

Dermal Neurovascular Dysfunction in Type 2 Diabetes

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OBJECTIVE — To review evidence for a relationship between dermal neurovascular dysfunction and other components of the metabolic syndrome of type 2 diabetes.

RESEARCH DESIGN AND METHODS — We review and present data supporting concepts relating dermal neurovascular function to prediabetes and the metabolic syndrome. Skin blood flow can be easily measured by laser Doppler techniques.

RESULTS — Heat and gravity have been shown to have specific neural, nitergic, and independent mediators to regulate skin blood flow. We describe data showing that this new tool identifies dermal neurovascular dysfunction in the majority of type 2 diabetic patients. The defect in skin vasodilation is detectable before the development of diabetes and is partially correctable with insulin sensitizers. This defect is associated with C-fiber dysfunction (i.e., the dermal neurovascular unit) and coexists with variables of the insulin resistance syndrome. The defect most likely results from an imbalance among the endogenous vasodilator compound nitric oxide, the vasodilator neuropeptides substance P and calcitonin gene-related peptide, and the vasoconstrictors angiotensin II and endothelin. Hypertension per se increases skin vasodilation and does not impair the responses to gravity, which is opposite to that of diabetes, suggesting that the effects of diabetes override and counteract those of hypertension.

CONCLUSIONS — These observations suggest that dermal neurovascular function is largely regulated by peripheral C-fiber neurons and that dysregulation may be a component of the metabolic syndrome associated with type 2 diabetes.

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A number of functional disturbances are found in the dermal microvasculature of diabetic subjects. These include decreased microvascular blood flow (1), increased vascular resistance (2), decreased tissue PO₂ (3), and altered vascular permeability characteristics, such as loss of the anionic charge barrier and decreased charge selectivity. Decreased microvascular blood flow and increased

vascular resistance in diabetes could result from alterations in dermal neurovascular function, such as impaired dilator responses to substance P, calcitonin gene-related peptide (CGRP), and reactivity to nociceptive stimulation. Diabetes also disrupts vasomotion—the rhythmic contraction exhibited by arterioles and small arteries (4,5). Unmyelinated C-fibers, which constitute the

central reflex pathway, are assumed to be damaged in diabetic neuropathy, contributing to abnormalities in cutaneous blood flow (6). Warm thermal sensation is a functional measure of C-fibers in the periphery, and the impairment of this function was paralleled by a reduction of vasomotion. These findings support an interaction between small unmyelinated C-fiber function and vasomotion, although it is not clear whether the neurological deficit precedes or follows the loss of baseline vascular response. A clear relationship between skin microvascular insufficiency and neuropathy has not yet been established. It is possible that skin ischemia precedes neuropathy, or it may be that both conditions are the result of separate processes caused by the same etiologic factors.

NEUROPEPTIDES AND OTHER FACTORS INVOLVED IN VASODILATION AND VASOCONSTRICTION

The major neuropeptides mediating vasodilation of the microvasculature are substance P and CGRP, in addition to bradykinin, vasoactive intestinal polypeptide (VIP), and histamine. Vasoconstriction is thought to be mediated by norepinephrine. However, endothelin, which is 300 times more potent as a vasoconstrictor than norepinephrine, has recently assumed a greater role as an endogenous vasoconstrictor in the microcirculation (7). Evidence suggests that the nociceptive neuropeptides may be regulated by the vanilloid receptor 1 (VR1) (VR1 receptor for capsaicin). It is expressed in primary sensory neurons and vagal nerves. VR1 seems to play an important role in the activation and sensitization of nociceptors. Heat, protons and endocannabinoids, and capsaicin lead to the opening of a cation/Ca²⁺ channel. The accumulation of intracellular Ca²⁺ causes exocytosis of neuropeptide-containing vesicles and release of substance P and CGRP. Substance P diffuses through the vascular wall and binds to neurokinin 1 receptors (or substance P receptors) on the endothelial cells, which leads to activation of second messenger systems and relaxation of smooth muscle cells. Activation of both cAMP and cGMP second

