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Subcutaneous Blood Flow in Psoriasis

PER KLEMP, M.D.

Departments of Dermatology and Clinical Physiology, The Finsen Institute, Copenhagen, Denmark

The simultaneously recorded disappearance rates of ^{133}Xe from subcutaneous adipose tissue in the crus were studied in 10 patients with psoriasis vulgaris using atraumatic labeling of the tissue in lesional skin (LS) areas and symmetrical, nonlesional skin (NLS) areas. Control experiments were performed bilaterally in 10 younger, healthy subjects.

The subcutaneous washout rate constant was significantly higher in LS, $0.79 \pm 0.05\ min^{-1} \cdot 10^2$ compared to the washout rate constant of NLS, $0.56 \pm 0.07\ min^{-1} \cdot 10^2$ ($p < 0.05$), or the washout rate constant in the normal subjects, $0.46 \pm 0.17\ min^{-1} \cdot 10^2$ ($p < 0.01$). The mean washout rate constant in NLS was 25% higher than the mean washout rate constant in the normal subjects. The difference was, however, not statistically significant.

Differences in the washout rate constants might be due to abnormal subcutaneous tissue-to-blood partition (λ) in the LS—and therefore not reflecting the real differences in the subcutaneous blood flow (SBF). The λ for ^{133}Xe was therefore measured—using a double isotope washout method (^{133}Xe and [^{133}I]antipyrine)—in symmetrical sites of the lateral crus in LS and NLS of 10 patients with psoriasis vulgaris and in 10 legs of normal subjects. In LS the λ was 4.52 ± 1.67 ml/g, which was not statistically different from that of NLS, 5.25 ± 2.19 ml/g ($p < 0.05$), nor from that of normal subcutaneous tissue, 4.98 ± 1.04 ml/g ($p < 0.05$).

Calculations of the SBF using the obtained λ values gave a significantly higher SBF in LS, 3.57 ± 0.23 ml/100 g/min, compared to SBF in the NLS, 2.94 ± 0.37 ml/100 g/min ($p < 0.05$). There was no statistically significant difference between SBF in NLS and SBF in the normal subjects.

The increased SBF in LS of psoriatics might be a secondary phenomenon to an increased heat loss in the lesional skin.

Recently, we have shown the cutaneous blood flow in lesional psoriatic skin to be 10 times higher than in normal subjects. In uninvolved psoriatic skin, cutaneous blood flow was approximately twice that of normal subjects [1].

Obviously, an increase of this magnitude in cutaneous blood flow in psoriatics should influence the systemic distribution of the cardiac output significantly in those with even moderate psoriatic involvement of the skin. The present study was initiated to determine whether this increase in cutaneous blood flow in patients with psoriasis is an expression of an overall higher peripheral tissue blood flow or the higher cutaneous blood flow is compensated by a lower subcutaneous blood flow (SBF). The measurements of the SBF were performed by the ^{133}Xe method.

MATERIALS AND METHODS

Patients

Twenty patients with typically untreated psoriasis involving 10–50% of the skin surface were examined after having given informed consent; their age and sex are shown in Tables I and II. Control experiments were performed in another 5 patients with psoriasis aged 40–18 years (mean 30 ± 9 SD years) and in 10 normal healthy subjects. Neither the patients nor the normal subjects received any medication that could interfere with blood flow, and habitual smokers abstained from smoking at least 3 h before the experiments started since smoking might interfere with cutaneous and subcutaneous blood flow for approximately 1 h [2,3].

Only patients with unilateral psoriatic plaques more than 10 cm in diameter on the crus and symmetrically normal skin were selected for this study. All measurements were performed with the patients in the supine position and at constant room temperature, 20–21°C.

Measurement of Subcutaneous Blood Flow

The SBF was measured by the ^{133}Xe washout method [4]. Atraumatic epicutaneous labeling technique was used as recently described [1]. After a labeling period of 3–3½ min, 2 NaI scintillation detectors were placed 15 cm above the radioactive fields and connected to a 2-channel printing gamma-spectrometer. The accumulated activity was printed out simultaneously from both sites at intervals of 20 s and followed for at least 70–90 min in the psoriatics and 90–120 min in the normal controls. A lead shield was placed between the legs in order to ensure that only one measuring field was seen by one detector.

