.8 ± 0.3 S.E.M. ml/100 g $\times$ min ($p > 0.8$). In 7 scleroderma patients flow values after epicutaneous tracer application was 13.7 ± 2.6 S.E.M. ml/100 g $\times$ min and after intracutaneous application 13.9 ± 2.9 S.E.M. ml/100 g min ($p > 0.6$). In the following, mean values are used in persons in whom multiple experiments were done.

Comparison of results in normals and in scleroderma patients. In the 18 normal persons, mean cutaneous blood flow on the dorsum of the hand was 8.6 ± 0.4 S.E.M. ml/100 g $\times$ min, while in the 26 patients, mean cutaneous blood flow was 14.5 ± 1.1 ($p < 0.001$). Mean subcutaneous clearance constant in normals was 0.0107 ± 0.0041 and in the patients 0.0237 ± 0.0148 ($p < 0.01$).

Grading of scleroderma. In Fig. 3 blood flow measurements in patients are grouped according to severity of cutaneous sclerosis and compared with the results in normals. "Slight" sclerosis: $f = 10.8 \pm 0.6$ S.E.M. (significantly different from normal, $p < 0.01$). "Moderate" sclerosis $f = 13.8 \pm 0.9$ (different from normal, $p < 0.001$). "Severe" sclerosis $f = 20.8 \pm 3.1$ S.E.M. (different from normal, $p < 0.05$). "Slight" sclerosis was significantly different from "moderate" sclerosis ($p < 0.01$) and

"moderate" sclerosis differed from "severe" sclerosis ($p < 0.05$).

DISCUSSION

The main finding in the present study is that the washout rate of ¹³³Xenon is increased in sclerodermic cutaneous tissue when compared with normal cutaneous tissue. This increase might be due to one, two, or three of the following possibilities: (a) that ¹³³Xenon in sclerodermic cutaneous tissue was lost from the application site by routes other than the blood flow; (b) that the tissue-blood partition coefficient (λ) was decreased in sclerodermic tissue as compared with normal skin, and (c) the increase in blood flow in sclerodermic cutaneous tissue.

Intactness of the epidermal diffusion barrier

The observations during occlusion of blood flow by a tourniquet (Fig. 2) agree with previous results on normal skin. ¹³³Xenon is not to any significant degree lost from the skin by diffusion into the air, signifying intactness of the epidermal diffusion barrier (12, 26).

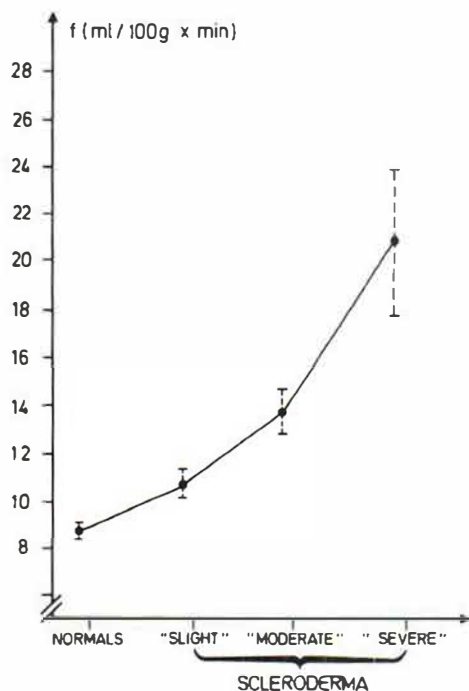


Fig. 3. Results of blood flow calculations in normals and in patients with increasing severity of dermal sclerosis. Bars signify mean blood flow ± 1 S.E.

Tissue-blood partition coefficient (λ)

The physical solubility of Xenon in a tissue can be calculated on the basis of the composition of the tissue when the solubility in the individual tissue component is known (28). The tissue components of significance in this connection are lipid, water and protein. In equation form it is stated as: solubility of gas in tissue = (solubility coefficient of lipid $\times$ % lipid) + (solubility coefficient of water $\times$ % water) + (solubility coefficient of protein $\times$ % protein).

In the case of normal cutaneous tissue, a λ -value of 0.7 ml/g has so far been used because cutaneous and muscle tissue correspond very closely in their composition with regard to lipid, water and protein (1, 27). Normal cutaneous tissue contains about 71.5% water, 27% protein and 1–2% fat (8). Some estimations of fat content provide upper values around 3.5% (24). In the case of scleroderma, quantitative estimations of fat content in cutaneous tissue have not been reported, but some histologic evidence of a decreased amount of fatty tissue in cutis and subcutis has been provided (7). There is no evidence that the water or protein content is

abnormal (5, 6). Assuming then as a worst case that sclerodermic cutaneous tissue contains no lipid, 73% water and 27% protein, the solubility of ^{133}Xe in sclerodermic tissue will be about 15% less than in normal cutaneous tissue. As the blood concentration of haemoglobin was similar in normals and patients, this indicates that λ of ^{133}Xe in cutaneous tissue is diminished by less than 15% in patients, as compared with normals. Thus maximally 20% of the observed increase in ^{133}Xe washout rate of about 69% from sclerodermic cutaneous tissue can be explained by a decrease in λ . The results therefore indicate that blood flow in cutaneous tissue on the dorsum of the hand is increased in GS as compared with normals.

Pathophysiology of blood flow in GS

The nature of the vascular disease in generalized scleroderma is not yet completely elucidated. The concept of a local defect of blood vessels put forward by Lewis and Landis (17) has been strengthened in recent years, in which evidence has been provided of widespread microvascular injury (3, 18, 20, 21, 22, 23, 25). The following alterations have been described: Reduction in the number of capillaries in skin and muscle, swelling of endothelial cells, thickening of the media of small arteries, hyaline or fibrinoid degeneration, intimal thickening by mucinous connective tissue, or by proliferation of mesenchymal cells and collagen deposition eventually leading to cutaneous necrosis. The nailfold capillary bed reveals dilated and distorted capillary loops alternating with avascular areas. Positive correlation was found between the degree and extent of abnormal microvascular patterns and multisystem involvement (18). Investigation of the size distribution of blood vessels in skin and muscle in scleroderma reveals an increase in the mean diameter due to dilatation of capillaries and an increased number of larger blood vessels (21, 25).

The present results constitute evidence of an increased blood flow in cutaneous tissue in GS, an increase which could be a result of a decrease in resistance to flow offered by defective, dilated arterioles.

Previous studies have provided evidence of defective intrinsic myogenic mechanisms in local regulation of blood flow in cutaneous tissue in GS (14) and a defective vasoconstrictor response in subcutaneous tissue (9, 13). The findings of the present study are compatible with these observations, indi-

cating that the mechanisms underlying local regulation of blood flow in cutaneous tissue are defective in generalized scleroderma.

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