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Abbreviations: Ang, angiotensin; CGRP, calcitonin gene-related peptide; eNOS, endothelial NOS; ET, endothelin; iNOS, inducible NOS; IR, insulin resistance; L-NAME, N^G-nitro-arginine-methyl ester; NGF, nerve growth factor; nNOS, neuronal NOS; NO, nitric oxide; NOS, nitric oxide synthase; PGP 9.5, protein gene product 9.5; VIP, vasoactive intestinal polypeptide; VR1, vanilloid receptor 1.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

messenger systems are required for the activation of nociceptors (8–10). No studies, however, have been performed on the VRI in human skin.

In diabetes, a reduction of protein gene product 9.5 (PGP 9.5), substance P, and CGRP in sensory neurons has been shown (10–12). PGP 9.5 is a neuronal cytoplasmic protein and is found in all types of efferent and afferent nerve fibers. Studies have shown a loss of cutaneous nerve fibers that stain positive for the neuronal antigen PGP 9.5 in small fiber neuropathy (13–17). These neurons depend on nerve growth factor (NGF) for their integrity and survival (18,19). The effect of NGF depletion may be mediated through downregulation of neurofilament gene expression or RNAs that encode the precursor molecule of substance P or CGRP, both of which are NGF-dependent and downregulated in diabetes (19).

Angiotensin (Ang)-II plays a major role in modulating the extracellular fluid volume, systemic vascular resistance, and cell growth and differentiation (20). It is also now known that AngII is generated independently from the traditional synthesis pathway, whereas AngI is generated from angiotensinogen via ACE activity. AngII can be generated directly from angiotensinogen by tissue plasminogen activator cathepsin G, elastase, and tonin, and from AngI by chymostatin-sensitive AngII-generating enzyme, cathepsin G, and chymase. This explains why levels return toward normal with long-term inhibition of the ACE pathway of synthesis. Interestingly, ACE is identical to kininase II, which degrades bradykinin and other kinins to inactive metabolites. Blockade of ACE is therefore associated with increased levels of bradykinin and substance P, which are direct vasodilators and are known to stimulate the production of nitric oxide (NO), cGMP, prostaglandin E₂ and prostacyclin release from endothelium (21,22). These substances are all vasodilators and exert antiproliferative properties. ACE inhibition not only decreases levels of the potent vasoconstrictor AngII but also may benefit from the effects of kinins, such as bradykinin and substance P (23).

NEUROVASCULAR FUNCTION IN BLOOD FLOW

Regulation of blood flow to the skin is complex, involving long descending autonomic fibers that mediate

central reflex control of vascular tone, short reflex arcs through the spinal cord, and local reflexes within the skin (24,25). Neural regulation of skin blood flow is further complicated by the presence of arteriovenous anastomoses, which are highly innervated structures involved in thermoregulatory processes. Arteriovenous shunts provide a potential low-resistance pathway by which blood flow can be diverted from the arteriolar to venular circulations, bypassing the capillary bed. These shunts are maintained in a constricted state by sympathetic tone. Loss of this tone because of sympathetic neuropathy results in the opening of the shunt and deviation of blood flow from the skin.

Boulton et al. (26), Edmonds et al. (27), and Timperley et al. (28) suggested that a possible relationship exists between increased shunting of blood flow in diabetes and the development of neuropathic ulcers. These authors demonstrated that increased venular oxygen levels, apparent ischemic lesions despite the presence of palpable pulses, and raised skin temperatures in the distal extremities are observations that appear consistent with arteriovenous shunting. Others have used a combination of video microscopy and laser Doppler techniques to confirm and further describe this hypothesis (29).