The washout curve following epicutaneous labeling bends spontaneously in a semilogarithmic plot due to washout of the tracer from the cutaneous tissue and to accumulation of the tracer in subcutaneous adipose tissue. ^{133}Xe is highly soluble in lipid and the rate of removal from the subcutaneous fat is therefore slow. A monoexponential washout curve was identified after approximately 15–20 min in the psoriatics and after approximately 30–40 min in the normal subjects. This monoexponential washout represents the washout of the tracer from the subcutaneous tissue. The washout rate constant (k) was computed from the monoexponential washout plot 40–60 min after labeling and after correcting for background activity using the equation:

$$k_{subc} = \frac{\ln 2}{T_{1/2}}\ (min^{-1}) \qquad (1)$$

where $T_{1/2}$ is the time in minutes for the decay of the monoexponential washout to half the initial value.

Control experiments were performed in 5 patients in whom 100 μCi ^{133}Xe dissolved in 0.03–0.06 ml isotonic saline was injected simultaneously on symmetrical sites into the subcutaneous tissue of lesional skin (LS) and nonlesional skin (NLS). The washout rate constant was then calculated from the monoexponential washout 60–70 min after the injection, since the injection trauma, which induces hyperemia, might last for 30–40 min in subcutaneous tissue [5].

The SBF can then be calculated from the Kety equation:

$$SBF = k_{subc} \cdot \lambda_{subc} \cdot 100 (ml/100g/min) \qquad (2)$$

where λ_{subc} denotes the tissue-to-blood partition coefficient for ^{133}Xe in subcutaneous tissue.

However, since there are no reported data on the partition coefficient between subcutaneous tissue and blood in psoriatics and since substantial variation from the conventionally used $\lambda_{subc} = 10$ ml/g was recently reported in other patients [6], it was necessary to measure the tissue-to-blood partition coefficient in subcutaneous adipose tissue of the crus of both normal subjects and psoriatics.

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Reprint requests to: Per Klemp, M.D., Departments of Dermatology and Clinical Physiology, The Finsen Institute, Strandboulevarden 49, DK-2100 Copenhagen Ø, Denmark.

Abbreviations:
LS: lesional skin
NLS: nonlesional skin
SBF: subcutaneous blood flow

Measurement of λ_{subc} by a Double Isotope Washout Method

A mixture of ^{133}Xe (100 μCi) and [^{131}I]antipyrine (30–50 μCi) was injected s.c. laterally on the calf. The γ emission of ^{133}Xe and ^{131}I was detected simultaneously with 2 NaI scintillation detectors connected to a 2-channel gamma-spectrometer with one window set around the photopeak of ^{131}I and the other around the photopeak of ^{133}Xe. Prior to the experiments the "cross talk" (i.e., the γ emission from the ^{131}I detected by the ^{133}Xe channel and the γ emission from the ^{133}Xe detected by the ^{131}I channel) was determined and the obtained count rates from a measuring period of 10–15 min starting 45–60 min after the injection was then corrected for background activity and the "cross talk."

Since the perfusion rates are equal for the washout of both isotopes injected in the same area

$$\lambda_{Xe} \cdot k_{Xe} = \lambda_{I\text{-antipyrine}} \cdot k_{I\text{-antipyrine}} \quad (3)$$

and assuming $\lambda_{I\text{-antipyrine}}$ is 1.0 ml/g [6], the ^{133}Xe for subcutaneous tissue can be calculated

$$\lambda_{Xe} = \frac{\lambda_{I\text{-antipyrine}} \cdot k_{I\text{-antipyrine}}}{k_{Xe}} \quad (4)$$

The principles of the double isotope washout method for determination of the tissue-to-blood partition coefficient are seen in Fig 1. The method has recently been described [6]. To block thyroid iodine uptake, potassium iodide was given for 5 days.

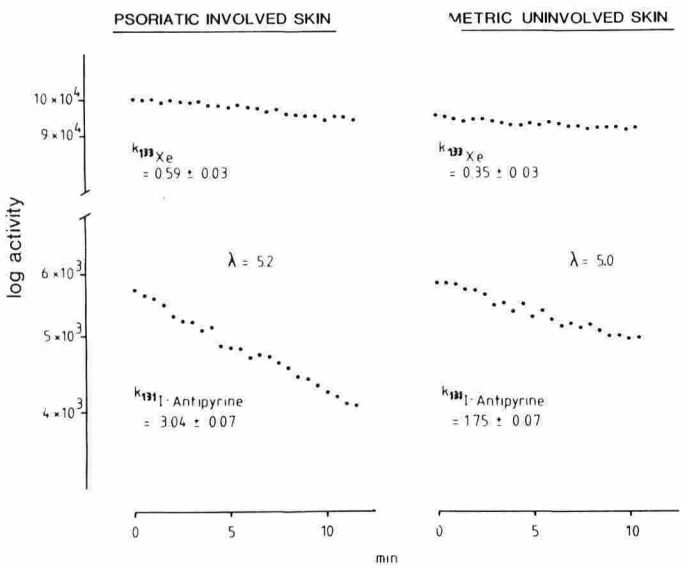

FIG 1. Principles of tissue-to-blood partition coefficient measurements in subcutaneous tissue using double isotope washout technique. ^{133}Xe and [^{131}I]antipyrine washout curves (corrected for background activity and "cross talk") from the subcutaneous depots. The tissue-to-blood partition coefficient for ^{133}Xe in the subcutaneous tissue was calculated by dividing the washout rate constant for [^{131}I]antipyrine by the washout rate for ^{133}Xe (patient no. 1, Table I).

