Control of Cutaneous Blood Vessels in Psoriatic Plaques

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The aim of this study was to compare local blood flow in psoriatic plaques before and after provocations known to alter cutaneous vascular resistance, in order to determine whether plaque hyperemia is caused by a failure of normal vascular control mechanisms. Cutaneous blood flow was recorded using a laser Doppler flowmeter over plaque skin (plaque site) and clinically normal skin (nonplaque site) on the opposite arm, at least 5 cm away from the nearest plaque. It is important to note that most of the laser Doppler signal comes from the subpapillary plexus of the skin and only a small portion (2%–10%) is produced by capillary blood flow. In the psoriatic plaques the basal flux was between nine and 13 times greater than nonplaque skin. The biologic zero (a signal independent of perfusion, which also persists after complete proximal arterial occlusion) was also significantly greater at plaque sites compared with nonplaque sites. Sympathetic and local vasoconstriction in psoriatic skin was shown to be intact and responses to vasodilator tests were likewise intact, i.e., there was no failure of response to normal vascular control mechanisms, albeit some quantitative differences. Tests of vasodilatation indicated that, although basal flux is high in plaque compared with nonplaque skin, arterioles supplying plaque skin can dilate further, i.e., lesional arterioles are not normally maximally dilated but have a basal constrictor tone. Interestingly, the red cell flux at maximum dilatation in nonplaque skin is less than even the basal flux in plaque skin. This means that in plaque skin either there are more arterioles than in nonplaque skin, or there is chronic, structural widening of the existing arterioles in plaque skin. Key words: autonomic control/blood vessels/psoriasis. J Invest Dermatol 113:127–132, 1999

Microvascular abnormalities are a characteristic histopathologic feature of psoriasis. Both histologic and intravital capillaroscopic studies have shown elongation and tortuosity of the capillary loop within the papillary dermis (Mordovstev and Albanova, 1989; Bull et al, 1992). Morphometric analysis of the vascular changes in psoriasis has shown that there is an increase in the capillary mass, compared with normal skin, along with structural expansion of the capillaries within psoriatic lesions and to a lesser extent in clinically uninvolved skin in the same patients (Barton et al, 1992). Other studies have demonstrated that the structural expansion and increased tortuosity of the dermal capillary loops occurs early in the progression of a lesion, before epidermal hyperplasia can be detected histologically or clinically (Pinkus and Mehregan, 1961; Telner and Fekete, 1961; Speight et al, 1993). Furthermore, when these structurally expanded capillaries are selectively destroyed with yellow light lasers, the psoriatic plaque clears. Patients responding to treatment with a pulsed dye laser can remain in remission for up to 13 mo at treatment sites (Zelickson et al, 1996). The tortuous, widened, elongated capillaries therefore play a central role in the pathogenesis of psoriasis and indeed they form one of the pathologic criteria for diagnosis.

The expanded capillary bed in psoriasis has an increased blood flow. Blood flow is principally determined, however, by feeding resistance vessels (arterioles and terminal arteries), concerning which little is known in psoriasis. Our aim was to compare blood flow before and after provocations that alter cutaneous vascular resistance, in order to test whether the increased flow was caused by a failure of normal vascular control processes in plaque skin. Clinically uninvolved skin in the same subject served as a control.

Vascular control was investigated by applying a range of provocations previously shown in our laboratory to produce reliable alterations in cutaneous vascular resistance in healthy subjects (Stanton et al, 1995). These tests have also been used to assess the control of blood flow in the arms of women with chronic postmastectomy edema (Stanton et al, 1996). The provocations and the accepted physiologic mechanisms of regulation concerned are as follows: reactive hyperemia (R/H; locally mediated vasodilatation), core heat load (sympathetically mediated vasodilatation), inspiratory gap and cool reflex (CR; both sympathetically mediated vasoconstriction), and arm dependency (AD; locally mediated vasoconstriction). Cutaneous blood flow was recorded using a laser Doppler flowmeter.