An attractive hypothesis is that diabetes leads to the loss of neural control of these vessels such that shunt flow increases, thus creating a deficit in skin blood flow at the nutritive capillary level (26–28,30). Evidence to support this hypothesis includes the finding of increased venous oxygen tension, raised pedal skin temperature, and venous distension (26). However, it remains uncertain whether excessive shunt blood flow occurs as a result of a specific nerve fiber–type defect or whether it is a reflection of microvascular damage.

ASSESSMENT OF SKIN BLOOD FLOW

The development of noninvasive methods for assessing skin blood flow has enabled clinical measurements of the effects of diabetes on microvascular perfusion (31). To date, measurements of skin blood flow in subjects with diabetes have provided conflicting results. Rendell et al. (31) reported that diabetes was associated with decreased blood flow in areas of the skin both rich and relatively devoid of arte-

riovenous shunts, whereas Hauer et al. (32) found that palmar blood flow was increased relative to flow in the fingertips. Jorneskog et al. (33,34) found that skin flow was considerably worse in the lower limbs of type 1 diabetic patients. Other studies have reported increased foot blood flow in subjects with diabetes compared with control subjects (27,35).

The resultant effects of diabetes on skin blood flow in conditions of vasoconstriction or vasodilation also conflict (30,35,36). These discrepancies seem to indicate that the diabetes-induced changes in skin blood flow result from multiple mechanisms, presumably of neural and microvascular origin. Differences in the blood circulation to hairy skin versus glabrous skin, for example, have not been accounted for previously.

ROLE OF NO — NO is one of the primary agents eliciting a vasodilatory response by relaxing vascular smooth muscle, thereby producing an increase in skin blood flow. NO is synthesized from L-arginine and N- ω -hydroxyarginine, catalyzed by the enzyme nitric oxide synthase (NOS) controlling the intermediate steps. Three isoforms of NOS have been isolated. Neuronal NOS (nNOS) and endothelial NOS (eNOS) are both calcium dependent, whereas inducible NOS (iNOS) is calcium independent and generally thought to be involved primarily in local inflammatory and immune reactions.

nNOS is localized primarily in neurons and skeletal muscle cells. Some types of nonadrenergic-noncholinergic mediated vasodilation appears to be mediated by nitrergic nerves that use NO as their primary “neurotransmitter” of action. eNOS-generated NO is synthesized almost exclusively in vascular endothelium. Through paracrine signaling, NO activates soluble guanylate cyclase in vascular smooth muscle, resulting in vasorelaxation. iNOS operates through gene transcription and is responsible for production of NO in nanomolar concentrations. Several cell types contain iNOS, including vascular smooth muscle, nonadrenergic-noncholinergic nerves, and endothelium. nNOS and eNOS are thought to be the predominant isoform involved in the regulation of skin blood flow. NO production can be inhibited by blocking NOS activity through the administration of a dimethylarginine com-

pound, such as N^G -nitro-arginine-methyl ester (L-NAME), which is a nonspecific inhibitor of all NOS isoforms. Some recent work indicates the existence of more specific inhibitors of nNOS, but none of this work has thus far been done in models of diabetes.

The cytotoxic effects of NO are believed to be the result of iNOS-produced NO. Inhibitors of iNOS include aminoguanidine, dexamethasone, and other glucocorticoids. Recent work has shown that NOS production of NO is required for full expression of active vasodilation in response to heat (37). Studies in humans have shown that NO can increase blood flow in skin directly, and NO contributes to vasodilator tone in the forearm and finger skin (38).

ENDOTHELIN AND NO — Endothelial cells also generate the vasoconstrictor peptide endothelin (ET)-1. ET-1 acts on ET_A and ET_B receptors in vascular smooth muscle cells. An imbalance between the production of NO and ET-1 could lead to pathologically elevated vascular tone. NO not only inhibits ET-1 production in vascular endothelium but also reduces bioactivity.

