Transcutaneous Oxygen Tension in Legs and Feet of Diabetic Patients

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Transcutaneous oxygen tension ($tcPo_2$) of the legs and feet was measured at 37 and 44°C in 21 patients with diabetes mellitus, 9 of whom had peripheral neuropathy. At 37°C, $tcPo_2$ in the legs and feet of diabetic patients with peripheral neuropathy was significantly higher ($P < .02$) than in control subjects and diabetic patients without neuropathy. Whereas $tcPo_2$ in the legs of control subjects and nonneuropathic diabetic patients was greater than in the feet ($P < .02$), this leg-to-foot difference was absent in diabetic patients with neuropathy. After an increase in skin temperature to 44°C, $tcPo_2$ increased in the legs and feet of all three groups, but the increase was smallest in diabetic patients with neuropathy and greatest in control subjects. In neuropathic ($P < .02$) and nonneuropathic ($P < .02$) diabetic patients, $tcPo_2$ was significantly lower than in control subjects. These data are consistent with a loss of vasoconstrictor tone in the blood vessels perfusing skin and subcutaneous tissue at 37°C and an inability of these vessels to vasodilate and increase blood flow at 44°C in diabetic patients in general and neuropathic diabetic patients in particular. This inability to increase $tcPo_2$ after an increase in temperature and possibly other vasodilatory stimuli may contribute to the pathogenesis of nonhealing ulcers, protracted infections, and gangrene, which characterize the diabetic foot. *Diabetes* 37:714–16, 1988

Skin blood flow of the lower leg is known to be altered in patients with diabetes (1). Also, the feet and toes of patients with diabetic neuropathy are warmer than those of nondiabetic subjects (2). Despite this evidence, it is widely believed that the development of cutaneous ulcers in the lower leg in patients with diabetes results from diminished tissue perfusion. To explain this paradox, it has been postulated that the increase in blood flow results from the opening of arteriovenous anastomoses (3), but this hypothesis is not supported by direct demonstration of such shunts.

The transcutaneous oxygen electrode has been used to study the effect of physiological maneuvers on skin blood flow, because tissue oxygen tension is a function of blood flow (4,5). The oxygen electrode has both advantages and drawbacks compared with other established techniques, but the most important point in favor of its use as a monitor of a flow-related parameter is that it may be used continuously to provide a record during changes in posture and during exercise (5,6). Transcutaneous oxygen tension ($tcPo_2$) is determined by the rate of flow in blood vessels near the skin surface (7), and diminished perfusion would result in decreased levels of oxygen in the skin. Therefore, we have measured skin oxygen tension with a transcutaneous polarographic oxygen electrode thermostatically controlled both at 37 and 44°C in diabetic patients with or without neuropathy to determine the response in blood flow to changes in local temperature.

SUBJECTS AND METHODS

Patients. Twenty-three patients with diabetes mellitus were included in this study. The clinical characteristics of the patients are summarized in Table 1. Eleven patients had peripheral neuropathy as shown by the absence of ankle reflexes, a variable loss of sensation in the feet (and sometimes legs), and impaired motor and sensory nerve conduction velocity. Two of these patients had clinical evidence of autonomic neuropathy. Twelve patients had diabetes without neuropathy: ankle jerks were present in all 12 patients, 9 were completely asymptomatic, and nerve-conduction studies were performed and found to be normal in 3 who had atypical symptoms. Fourteen nondiabetic subjects were included as control subjects. All had fasting blood glucose concentrations <5.0 mM and/or random blood glucose con-

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TABLE 1
Clinical characteristics of patients

	Patients	
	Neuropathic (n = 11)	Nonneuropathic (n = 12)
Median age (yr)	59 (18–75)	61 (23–73)
n (M/F)	4/7	5/7
Type of diabetes (IDDM/NIDDM; n)	5/6	4/8
Median duration of diabetes (yr)	10 (2–33)	8 (1–20)
Treatment		
Insulin	7	4
Oral hypoglycemics	5	8
Control		
Good* (n)	6	7
Poor (n)	5	5
With retinopathy (n)	4	1
With proteinuria (n)	2	0

Where applicable, range is given in parentheses.
*Defined as postprandial glucose <9 mM and hemoglobin A <8%.

centrations <6.0 mM and had no symptoms related to neurologic disease. Patients and controls with evidence of peripheral macrovascular disease (ankle pressure index <0.9) were excluded from the study.