The control of the cutaneous circulation differs dramatically between these sites, our investigations were limited to the forearm and elbow. Furthermore, the original work in our laboratory to validate the provocation tests, in healthy subjects and in disease, was originally performed on the forearm (Stanton et al, 1992).
Table I. Summary of the tests of forearm and elbow cutaneous vascular control in the sequence in which they were performed

<table>
<thead>
<tr>
<th>Tests</th>
<th>Proposed mechanism</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 and 6. BZ</td>
<td>Non-flow related signal</td>
<td>Colantuoni et al (1993)</td>
</tr>
<tr>
<td>RH</td>
<td>Myogenic and/or local vasodilator chemical factors</td>
<td>Wahlberg et al (1992)</td>
</tr>
<tr>
<td>2. IG</td>
<td>Increased sympathetic vasoconstrictor nerve activity</td>
<td>Shepherd (1963)</td>
</tr>
<tr>
<td>3. AD</td>
<td>Locally derived vasoconstriction mediated by a myogenic or local axon reflex</td>
<td>Browse and Hardwick (1969)</td>
</tr>
<tr>
<td>5. CHL</td>
<td>Increased sympathetic vasodilator nerve activity</td>
<td>Levick and Michel (1978)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Henriksen (1976)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pickering (1933)</td>
</tr>
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<td></td>
<td></td>
<td>Pickering, 1933</td>
</tr>
</tbody>
</table>

1995; Stanton et al, 1996). Forearm plaques were also selected for comfort and convenience.

MATERIALS AND METHODS

Patients Nine white, European patients (four men and five women), aged 25–67 y (mean 45 y), with mild to moderate plaque psoriasis participated in this study. Approval was obtained from our Local Ethics Committee and informed consent given. Topical therapies were stopped 3 wk prior to the investigation. Phototherapy (psoralen ultraviolet A and ultraviolet B) had been discontinued for at least 3 mo prior to the study and none of the patients was on systemic therapy. No descaling treatment was applied prior to measurements. The use of simple emollients was permitted throughout. All the patients were otherwise healthy and normotensive.

Subjects emptied their bladders and sat with their arms and legs exposed in a temperature-controlled laboratory (25.0 ± 0.6°C; mean ± SD). The forearms were supported by armrests at heart level and subjects acclimatized for 20 min while the probes were attached. Laser Doppler red cell flux (LDF, Moor Instruments MBF3D, Axminster, Devon, U.K.) was recorded from psoriatic plaques on the forearm or elbow (plaque site) and from clinically uninvolved skin at an equivalent site on the opposite limb (nonplaque site). Non-plaque skin sites were selected for study at least 5 cm from the edge of the nearest plaque.

LDF output was set at 100 arbitrary units (AU) equivalent to 2.5 V. The time constant was 1.0 s. Before the start of each experiment, the laser Doppler probes (P1) were placed on a white plastic surface and the instrumental zero recorded. This was 0.03 AU and was ignored when recording LDF.

Skin temperatures (Tsk) were recorded from each forearm (Tele-thermometer, Yellow Springs Instruments, OH). Core temperature (Tc) was recorded sublingually using a clinical thermometer.

In the previous studies by our group (Stanton et al, 1995, 1996), local vascular resistance was calculated as digital blood pressure/red cell flux. Although small, transient changes in blood pressure were evoked by some of the tests, the red cell flux and resistance changed in parallel. In this study therefore changes in red cell flux are taken to reflect changes in local vascular resistance.

Tests were performed in sequence as outlined below (see Table I). The basal flux was recorded for 20 s before each test.

Tests 1 and 6: biologic zero (BZ) and RH  The BZ flux signal is the signal that persists after complete proximal arterial occlusion. It is not related to tissue perfusion (Colantuoni et al, 1993) and its origin remains obscure. BZ flux was subtracted from all flux readings as recommended by others (Wahlberg et al, 1992; Colantuoni et al, 1993). To measure BZ, arterial blood flow into the arm was arrested for 2 min by placing a sphygmomanometer cuff around the upper arm and inflating it to 200 mmHg. The cuff was then rapidly deflated by abruptly breaking the connection and the subsequent peak RH recorded.

RH is a vasodilator response mediated by myogenic and/or local chemical factors (Shepherd, 1963). Time to reach the peak response for RH was measured from the moment the cuff was released to the midpoint of the peak response. The area under the curve was also calculated. This gives a measure of the cumulative response to the RH test as it takes into account the duration of the response along with the magnitude.

Test 2: inspiratory gasp (IG2–3) Sharp, deep inspiration results in a reflex cutaneous vasoconstriction mediated by increased activity in sympathetic vasoconstrictor nerves (Browse and Hardwick, 1969). Subjects were asked to inhale deeply and rapidly, hold their breath for 5 s and then quickly exhale and breathe normally. This was performed three times, at 1 min intervals.