ET-1 also plays a role in the control of vascular resistance. Wenzel et al. (39) demonstrated that in human skin microcirculation, ET-1 causes neurogenic vasodilation associated with burning pruritus mediated by polymodal nociceptor fibers and suggested that stimulation of these fibers by ET-1 via ET_A receptors leads to the local release of NO. Recently, Lipa et al. (40) showed that ET-1 is a potent skin vasoconstrictor and that skin vasoconstriction is primarily mediated by ET_A receptors. Local blood vessel tone is reduced by antagonists of ET_A receptors (41). Verhaar et al. (42) demonstrated that the local vasodilator response to selective ET_A receptor antagonism in human forearm resistance vessels is derived in large part from increased NO-mediated vasodilation, most probably mediated by the endothelial ET_B receptor.

MECHANISMS OF CUTANEOUS BLOOD VESSEL DILATATION — In humans, cutaneous blood vessels are controlled by both neurogenic reflexes and local factors (43). Local warming of the skin causes vasodilation that can reach

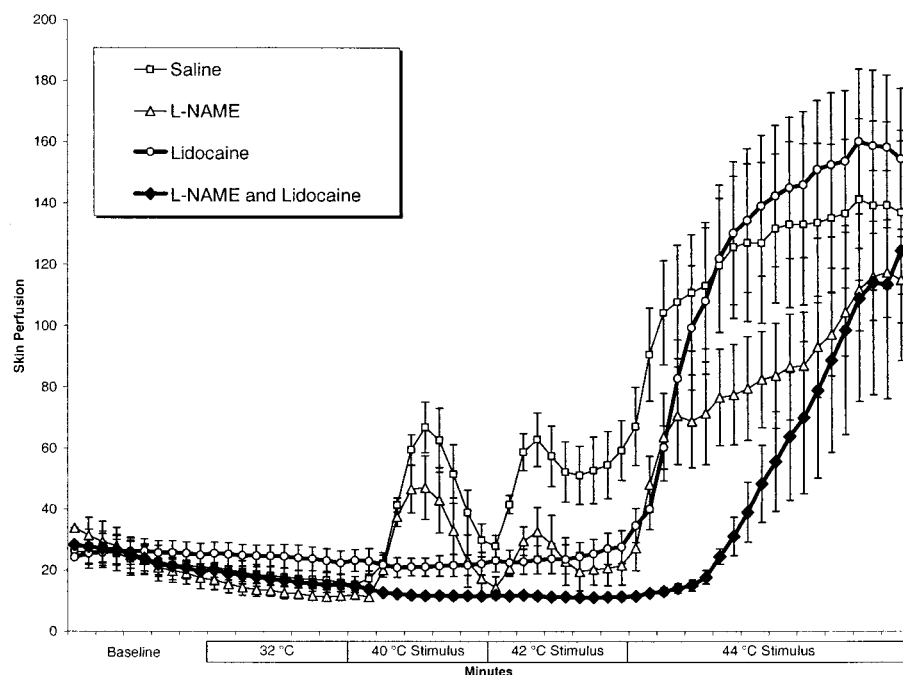


Figure 1—The contribution of cutaneous neurons and NOS to neurogenic vasodilation in human skin. Compared with saline, L-NAME partially inhibits the vasodilation at all levels of heat (40, 42, and 44°C). Blocking the neurons with lidocaine blocks the reflex entirely at moderate temperatures (40 and 42°C) but only delays it at 44°C, demonstrating the importance of cutaneous neurons at moderate temperatures. Both inhibitors combined further inhibit all of the responses and even delay the response to near-pain-threshold levels of heat (44°C).

maximal levels if the local temperature is raised to 42°C for 20–40 min (44). This vasodilation with increased temperature is caused in part by a reduction in noradrenergic effectiveness through decreased affinity of α_1 and α_2 receptors for norepinephrine, but this reduced noradrenergic effectiveness only accounts for 10% of the cutaneous response to heating.