Methods. The patients and control subjects were placed in a recumbent position in a quiet draft-free room at an air temperature between 22 and 24.5°C. Room temperature varied by <0.5°C during each study. A Hellige Oxymonitor (Freiberg im Breisgau, FRG) was used to record $tcPo_2$ over the anterolateral surface of the lower right leg 20 cm above the sole of the foot and from the dorsum of the right foot proximal to the base of the second toe as described previously (5). Initial recordings were made at an electrode temperature of 37°C (thermostatically controlled), and the electrode temperature was subsequently increased to 44°C; $tcPo_2$ was noted when a new stable value was reached after 20–30 min. Heating to 44°C was chosen because the machine is designed to measure $tcPo_2$ at 37 and 44°C, and a temperature of 44°C ensures adequate arteriolization of capillary blood. Most previous studies on $tcPo_2$ have been carried out at this temperature.

Statistical analysis was carried out with the Mann-Whitney U test for nonparametric data.

RESULTS

In recumbent subjects at 37°C, $tcPo_2$ was significantly increased ($P < .02$) in the legs (median 15.6 mmHg) and feet (median 13.1 mmHg) of patients with peripheral neuropathy compared with that of control subjects (leg, 8.0; foot, 4.9 mmHg; Table 2). Nonneuropathic diabetic patients had a $tcPo_2$ intermediate (leg, 12.9 mmHg; foot, 5.4 mmHg) between those of control and neuropathic diabetic subjects. These values were not significantly different from those of control subjects, but $tcPo_2$ in the feet of nonneuropathic diabetic patients was significantly lower than that in neuropathic diabetic patients ($P < .02$).

In the legs of control and nonneuropathic diabetic subjects at 37°C, $tcPo_2$ was significantly greater than in the feet (Table 1). This leg-to-foot gradient was not observed in neuropathic diabetic patients, because $tcPo_2$ in both the legs and feet of these patients was increased.

At 44°C, there was an increase in $tcPo_2$ of the legs and feet of all groups examined. However, the median $tcPo_2$ values were significantly greater in the control group (leg, 67; foot, 75 mmHg) than those in neuropathic (leg, 60; foot, 51 mmHg) and nonneuropathic diabetic patients (leg, 62; foot, 54 mmHg). The increase in $tcPo_2$ at 44°C was proportionately greatest in the legs and feet of control subjects and least in neuropathic diabetic patients. The leg-to-foot difference observed in control subjects and nonneuropathic diabetic subjects at 37°C also disappeared at 44°C.

DISCUSSION

These data demonstrate that the regulation of $tcPo_2$ in the legs and feet of diabetic patients, especially those with neuropathy, is abnormal. Thus, neuropathic diabetic patients did not have the leg-to-foot gradient of $tcPo_2$ seen in control subjects and nonneuropathic diabetic patients at 37°C. Their $tcPo_2$ at 37°C was greater than that observed in control and nonneuropathic diabetic subjects.

In contrast, after an increase in local skin temperature to 44°C, the neuropathic diabetic patients were not able to increase their $tcPo_2$ to the same extent as the control subjects. At this temperature, the increase in $tcPo_2$ of nonneuropathic diabetic patients was also significantly less than that in control subjects.

Our data are consistent with the observations made by Rayman et al.(8) on blood flow in the foot with a laser Doppler flowmeter. They demonstrated that the skin temperature of and the blood flow to the feet of neuropathic diabetic patients were significantly greater than those in control subjects and that the fall in blood flow observed on dependency is less in neuropathic diabetic patients than in control subjects. They also demonstrated that in the dependent foot, after an increase in abdominal skin temperature, blood flow is significantly greater in neuropathic diabetic patients than in control subjects. Thus, in all aspects of their data, the blood flow to the foot of patients with diabetic neuropathy was shown to be greater than that in control subjects.