Test 3: arm dependency (AD)  Lowering the arm below heart level elicits the veno-arteriolar response, a locally derived vasoconstrictor response mediated by a myogenic or local axon reflex (Henrikсен, 1976; Levick and Michel, 1978; Hasan and Tooko, 1988). Each arm was lowered in turn and allowed to hang in the dependent position for 2 min, such that the recording site and attached laser Doppler probe was 25–30 cm below heart level.

Test 4: cool reflex (CR1–2) The CR is a reflex vasoconstrictor response mediated by increased activity in sympathetic vasoconstrictor nerves (Pickering, 1933). Subjects immersed both feet in water at 15°C for 1 min. The feet were then transferred to water at 33°C (thermonutral) for 2 min before the test was repeated. The temperature of the water for the CR test was maintained at 15°C because lower temperatures may activate pain fibers, with a resultant reflex rise in blood pressure.

Test 5: core heat load (CHL) Indirect heating of the body results in a reflex vasodilation in the skin mediated by increased activity of sympathetic vasodilator nerves (Pickering, 1933). After removal of the feet from the cool water (CR), subjects were asked to place both legs, to just below the level of the knee, into a deep container of water at 45°C. In order to minimize transient movement artifacts in the LDF recording patients were assisted with this maneuver. The temperature of the water was maintained by a Thermocirculator (Harvard Instruments, Edenbridge, Kent, U.K.). The legs were heated in this manner for 30 min. In the first five subjects, the core temperature was slow to rise. Therefore, for the last four individuals, a domestic electric blanket draped around the shoulders was used to provide additional heating (Stanton et al, 1995). By the end of the 30 min period Tc had risen by 0.4 ± 0.2°C. Tsk had increased by 0.3 ± 0.4°C on the nonplaque forearm and by 0.6 ± 0.6°C on the plaque forearm. This difference in Tsk between the arms did not quite reach conventional significance, p = 0.06 where n = 9.

Statistics Results are presented as mean ± SD. Paired analysis was performed using the Student’s t-test. Where results were skewed, logarithmic transformations were calculated (denoted by an asterisk in the text when used) in order to normalize their distribution. Probability values of 0.05 or less were taken as significant differences. Unless otherwise indicated in the text, n = 9 for RH1 and AD and n = 8 for RH2, CHL, and CR1–2.

RESULTS

Basal flux After values were corrected for the BZ, the ratio of the red cell flux at the plaque site to the nonplaque site at the beginning of the protocol was 13.1 ± 10.3. The mean red cell flux in plaques was 200.5 ± 134.6 AU (n = 9) and in nonplaque sites was 18.5 ± 13.1 AU (n = 9). This difference in red cell flux between the two sites was significant, p < 0.01.

When measured again at the end of the experiment the ratio of the red cell flux at the plaque site to the nonplaque site was 9.3 ± 8.4. The mean red cell flux in plaques was 121.7 ± 101.5 AU (n = 8) and in nonplaque sites was 15.1 ± 10.0 AU (n = 8). This difference in red cell flux between the two sites was also significant, p = 0.01.
BZ and RH  BZ at the nonplaque sites was 3.9 ± 0.63 AU and at the plaque sites was 5.7 ± 3.5 AU, where n = 17 (BZ1 and BZ2 combined). This difference in BZ between the two sites was significant, p < 0.04. The BZ1 was then subtracted from all the remaining results (below) as recommended by others (Wahlberg et al., 1992; Colantuoni et al., 1993).

Results for the RH responses are illustrated in Fig. 1. Both baseline and maximal flux are greater in the plaque than the nonplaque sites. When the ratio of maximum to baseline responses are calculated, however, the nonplaque site demonstrates a greater magnitude of change (Table II).

Time to attain peak response at the start of the experiment was 8.8 ± 2.5 s at the nonplaque site and 22.0 ± 10.9 s at the plaque site. This difference in times between the two sites is significant, p < 0.03. Values were similar from a vasodilated baseline, namely 10.0 ± 5.2 s at the nonplaque site and 19.0 ± 5.2 s at the plaque site. Once again the difference in time to attain the peak response between the two sites is significant, p = 0.02. Therefore, plaque skin takes significantly longer to attain the peak response than nonplaque skin.

At the start of the experiment the area under the hyperemia curve was 1712.7 ± 1245.5 AU s at the nonplaque site and 4659.0 ± 2224.0 AU s at the plaque site. The difference in area under the curve between the two sites is significant, p < 0.01. At the end of the protocol area under the curve at the control site was 1108.2 ± 1100.8 AU s and at the plaque site was 3685.8 ± 1201.2 AU s. Again there was a significant difference in area under the curve between the nonplaque and plaque sites, p < 0.01. Figure 2 demonstrates an RH response as recorded by the laser Doppler.