The largest factor in most skin (hairy skin), which also is present in skeletal muscle as well as in many internal organs, has only recently been described and includes the neurogenic action of small-fiber nociceptive sensory neurons (45). These neurons have been shown to be capsaicin-sensitive primary afferent neurons responsible for most pain transmission. In hairy skin, these sensory neurons are activated by heat $>39^\circ\text{C}$ or other noxious stimuli and locally release neuropeptides from their terminals in skin and other tissues that they innervate. These neuropeptides include substance P, CGRP, and the adenosine analog ATP, which cause more intense vasodilation limited to the immediate area of the receptive field of particular sensory neu-

rons. They may act directly on vascular smooth muscle or may act through secondary pathways. Secondary pathways include mast cell release of histamine and sweat gland secretion of bradykinin and VIP, although their specific roles have yet to be described. This reflex has been referred to as neurogenic inflammation in many tissues or the axon-flare reflex when induced by antidromic stimulation of sensory nerves. This mechanism accounts for 75–90% of the dilatory capacity in hairy skin (6).

Figure 1 demonstrates heat-induced vasodilation and illustrates the neurogenic and nitrenergic nature of the reflex. Note that there is a nitrenergic component to moderate heating (40 and 42°C), but at these levels, the reflex is completely blocked by lidocaine, demonstrating that the neuron is a necessary part of this reflex. At higher temperatures (44°C), the response is only partially blocked by either agent. The combination of nitrenergic and neuronal blockade further delays the response. This suggests that there is a nitrenergic neuronal component at this level of heating or duration, but the incomplete

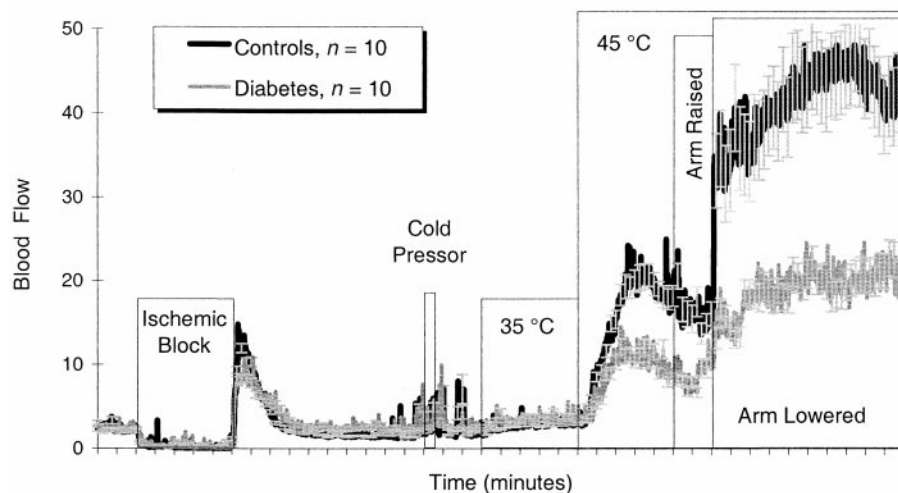


Figure 2—Skin blood flow from the dorsum of the hand in closely matched subjects with and without type 2 diabetes (matched for age \pm 2 years and BMI within 10%). The only stimulus that produced a significant difference was the neurogenically mediated response to heating (44°C).

blockade implies other unidentified mechanisms.

ABNORMALITIES IN SKIN BLOOD FLOW IN DIABETES

In type 2 diabetes, the predominant abnormality in skin blood flow is the loss of the active neurogenic vasodilative mechanism in hairy skin (6). Even studies using direct agonists of endothelium and smooth muscle relaxation appear to rely on neuronal regulation (46–48). In these studies of closely matched subjects (age- and BMI-matched) the glabrous skin of the foot (toe pulp) was affected by diabetes much more than the glabrous skin of the hand (finger pulp) (Fig. 2) (6). In contrast, the vessels in the dorsum of the hand showed a moderate endothelial defect and a profound inability to dilate with heat and the added hydrostatic gradient of lowering the limb. This loss of neurogenic vasodilation in the upper limb, which is spared severe neuropathy and ulceration, may precede other microangiopathic processes that are accelerated in the lower limb because of increased systemic pressure. To further clarify the role of the nervous system in these responses, Stansberry et al. (5) examined vasomotion (the spontaneous rhythmic oscillations seen in resting cutaneous vessels) and showed that these oscillations were nearly absent in patients with diabetes. While the origins, mechanisms, and physiological functions of vasomotion remain topics of considerable controversy, they appear to play a role in