Statistics

Linear correlation by the least squares method and Wilcoxon rank sum test for paired and unpaired samples were used to analyze the data. A $p < 0.05$ was chosen as the limit of significance. The washout rate constant, k, was expressed as k · 10^2 min^{-1}. The coefficient of variation, C.V., was calculated from the SD of the washout rate constants of k_{Xe} and $k_{I\text{-antipyrine}}$ using the formula

$$\text{C.V.} = \sqrt{\frac{(^{SD}k_{I\text{-antipyrine}})^2}{(k_{I\text{-antipyrine}})^2} + \frac{(^{SD}k_{Xe})^2}{(k_{Xe})^2}} \quad (5)$$

RESULTS

Subcutaneous Tissue-to-Blood Partition Coefficient for Xe

Three experiments in the psoriatics failed due to technical reasons (too low radioactivities). The mean tissue-to-blood partition coefficient in LS was $\lambda_{subc,psor} = 4.52 \pm 1.66$ ml/g and in NLS $\lambda_{subc,unpsor} = 5.25 \pm 2.19$ ml/g. There was no statistical difference between $\lambda_{subc,psor}$ and $\lambda_{subc,unpsor}$, $p > 0.05$.

In the group of younger, healthy subjects the subcutaneous tissue-to-blood partition coefficient was $\lambda_{subc} = 4.98 \pm 1.04$ ml/g, which was not statistically different from either $\lambda_{subc,psor}$ ($p > 0.05$) or $\lambda_{subc,unpsor}$ ($p > 0.05$). In 3 of the normal subjects who were measured on symmetrical areas, the mean side-to-side C.V. was 35% (range, 0.2–66%). The results are shown in Table I.

Subcutaneous Blood Flow

In 9 of 10 measurements the subcutaneous washout rate constant in LS was higher than the washout rate constant in symmetrical NLS (Table I). The mean washout rate constant in LS was 0.79 ± 0.15 min^{-1} and in symmetrical NLS was 0.56 ± 0.21 min^{-1}. The difference was statistically significant, $p < 0.05$. In the group of 10 younger normal subjects the mean washout rate constant was 0.46 ± 0.19 min^{-1} on the right side of the crus and simultaneously symmetrical measurement of the left side gave 0.46 ± 0.17 min^{-1}. There was no statistically significant difference between the two sides ($p > 0.05$) although

TABLE I. *Subcutaneous tissue-to-blood partition coefficient for ^{133}Xe (λ_{subc} ± C.V. ml/g) in psoriatic lesional skin (LS), in nonlesional skin (NLS) and in normal skin (NS) of normal subjects—simultaneous measurements in symmetrical sites using double isotope washout method (^{133}Xe and [^{131}I]antipyrine)*

		Psoriatric patients			Normal subjects			
Patient no.	Sex	Age	LS	NLS	Sex	Age	NS	
1	F	59	5.15 ± 0.06	5.00 ± 0.09	M	26	3.81 ± 0.03	
2	F	78	5.84 ± 0.13	5.82 ± 0.24	M	27	6.03 ± 0.02	Symmetric sites
3	F	26		4.89 ± 0.19	M	27	4.00 ± 0.03	
4	F	60	3.40 ± 0.09	9.17 ± 0.10	F	27	5.21 ± 0.10	Symmetric sites
5	F	50	6.75 ± 0.09		F	27	5.22 ± 0.31	
6	F	35	6.69 ± 0.09	7.38 ± 0.20	F	26	5.17 ± 0.04	
7	M	27	2.07 ± 0.07	2.67 ± 0.15	M	29	5.80 ± 0.06	
8	M	29	3.02 ± 0.18	3.00 ± 0.06	M	24	6.21 ± 0.11	Symmetric sites
9	F	64	3.96 ± 0.28	4.07 ± 0.13	M	24	3.04 ± 0.02	
10	M	63	3.79 ± 0.08		M	23	5.34 ± 0.07	
Mean		49	4.52	5.25		26	4.98	
±1 SD		19	1.66	2.19		2	1.04	
p			NS		NS			
			NS					