Inspired gas  All three inspirations were associated with a fall in red cell flux (Fig 3), although in all cases flux rose transiently before falling. The reduction in flux was significant for each of the three inspirations, in both the nonplaque and plaque sites. When ratios of minimum to basal flux were analyzed, the ratio was significantly smaller for nonplaque skin (0.52 ± 0.28) than plaque skin (0.64 ± 0.16), t = 0.01.

In all three tests, there was no significant difference in the time to attain the maximum response for nonplaque and plaque sites. For IG1 this was 8.0 ± 3.1 s at the nonplaque site and 7.9 ± 2.9 s at the plaque site, p = 0.9. For IG3, the nonplaque site took 8.1 ± 2.8 s to reach the peak response and the plaque site took 7.7 ± 2.2 s, p = 0.4. In IG2, the nonplaque site took 9.7 ± 4.6 s and the plaque site took 7.4 ± 1.9 s, p = 0.2.

Arm dependency  Following an initial, brief rise in red cell flux (a movement artifact), flux fell and stabilized at a level below baseline (Fig 4). Basal red cell flux was 17.0 ± 10.6 AU at the nonplaque site and 192.5 ± 115.9 AU at the plaque site. The reduced flux at the nonplaque site was 7.4 ± 6.0 AU and 116.0 ± 102.9 AU at the plaque site. The reduction in flux at both the nonplaque and plaque sites was significant (p < 0.01 at the nonplaque site and at the plaque site). Ratios of the reduced, dependent flux to basal flux were calculated for both nonplaque (0.42 ± 0.22) and plaque sites (0.55 ± 0.19). The ratio was significantly smaller at the nonplaque site, t = 0.03.

Cutaneous CR  Initial movement artifacts were ignored. Thereafter, the CR caused a fall in the red cell flux to below baseline. The results of the response are illustrated in Fig. 5. When ratios of minimum to basal flux for nonplaque and plaque sites were compared, these were not significantly different in both CR1 and CR2. For CR1, the ratio at the nonplaque site was 0.56 ± 0.29 and the plaque site was 0.63 ± 0.19, t = 0.3. For CR2, the ratio at the nonplaque site was 0.62 ± 0.29 and the plaque site was 0.61 ± 0.19, t = 0.4. When the results for both experiments were pooled, once again the ratio of minimum to basal flux was not significantly different between the two sites (Table IV).

Core heat load  This resulted in a progressive, bilateral increase in red cell flux, which was more marked in four subjects where an electric blanket was used to provide additional heating. The basal red cell flux of 15.1 ± 10.0 AU at the nonplaque site was less than that at the plaque site (121.7 ± 101.5 AU). The maximum flux attained at the nonplaque site was also less (63.3 ± 59.8 AU) than at the plaque site 216.7 ± 171.7 AU.

Ratios of maximum to basal values were calculated for both nonplaque and plaque sites. The nonplaque site showed an increase of 5.7 ± 3.1 times, whereas the increase at the plaque site was 1.9 ± 0.77 times. The difference in the response ratio between
Table II. Summary of red cell flux measured during the RH response at the beginning (RH1) and end (RH2) of the protocol

<table>
<thead>
<tr>
<th></th>
<th>Non-plaque (NP)</th>
<th>Plaque (P)</th>
<th>Ratio of P/NP</th>
<th>p value for P versus NP</th>
</tr>
</thead>
<tbody>
<tr>
<td>RH1 (Basal flux (AU))</td>
<td>18.5 ± 13.1</td>
<td>200.5 ± 134.6</td>
<td>13.1 ± 10.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>82.3 ± 35.3</td>
<td>319.4 ± 165.0</td>
<td>4.3 ± 2.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Ratio of maximum flux/basal flux</td>
<td>5.1 ± 2.0</td>
<td>1.9 ± 0.74</td>
<td>—</td>
<td>&lt;0.001ᵇ</td>
</tr>
<tr>
<td>p value for maximum versus basal response</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Table III. Summary of red cell flux measured during the inspiratory gasp responses (IG1–3)