recovery from ischemia and possibly the maintenance of capillary pressure gradients necessary for capillary flow and extravasation (5,49,50). These researchers found a relationship between warm thermal sensation, an index of C-fiber neuropathy, and vasomotion. It was feasible that the susceptibility to foot ulceration was the consequence of impaired microvascular perfusion of skin and subcutaneous tissue and a concomitant decrease in vascular supply to small C-fibers subserving pain and warm thermal perception, allowing increased heat and tissue injury in an ischemic limb.

It is not clear whether these changes were a consequence of sclerotic vessels (and therefore permanent) or whether they were functionally reversible. To further examine these possibilities, Stansberry et al. (6) examined two additional indexes of peripheral vascular function: 1) the hyperemic response to experimental (occlusive) ischemia and 2) the physical distensibility of the same vessel beds in type 2 diabetes compared with 10 age- and BMI-matched healthy control subjects.

Postischemic hyperemia is thought to be endothelium dependent, largely the result of the release and action of endothelial-derived NO and prostaglandin. In addition, we devised a simple stimulus for vessel distension that relies purely on the hydrostatic gradient imposed by elevation and lowering of the upper limb, reflecting the degree of microvascular distensibility. In these studies, the vessels in the finger pulp show essentially no dif-

ferences between the matched groups (6). In contrast, however, both the upper and lower limbs showed profoundly impaired heat-stimulated vasodilation. Both skin sites rely on endothelium for initial vasodilation after ischemia or release of sympathetic output. However, in hairy skin (the hand dorsum), the active neurogenic vasodilative mechanism described above is responsible for most of this dilation. Thus, these new findings provide evidence of defective neurogenic vasodilation in hairy skin that is independent of vascular elasticity (i.e., sclerosis is not the cause of this nondistensibility). Together, these results suggest that these defects are likely to precede structural changes in the vessels (e.g., advanced glycation end product accumulation in vessels and connective tissues [51–54]). Defective vasodilation may depend on sorbitol accumulation in nerves (55–57), abnormalities in protein kinase C metabolism (53,58–62), or other metabolic factors that remain poorly understood.

DERMAL NEUROVASCULAR DYSFUNCTION AND INSULIN RESISTANCE

The study by Stansberry et al. (6) showed that significant inverse correlations exist between systolic blood pressure and the hyperemic response to ischemia and heated arm lowering. Significant correlations also exist between flow at 35°C and LDL cholesterol, triglyceride, and C-peptide levels. Therefore, it seems that these defects in skin blood flow are part of the metabolic syndrome and may play a role in the pathogenesis of the condition as well as its complications.

Jaap et al. (63) suggested that the failure of skin vasodilation occurs before the onset of type 2 diabetes and that this failure is related to insulin resistance (IR). More recently, these researchers showed that failure of both endothelial-dependent vasodilation and direct vasodilation occurs in family members of patients with type 2 diabetes (64). Caballero et al. (65) showed that vascular reactivity in the skin microcirculation was impaired in individuals with impaired glucose tolerance and in normoglycemic subjects with a parental history of type 2 diabetes. They found a significant inverse correlation between microvascular reactivity and systolic blood pressure, fasting plasma glucose, HDL cholesterol, fasting plasma insulin, and homeostasis model assessment of IR

(65), supporting the existence of a vascular reactivity abnormality that may precede the onset of hyperglycemia.