TABLE II. *Simultaneous measurements of ^{133}Xe washout rate constants ($k \cdot 10^2 \pm 1$ SD min^{-1}) from symmetric sites of the crus in lesional psoriatic skin (LS) and nonlesional skin (NLS) compared to measurements in younger, normal subjects—subctuaneous blood flow (SBF ± 1 SD ml/100g/min)*

	Psoriatic patients				Normal subjects			
Patient no.	Sex	Age	LS (k ± 1 SD)	NLS (k ± 1 SD)	Sex	Age	Right (k ± 1 SD)	Left (k ± 1 SD)
1	M	25	0.68 ± 0.02	0.46 ± 0.01	F	20	0.26 ± 0.01	0.45 ± 0.01
2	F	15	0.95 ± 0.02	0.39 ± 0.01	M	26	0.55 ± 0.06	0.52 ± 0.01
3	M	18	0.67 ± 0.06	1.00 ± 0.03	M	27	0.56 ± 0.02	0.62 ± 0.01
4	F	16	0.88 ± 0.04	0.50 ± 0.03	F	27	0.77 ± 0.02	0.43 ± 0.01
5	F	43	0.58 ± 0.02	0.48 ± 0.02	F	26	0.56 ± 0.01	0.37 ± 0.01
6	F	26	0.81 ± 0.02	0.25 ± 0.05	M	29	0.58 ± 0.01	0.83 ± 0.01
7	F	82	0.74 ± 0.12	0.51 ± 0.03	F	22	0.25 ± 0.01	0.26 ± 0.01
8	F	37	1.06 ± 0.03	0.56 ± 0.02	F	25	0.20 ± 0.01	0.25 ± 0.01
9	F	23	0.68 ± 0.01	0.61 ± 0.01	M	24	0.53 ± 0.01	0.39 ± 0.01
10	F	60	0.87 ± 0.01	0.82 ± 0.01	M	23	0.33 ± 0.01	0.44 ± 0.01
Mean		35	0.79	0.56		25	0.46	0.46 0.46
±1 SD		22	0.15	0.21		3	0.19	0.17 0.17
P				<0.05				NS
								NS
				<0.01				
SBF ml/100g/min			3.57	2.94				2.36
±1 SD			0.68	1.94				0.87

the side-to-side coefficient varied from 3.9–56.7% (mean 28.8%). There was no statistically significant difference between the washout rate constant in normal subjects and the washout rate constant in NLS in the psoriatic patients ($p > 0.05$). Using the obtained λ values, the mean SBF was 3.57 ± 0.68 ml/100 g/min in LS, and in symmetrical NLS areas 2.94 ± 1.94 ml/100 g/min. In the group of normals the mean SBF was 2.36 ± 0.87 ml/100 g/min. The results are summarized in Table II.

In all 5 control patients in whom SBF was measured after s.c. injection of ^{133}Xe the SBF was higher in the LS compared to the symmetrical NLS, 3.75 ± 0.41 ml/100 g/min and 3.05 ± 0.21 ml/100 g/min, respectively.

DISCUSSION

Selective measurements of SBF in psoriatics have not previously been published. Venous occlusion plethysmographic measurements might give rough selective quantitative estimations of the SBF. This method demands complicated subtraction procedures to correct for the cutaneous and the muscle blood flow. However, the conclusions from previous plethysmographic investigations in psoriatics [7,8] did not account for a possible subcutaneous pathologic involvement in psoriatic peripheral blood flow. The tracer washout technique seems today the most precise method for selective quantitative measurements of local tissue blood flow. ^{133}Xe being an inert gas, it is freely diffusible in tissue and the washout from the tissue is therefore entirely perfusion limited. The ^{133}Xe washout method can be used if (1) the tissue is homogenous in structure, and (2) homogenously perfused. Both these assumptions seem a priori reasonably fulfilled for the subcutaneous tissue. The possibility of local, small area variations in subcutaneous tissue blood flow does exist. Using a relatively large labeling area—as in this study (10 cm^2)—should theoretically minimize this effect. Assuming that no recirculation of the tracer takes place, the decay in tracer concentration with time [c(t) where C_0 is the initial concentration] is described by an equation of monoexponential washout

$$c(t) = C_0 \cdot e^{-k \cdot t} \quad (6)$$

where the rate constant is the perfusion coefficient divided by the partition coefficient for ^{133}Xe between the subcutaneous tissue and blood [see equation (2)]. The xenon washout method has, however, its own limitations. First, generally it is an empirical finding that the washout rate constant from subcutaneous tissue is not ideally constant but tends to diminish with time (less than a few percent per hour), thus indicating that the best perfused parts of the labeled tissue have a more rapid washout. For practical purposes this factor is of minor importance.