<table>
<thead>
<tr>
<th></th>
<th>Non-plaque (NP)</th>
<th>Plaque (P)</th>
<th>Ratio of P/NP</th>
<th>p value for P versus NP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal flux (AU)</td>
<td>19.0 ± 13.3</td>
<td>188.8 ± 113.2</td>
<td>12.2 ± 8.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Minimum flux (AU)</td>
<td>8.8 ± 6.1</td>
<td>114.1 ± 61.7</td>
<td>20.8 ± 20.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Ratio of minimum flux/basal flux</td>
<td>0.52 ± 0.28</td>
<td>0.64 ± 0.16</td>
<td>—</td>
<td>0.001ᵇ</td>
</tr>
<tr>
<td>p value for minimum versus basal response</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.001ᵇ</td>
<td>—</td>
</tr>
</tbody>
</table>

DISCUSSION

Basal flux In our study the laser Doppler red cell flux at plaque sites was between nine and 13 times that at the nonplaque sites. Investigation of the cutaneous blood flow in psoriasis using the 133Xenon washout technique demonstrated that cutaneous blood flow in psoriasis was 10 times greater than that in the skin of normal subjects. In addition, the cutaneous blood flow in the clinically normal skin of the psoriatic subjects was found to be two times greater than that in the skin of normal subjects (Klep et al, 1983). Subsequent investigations of the cutaneous blood flow in psoriasis using the LDF technique have shown a 6-fold and 9-fold increase (Khan et al, 1987; Staberg and Klemp, 1984) in plaques compared with clinically normal skin. When cutaneous blood flow in psoriatic plaques was compared with that in clinically uninvolved skin in psoriatic patients, there was a 5-fold increase in plaque blood flow as recorded by the LDF technique (Khan et al, 1987). It must be noted that other factors such as laser penetration depth and skin composition at the recording site will also influence results. Disease activity with variable degrees of hyperkeratosis, acanthosis, and interstitial edema within psoriatic plaques, which may not be clinically apparent, will alter the depth of penetration of the laser, causing variation in the signal recorded within different areas of the same plaque and also between plaques.
Table IV. Summary of red cell flux measured during the CR responses (CR1–2)

<table>
<thead>
<tr>
<th></th>
<th>Non-plaque (NP)</th>
<th>Plaque (P)</th>
<th>Ratio of P/NP</th>
<th>p value for P versus NP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal flux (AU)</td>
<td>15.9 ± 11.5</td>
<td>160.8 ± 106.4</td>
<td>13.5 ± 11.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Minimum flux (AU)</td>
<td>67.7 ± 5.4</td>
<td>88.4 ± 57.8</td>
<td>19.5 ± 19.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ratio of minimum flux/basal flux</td>
<td>0.59 ± 0.28</td>
<td>0.62 ± 0.19</td>
<td>—</td>
<td>0.16*</td>
</tr>
<tr>
<td>p value for minimum versus basal response</td>
<td>0.02</td>
<td>0.001</td>
<td>0.16*</td>
<td>—</td>
</tr>
</tbody>
</table>

Basal flux was recorded for 20 s prior to the test. Subjects then immersed both feet in water at 15°C for 1 min. This resulted in a fall in flux. The minimum flux was taken as the lowest point of the trough generated. Results, presented as mean ± SD, are pooled from two independent experiments and are all corrected for BZ.

*Owing to skewing of the results for ratios, these p values are calculated after logarithmic transformations (n = 16).

Measurements will also vary according to the position of the probe, e.g., if the probe is placed over an ascending arteriole and/or at the active, spreading edge of the plaque then high values will be recorded. All these factors contribute to the differences in values of cutaneous blood flow calculated in the various experiments. However, all these investigations have demonstrated an elevated cutaneous blood flow in psoriatic plaques compared with nonplaque skin and the skin in normal subjects, and our results are in accordance with this.

Some of the tests alter systemic blood pressure as well as cutaneous blood flow (Stanton et al., 1995, 1996), influencing the latter through changes in local perfusion pressure. For RH and AD these changes are very small and changes in blood flow reflect changes in vascular tone. The fall in blood pressure accompanying the IG and CR is 3%–7% (Stanton et al., 1996), which would be unlikely to have substantially influenced the marked falls in flux observed here. During CHL, blood pressure falls more substantially (26%) (Stanton et al., 1996). As this would attenuate a rise in flux, the bilateral increase observed here clearly signifies a decrease in vascular resistance.

Biologic zero The BZ signal tended to be higher in plaque than in nonplaque skin. It has been postulated that Brownian motion of macromolecules may in part contribute to the BZ signal. A raised BZ has been observed in localized skin edema induced by application of histamine (Wahlberg et al., 1992), in the lymphedematous arms of postmastectomy female patients (Stanton et al., 1996) and following a rise in skin temperature of 6°C (Caspari et al., 1988).