Stansberry et al. (6) showed that abnormalities exist in C-fiber-mediated nociceptive vasodilation in the upper limbs of people with diabetes in the absence of overt neuropathy, which correlates with the metabolic markers of the IR syndrome. Animal studies suggest that capsaicin-sensitive sensory neurons play a role in the regulation of glucose tolerance and insulin sensitivity (66). These findings suggest that defective neurogenic vasodilation, in addition to its pathophysiological role in causing complications, could be responsible for as much as 25% of impaired insulin sensitivity (67,68). Avogaro et al. (69) and others question its significance.

EFFECTS OF HYPERTENSION ON VASCULAR REACTIVITY

— Type 2 diabetes is commonly associated with hypertension. This association may be mediated through shared causal factors, such as IR, obesity, sedentary lifestyle, and maladaptive diets. In patients with diabetes, even moderate hypertension magnifies the risk of cardiovascular disease, stroke, peripheral vascular disease, and renal failure (70). Aggressive treatment of blood pressure improves the prognosis in these patients (71–73).

As a corollary, it appears that hypertension coexists with features of the metabolic syndrome. In the Tecumseh Blood Pressure Study in Michigan (74), hypertension was associated with elevated LDL cholesterol, elevated triglycerides, obesity, impaired glucose tolerance, diabetes, and elevated basal insulin levels. The mechanism by which hypertension is induced is not entirely clear but is thought to operate through sympathetic overactivity (75). Among other considerations, higher levels of circulating insulin in hypertension may cause increased activity of the sodium pump, retention of fluid, and increased sensitivity to an activated autonomic system. In previous studies, little attention was focused on the fact that insulin is a vasodilator. Therefore, rather than ascribing the hypertension to the effects of high levels of insulin, the answer should have been sought by examining the impact of IR on dermal neurovascular function.

The most consistent change, the rar-

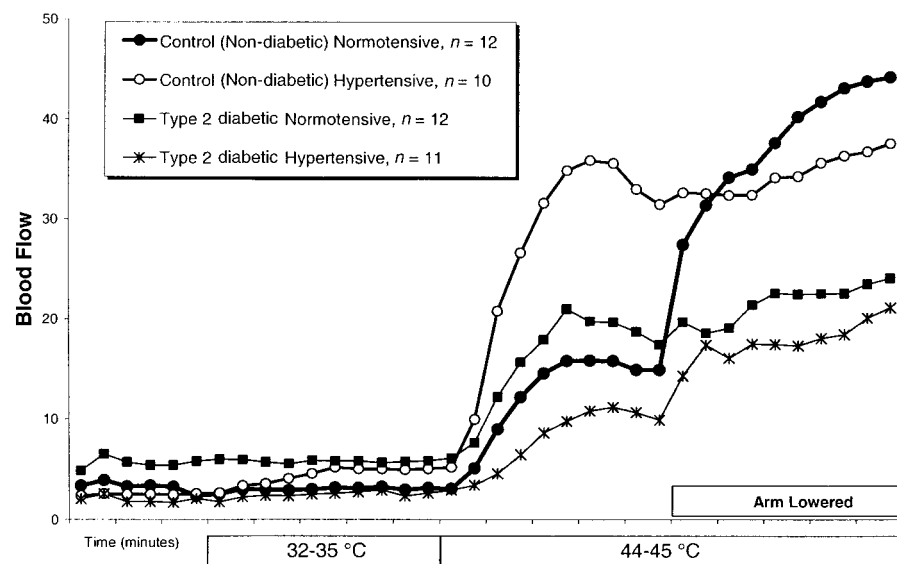


Figure 3—Skin blood flow measured from the dorsum of the hand. Data are displayed as group means.

efaction of the microvascular bed in the early stages of hypertension, is the decrease in the number of small arterioles and capillaries, causing increased resistance in the microvascular bed (76). There has been some speculation that vasomotion may be a compensatory attempt to overcome rarefaction and that the loss of vasomotion in diabetes compounds the effects of hypertension in people with diabetes (77). Rendell et al. (78) explored the possibility that chronically elevated vascular pressure in spontaneously hypertensive rats might affect the microvascular constitution of the skin. These researchers measured skin blood flow on the back and the paw in hypertensive and nonhypertensive rats. They suggested that reduced capillary density on the back of the spontaneously hypertensive rats may be a developmental adaptation to high blood pressure. This reduction in the pathways for blood flow may help account for increased flow resistance at that site, independent of arteriolar vasoconstriction. These early findings may only have reflected the impact of hypertension on vascular changes and have not addressed vascular reactivity occurring before the onset of vascular sclerosis.