Second, and of much more importance for the interpretation of the results, is the fact that a precise quantitative estimation of the SBF demands the knowledge of the tissue-to-blood partition coefficient for all the tracer-marked subcutaneous tissue. The solubility coefficients for xenon are highest in lipids and hemoglobin, and the content of these substances in the tissue and blood will be the major determinants of the partition coefficient. The tissue contents of proteins and water as well as differences in the tissue temperature will be of minor importance in nonedematous subjects at rest. Biochemical analyses of human adipose tissue have shown that the lipid contents may vary considerably in different anatomic regions and possibly also in symmetrical sites [9–11]. ^{133}Xe washout rates from symmetrical sites in the individual subjects might therefore solely reflect differences in washout rates and not real differences in the SBF.

An exact estimation of the regional lipid, protein, and water content in the individual experimental subject is, however, impossible for obvious practical reasons. In this study the λ_{subc} was estimated in involved and uninvolved subcutaneous tissue in a group of younger normal subjects as well as in patients, using double isotope washout techniques. This method seems of great clinical importance since it is easy to practice and has a small traumatizing effect on the patient. The amount of free radioactive iodine might influence the recorded washout rates for [^{133}I]antipyrine [12] since iodinated antipyrine is not stable in saline for more than hours and in water for more than days [13]. However, the amount of free iodine in the phosphate buffer of pH = 7.0 was less than 1% (according to the manufactor) and therefore of no significance. Measurements in lead-shielded, more distal areas of the legs showed only background activity and recirculation of [^{131}I]antipyrine was therefore of no importance for the results. In the calculations of λ_{Xe} a λ for antipyrine was assumed to be equal to 1.00 ml/g. This value might be slightly underestimated [6,13]. Furthermore, the injection volume of both isotopes should per se tend to dilute the subcutaneous fat contents. The obtained calculated figures for λ_{Xe} are therefore minimum values. Previously, a $\lambda_{subc} = 10.0$

ml/g has been recommended, but as Sejrsen pointed out this was only a mean λ value for all human subcutaneous tissue [4]. The results of this study show that measurements of the regional variations of the λ values should be performed when using the ^{133}Xe washout method for estimating absolute values of blood flow rates.

Since there was no significant difference between λ_{psor}, λ_{unpsor}, and λ_{subc} of normal subjects, it might therefore be concluded that the mean difference in the regional washout rate constants of a group of subjects reflects real differences in SBF in that region. The reason for the increased SBF in involved psoriatic skin is not clear. Although many reports during recent years have given much evidence of extracutaneous psoriatic manifestations (as reviewed in [14]), no abnormalities in the psoriatic subcutaneous microvasculature have been published.

It must be assumed that the blood supply to the subcutaneous tissue in psoriatics resembles that of normal subjects. Briefly, the blood supply to the rich capillary bed of subcutaneous adipose tissue originates chiefly from the deep subcutaneous plexus (also called the fascial network) and from ascending arteries throughout the subcutaneous tissue. The upper part of the subcutaneous tissue receives its blood supply from arterial branches of the subdermal plexus. It is therefore generally accepted that subcutaneous tissue receives its blood supply independently of the cutaneous blood supply.

The valve containing collecting veins at the cutaneous–subcutaneous junction, as recently described by Braverman [15], strongly supports the assumption that the vascular beds of the cutaneous and subcutaneous tissues functionally may act separately. However, both these vascular beds are supposed to act physiologically as integral parts in the temperature homostasis. The significantly increased SBF in psoriatic lesional skin areas might therefore be explained as a secondary phenomenon to an increased cutaneous temperature in the psoriatic skin due to the raised cutaneous blood flow leading to an increased subcutaneous temperature. The tendency to a slightly increased SBF in uninvolved psoriatic skin areas is in accordance with a twofold raised cutaneous blood flow in uninvolved psoriatic skin [1]. Another explanation might be that the observation of significantly increased SBF is new evidence of extracutaneous psoriatic manifestation of the disease. However, biochemical and histologic evidence for such an assumption is lacking.

Clinically the results of this study should imply that the absorption of s.c. injected drugs (i.e., insulin and morphine) into lesional psoriatic skin areas might be significantly increased, and unexpected effects might therefore occur. Moreover, even a moderate psoriatic involvement should be a further strain to psoriatics with heart failure due to the increased peripheral blood flow in both cutaneous and subcutaneous tissues.

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