Our observations add to those above in two ways. First, we have used $tcPo_2$ as the measured end point. This provides an index of tissue oxygenation distinct from blood flow, and it is of importance that observations based on $tcPo_2$ are

TABLE 2
Transcutaneous oxygen tension in legs and feet of nondiabetic subjects, diabetic patients without neuropathy, and diabetic patients with neuropathy

Skin site and electrode temperature	Transcutaneous skin oxygen tension (mmHg)		
	Nondiabetic subjects (n = 14)	Diabetic subjects	
		Nonneuropathic (n = 12)	Neuropathic (n = 11)
Leg, 37°C	8.0 (0.6–27.1)	12.9 (3.7–23.1)	15.6‡ (8.7–27.8)
Foot, 37°C	4.9* (0.5–17.3)	5.4*† (1.2–16.1)	13.1‡ (4.5–44.4)
Leg, 44°C	67 (51–100)	62‡ (42–77)	60‡ (10–66)
Foot, 44°C	75 (61–106)	54‡ (36–72)	51‡ (43–86)

Data are nonparametric in distribution and are expressed as medians, with ranges in parentheses.
*$P < .05$ vs. transcutaneous oxygen tension ($tcPo_2$) in leg at 37°C.
†$P < .02$ vs. $tcPo_2$ in diabetic patients with neuropathy.
‡$P < .02$ vs. $tcPo_2$ in nondiabetic subjects.

almost identical to those obtained by laser Doppler flowmetry in the qualitative sense. The consistency of data on capillary blood flow and $tcPo_2$ is of particular interest in diabetic patients, because capillary basement membranes are thickened in these patients and capillary blood flow and tissue oxygenation may show certain discrepancies. The demonstration of an increase in $tcPo_2$ and capillary blood flow in diabetic patients challenges the presence of significant arteriovenous shunting postulated by Ward (1) to account for the paradox of increased blood flow to the feet of patients with diabetic neuropathy and the increased frequency of indolent ulcers, recurrent infections, and gangrene in the feet of these patients. Furthermore, an actual study of arteriovenous shunts with radiolabeled albumin microspheres showed that whereas normal subjects had shunting of up to 5% in the lower limbs, those with ulceromutilating lesions of the foot had arteriovenous shunting of 8% (9). This 3% increase is unlikely to account for the marked increase (5–6 times) in total blood flow to the feet and legs of such patients (2).

Second, our data show that after an increase in local skin temperature the increase in $tcPo_2$ of diabetic patients with and without neuropathy was significantly lower than that observed in control subjects. Rayman et al. (8) were not able to observe this because they carried out their experiments on the effect of temperature with the foot in a dependent position. This would cause vasoconstriction in the feet of control subjects and thus "mask" the inability of diabetic patients to vasodilate adequately after an increase in temperature. Furthermore, their experiments on the effect of temperature were carried out by treating abdominal skin. The reflexes and mechanisms involved in such experiments may or may not be relevant to local changes in the foot.

These abnormalities in the regulation of $tcPo_2$ are probably based on alterations in the responses of local arterioles. Thus, in neuropathic patients, the arterioles in the cutaneous and subcutaneous tissue are probably in a relatively dilated state due to a loss of vasoconstrictor influences. This would also account for the inability of the arterioles to respond by sufficient vasodilation after an increase in temperature. Because this defect was also observed in nonneuropathic diabetic patients, it cannot be due entirely to denervations secondary to neuropathy. Diabetes itself is associated with altered blood viscosity (10,11), diminished prostaglandin I_2 release (12–14), platelet hyperaggregability (15,16), increased thromboxane A_2 release from platelets (16,17), and abnormalities of vascular permeability (18). These abnormalities could alter the vascular tone, blood flow characteristics, and elasticity of the vascular wall. Thus, patterns of tissue perfusion and oxygenation could be altered. Abnormalities in vascular reactivity have been demonstrated in diabetic patients in various organ systems, e.g., the brain (19,20) and the skin (21).

In terms of the mechanisms underlying the problems of the diabetic foot, i.e., nonhealing ulcers, recurrent infections, and gangrene, the most relevant fact to emerge from our studies is the inability of the diabetic patients, with or without neuropathy, to increase $tcPo_2$ (and probably to vasodilate) to the same extent as nondiabetic subjects after an increase in temperature as the vasodilatory stimulus. Other vasodilatory stimuli responsible for generating hyperemia during inflammation may be similarly ineffective. If so, further research into the restoration of the effect of vasodilatory influences in diabetic patients is necessary. The diabetic foot is still the cause of many admissions of diabetic patients to our hospital.

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