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# Cutaneous Blood Flow in Type 2 Diabetic Individuals After an Acute Bout of Maximal Exercise

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**OBJECTIVE** — We previously demonstrated a positive association between chronic aerobic exercise and dorsal foot skin blood flow during local heating in type 2 diabetic individuals. Thus, we hypothesized that a prior acute bout of maximal exercise would also have positive effects on postexercise blood flow.

**RESEARCH DESIGN AND METHODS** — Subjects consisted of 32 individuals with type 2 diabetes and 26 nondiabetic control subjects further subdivided based on their physical activity status: diabetic exerciser (DE), diabetic sedentary (DS), control exerciser (CE), or control sedentary. Dorsal foot cutaneous blood flow was measured noninvasively by continuous laser-Doppler assessment at baseline and during local heating to 44°C before and after a maximal bout of cycle exercise. Interstitial nitric oxide (NO) levels were measured concurrently in the foot dorsum.

**RESULTS** — Increases in blood flow and its responsiveness to local heating to 44°C were significantly lower in both diabetic groups compared with CE before maximal exercise, but perfusion responsiveness remained lower in DS subjects only after exercise ( $P < 0.05$ ). Baseline skin blood flow was not different among groups preexercise, but it was significantly increased postexercise in DE subjects only. Interstitial NO levels were not significantly different at either time. At baseline, groups differed only in HbA<sub>1c</sub>, fasting serum glucose, HDL cholesterol, and insulin resistance (homeostasis model assessment method).

**CONCLUSIONS** — All diabetic individuals exhibit a blunted responsiveness of cutaneous blood flow with local heating to 44°C before maximal exercise compared with active nondiabetic individuals, but after an exercise bout, it remains significantly blunted only in diabetic individuals who are sedentary. These findings occur independently of changes in interstitial NO levels.

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Skin blood flow is crucial to maintaining the flow of nutrients, regulating body temperature, and healing cutaneous injuries, but its regula-

tion is undeniably complex. Humoral and neurogenic factors affect flow; the more potent vasodilators are nitric oxide (NO), prostacyclin, and bradykinin, whereas va-

soconstrictors are angiotensin, endothelin, and norepinephrine (1–3). Cutaneous vasodilation in the foot dorsum is primarily dependent on neurogenic factors, small C-fiber nociceptors, which account for at least 75% of vasodilation during heating (4).

An increased shunting of blood flow away from skin may exist in the diabetic state, likely caused by the loss of neural control over the arteriovenous shunts active in thermoregulation, creating a deficit in cutaneous capillary blood flow (5–7). Along with neural impairment, attenuated NO-mediated forearm skin vasodilation has been reported in type 2 diabetes (8). Other studies suggest that such a defect may be the result of an imbalance among NO, vasodilator neuropeptides, and vasoconstrictors (9).

At rest and during exercise, endothelial-derived NO plays a role in matching blood flow to tissue metabolism (10). In nondiabetic subjects, chronic physical activities have been demonstrated to increase NO metabolism (11). Furthermore, hyperglycemia in poorly controlled diabetes may reduce NO synthesis or quench available NO (12), and vasodilation in type 2 diabetic subjects with an attenuated response to NO donors is impaired (13).

In a cross-sectional study, we previously demonstrated lower skin perfusion during heating in the dorsal foot in sedentary type 2 diabetic individuals (14). This defect was present despite normal increases in NO, suggesting that either NO is not the main effector or a decrease in its effectiveness played a role in the defect (15). If NO effectiveness can possibly be increased with exercise, then physical activity may be beneficial in preventing or reducing some of the impairment of vascular endothelial function prevalent in diabetes (13).

To our knowledge, no studies have examined the effects of prior maximal exercise on postexercise cutaneous blood flow and NO. The purpose of this study, therefore, was to examine the acute effect of a single prior bout of maximal cycle

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**Abbreviations:** AGE, advanced glycation end product; CE, control exerciser; CS, control sedentary; DE, diabetic exerciser; DS, diabetic sedentary; EDHF, endothelium-derived hyperpolarizing factor; HOMA, homeostasis model assessment; IRP, ischemia reperfusion; NOS, nitric oxide synthase;  $VO_{2peak}$ , peak oxygen consumption.

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

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exercise on dorsal foot blood flow and interstitial NO levels immediately after the activity during baseline conditions and local heating to 44°C.

## RESEARCH DESIGN AND METHODS

We recruited diabetic and nondiabetic subjects of both sexes free of known cardiovascular disease, severe peripheral neuropathy, unstable proliferative retinopathy, end-stage renal disease, uncontrolled hypertension, and use of angiotensin II receptor blockers or ACE inhibitors (known to enhance nerve blood flow) (16). Eligible subjects gave their written informed consent before any testing. During the study, subjects continued to take all of their normal medications.

Diabetic and control subjects were separated into four groups: control exerciser (CE;  $n = 13$ ), control sedentary (CS;  $n = 13$ ), diabetic exerciser (DE;  $n = 15$ ), or diabetic sedentary (DS;  $n = 17$ ). Exercisers had reportedly performed aerobic activities three or more times per week at least 30 min per session at moderate or higher intensity for at least 6 months. The sedentary individuals did very little regular exercise.

At the first visit, each subject underwent a complete history and physical examination. Percent body fat was estimated using skinfold measurements at three standardized sites. Standard fasting laboratory blood work was performed. Neuropathies were assessed using quantitative sensory testing—including vibration, pressure, cold and warm thermal, and cold- and heat-induced pain thresholds at the great toe—and assessment of autonomic function, with measures of cardiac variation with respiration (17).