Maximum microvascular flow and resistance to flow was examined by Jaap et al. (63,64), who found that maximum flow was similar in normotensive and hypertensive diabetic patients. However, resistance to flow was significantly increased in patients with both diabetes and

hypertension versus normotensive patients with diabetes. Although hypertension increased resistance, its presence in diabetes was associated with an additional rise in precapillary vascular resistance. In other studies, skin blood flow decreased and microvascular resistance increased as a function of systolic blood pressure. Thus, microvascular resistance may be important in hypertension but less so in individuals with diabetes (79).

Figure 3 demonstrates our findings in both essential hypertension and hypertensive diabetes. Interestingly, the two conditions demonstrate a paradoxically opposite effect during neurogenic vasodilation. In essential hypertensive subjects, neurogenic vasodilation is significantly enhanced ($P < 0.05$) and the response to gravity is maintained, whereas diabetic hypertensive subjects have lower vasodilation responses than nonhypertensive diabetic or control subjects. Diabetes impairs the response to both stimuli. Comorbid hypertension and diabetes obliterate the responses. Taken together, these findings suggest that hypertension in diabetes may have a different pathogenic mechanism from that of essential hypertension and may be part of the metabolic syndrome.

EFFECTS OF REDUCING INSULIN RESISTANCE ON BLOOD FLOW

— The beneficial effects of thiazolidinediones in human models of IR have been well documented.

Interestingly, there have now been reports of beneficial effects on cardiac performance and blood pressure (80). It is clear that insulin-mediated vasodilation (through endothelial release of NO) is impaired in insulin-resistant states, such as obesity, hypertension, and type 2 diabetes (81,82).

Studies have shown that treatment of insulin-resistant obese subjects with troglitazone or metformin for 8 weeks reduced IR, lowered blood pressure, and improved insulin sensitivity (83,84). Research in animal models has shown that troglitazone and pioglitazone caused peripheral vasodilation, which was mediated by prostaglandin production associated with increased calcium fluxes in smooth muscle (85,86). There also may be differential effects between rosiglitazone and troglitazone on human small arteries (87). Moreover, we have recently discovered that treatment of insulin-resistant obese type 2 diabetic patients with troglitazone enhances blood flow and sensitizes the dermal neurovascular system to directly measured NO (A.I.V., T.E., T.S.P., K.B.S., J.A.S., G.L.P.). Whether this is a class effect is being explored.

SUMMARY OF DERMAL NEUROVASCULAR DYSFUNCTION IN DIABETES

Attention has been focused on the dermal neurovascular abnormalities associated with diabetes, wherein warm, cold, and heat pain thresholds are disturbed in association with impairment in skin blood flow. There is a dysfunctional phase preceding organic structural damage to the dermal neurovascular unit. The disorder of the dermal neurovascular unit in type 2 diabetes coexists with elements of the metabolic syndrome, elevated IR, hypertension, and dyslipidemia. In the past, it has been difficult to link these elements causally. Although dysfunction of the dermal neurovascular unit may be yet another surrogate for the metabolic syndrome, there seems to be an argument for dysfunction of the neuropeptidergic arm of that unit contributing to IR due to compromised blood flow. If this proves to be the case, it will become important to refocus energies on the defective neuropeptidergic regulation of blood flow as an approach to ameliorating diabetes. There is a functional phase that precedes struc-

tural damage, indicating that reversibility of the defect may be achievable.

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