Tests of vasoconstriction Inspiratory gasp and cutaneous CR The vasoconstrictor response in plaque skin following deep inspiration and exposure of the feet to cool water was clearly present. In both the IG1–3 and CR1–2 tests there were no significant differences in the time to attain the peak response between the nonplaque and plaque sites. There was, therefore, no evidence of failure of sympathetic vasoconstrictor control in psoriatic skin.

Arm dependency Locally derived vasoconstriction mediated by a myogenic or local axon reflex was also clearly intact in psoriatic skin. The active myogenic response in the psoriatic plaque resistance vessels is one (of several) mechanisms that may contribute to their demonstrable basal tone.

As the major part of the signal generated by the LDF originates from subpapillary resistance vessels deep to the capillary loops (Bongard and Fagrell, 1990; Fagrell, 1995), this study indicates that the vascular abnormalities in psoriasis are not confined to the capillary loops but also extend to involve the resistance vessels feeding the subpapillary plexus. Many studies (Nishioka and Ryan, 1972; Braverman and Sibley, 1982; Barnhill et al., 1984; Malhotra et al., 1989; Parent et al., 1990) argue that the epidermis is the initiator of the microvascular changes observed in psoriasis. Factors produced by the epidermis are thought to diffuse into the superficial arterioles and around psoriatic plaques have the capacity to vasodilate and hence they retain a substantial basal tone, albeit less than nonplaque sites. A very important finding was that maximum dilatation in nonplaque resistance vessels failed to generate a red cell flux anywhere near as high as even the basal flux in psoriatic vessels. Therefore, there are either greater numbers of arterioles in and around psoriatic plaques compared with normal skin, or pre-existing arterioles are chronically, structurally widened. Loss of vascular smooth muscle tone alone cannot account for the very high basal flux in psoriatic lesions. The arteriolar changes raise local capillary blood flow. Endothelial cells have the capacity to sense alterations in shear stress via a combination of cytoskeletal elements and released/or activated biochemical signals. These signals are then transduced to the endothelial cell nucleus to regulate gene expression that is critical for endothelial cell function (Braddock et al., 1998). It is, therefore, possible that as a compensatory mechanism to counteract the effects of increased flow and to reduce shear stress, the endothelial cells may respond by undergoing hypertrophy or hyperplasia, resulting in widening and tortuosity of the capillary loops. It should be noted that the increased area of the capillary bed cannot by itself explain the large rise in blood flow, because most of the resistance to flow is precapillary (Levick and Michel, 1978).

Time to attain the peak response was longer in the plaque sites than in the nonplaque sites. This may represent a sluggish myogenic response because the vessels are already predilated and/or may be due to a decrease in release of mediators or dilution of mediators in the inflammatory, edematous interstitium.

Core heat load Results of the CHL test support the findings of the RH response, i.e., the psoriatic plaque resistance vessels exhibited basal tone. Unlike the RH test, the time to attain peak response is not significantly different in nonplaque and psoriatic skin. This may be because of the slow progressive nature of the CHL test, which has a time constant of minutes, as opposed to seconds for RH.

Tests of vasodilatation Reactive hyperemia When interpreting the results of these experiments it is important to note that several studies have shown that the dominant part of the LDF signal is generated by the movement of blood cells in the deeper, subpapillary vascular bed of the skin and only a very small portion of the signal (2%–10%) is produced by capillary blood flow (Bongard and Fagrell, 1990; Fagrell, 1995). Results of the RH response indicate that the
dermis to trigger the changes. Vascular endothelial growth factor/
vacular permeability factor is produced in strikingly increased
amounts by psoriatic epidermis and vascular endothelial growth
factor receptors are overexpressed by papillary dermal microvascular
endothelial cells. The implication is that the avascular epidermis
has the capacity to regulate dermal angiogenesis and microvascular
permeability by a paracrine mechanism involving the secretion of
vascular endothelial growth factor/vascular permeability factor
(Detmar et al, 1994; 1995). As the resistance vessels in the deeper
subpapillary plexus are also abnormal, however, i.e., structurally
expanded and/or increased in number, it becomes necessary to
postulate the following: either there is another, as yet unidentified,
deep trigger to the vascular abnormalities observed, or the
epidermal signal is able to diffuse down past the capillary loops,
without being fully cleared by diffusion into the plasma, to reach
the deeper dermis in biologically effective concentrations.

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