### Cutaneous blood flow

Dorsal foot skin blood flow was measured noninvasively on both feet during sequential stimuli using continuous laser Doppler assessment (18,19) before and after acute exercise. After baseline flow was assessed, a blood pressure cuff on the subject's calf was used to induce ischemia reperfusion (IRP), followed by immersion of the contralateral hand in ice water for 30 s (cold pressor). Finally, a small area of skin (2 cm diameter) on the dorsum of each foot was heated to 32°C for 5 min and then to 44°C for 10 min to induce neurogenic vasodilation (3,14). Postexer-

Table 1—Resting subject characteristics

	CE	CS	DE	DS
<i>n</i> (M/F)	13 (6/7)	13 (6/7)	15 (8/7)	17 (8/9)
Age (years)	57.5 ± 2.5	56.2 ± 2.6	54.4 ± 2.5	56.0 ± 2.1
Height (cm)	171.6 ± 2.8	172.0 ± 3.3	169.6 ± 3.0	169.2 ± 2.0
Weight (kg)	82.2 ± 4.8	90.6 ± 3.6	92.6 ± 3.3	89.4 ± 4.3
BMI (kg/m <sup>2</sup> )	27.8 ± 1.3	30.9 ± 1.7	32.6 ± 1.7	31.2 ± 1.5
Body fat (%)	28.2 ± 2.5	31.7 ± 2.0	30.0 ± 2.0	29.7 ± 2.1
SBP (mmHg)	131 ± 4	137 ± 4	136 ± 3	141 ± 4
DBP (mmHg)	81 ± 2	86 ± 3	85 ± 2	85 ± 2
Glucose (mmol/l)	5.0 ± 0.1	5.1 ± 0.1	6.5 ± 0.3*†	7.4 ± 0.6*†
HbA <sub>1c</sub> (%)	5.7 ± 0.1	5.7 ± 0.1	6.7 ± 0.1*†	6.9 ± 0.3*†
Insulin (μU/ml)	7.3 ± 0.8	9.8 ± 1.5	13.9 ± 1.9*	13.3 ± 2.2*
Insulin resistance	2.0 ± 0.2	2.6 ± 0.5	4.8 ± 0.6*	5.3 ± 1.0*†
Cholesterol (mmol/l)	5.28 ± 0.19	4.90 ± 0.27	4.98 ± 0.19	5.24 ± 0.23
HDL-C (mmol/l)	1.85 ± 0.15	1.41 ± 0.10*	1.43 ± 0.11*	1.42 ± 0.09*
LDL-C (mmol/l)	2.89 ± 0.16	2.78 ± 0.19	2.79 ± 0.15	3.03 ± 0.20
Triglyceride (mmol/l)	1.14 ± 0.19	1.49 ± 0.26	1.63 ± 0.22	1.69 ± 0.26

Data are means ± SE. Insulin resistance was determined by HOMA method (21) using fasting plasma insulin and glucose values. \* $P < 0.05$  vs. CE; † $P < 0.05$  vs. CS. DBP, diastolic blood pressure; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; SBP, systolic blood pressure.

cise measurements were begun within 10 min of the completion of exercise.

### Interstitial NO levels

We conducted real-time measurement of cutaneous interstitial NO in vivo during the blood flow testing as previously described (14,20). In brief, a subcutaneous microsensor was placed to sample circulating cutaneous interstitial fluids, removed during exercise, and then reinserted in the contralateral foot postexercise. We attempted to control for any artifactual, heat-related changes in NO by fully equilibrating the sensor at each new temperature.

### Maximal cycle ergometry exercise

Each subject then performed a graded maximal protocol on a cycle ergometer (Monark 828e) at a cadence of 50 rpm. Subjects began at an external power output of 0 and 20 watts for female and male subjects, respectively, increasing by 20 watts every 3 min until volitional test termination. An online open indirect calorimetry system (K4b<sup>2</sup> System) measured oxygen uptake and respiratory exchange ratio during testing; peak oxygen consumption (VO<sub>2peak</sub>) was determined as the highest oxygen uptake averaged over 30 s. Glucose and lactate values were measured with a glucose/lactate analyzer (YSI 2300; YSI, Yellow Springs, OH) using fingerstick whole-blood samples obtained during the final minute of each exercise stage.

### Statistical analyses

ANOVAs were used to compare the group means on various measures, and repeated measures were used to compare results from before and after maximal exercise, with Tukey-Kramer post hoc analyses where appropriate. Pearson product-moment correlational analysis was also used to examine associations between selected measured variables. Significance was set at  $P \leq 0.05$ .

### RESULTS

Resting subject characteristics are given in Table 1. Subjects differed by group on measures of fasting serum glucose, HbA<sub>1c</sub>, fasting insulin levels, insulin resistance (homeostasis model assessment [HOMA] method) (21), and HDL cholesterol. Significant differences also existed in one measure of autonomic function (Valsalva index), which was higher (mean ± SE) only in the combined exercise groups (1.62 ± 0.47) compared with all sedentary subjects (1.45 ± 0.45,  $P < 0.05$ ). In sensory measures, heat pain in the great toe was significantly different between control subjects and the combined diabetic groups (16.79 ± 0.52 and 15.10 ± 0.57°C, respectively), but no differences existed in other sensory measures (data not shown).

In Table 2, the subjects' responses to maximal cycle ergometry work are shown. Subject groups were comparable in all variables, with the exception of

Table 2—Peak responses to exercise

	CE	CS	DE	DS
VO <sub>2</sub> (m · kg <sup>-1</sup> · min <sup>-1</sup> )	25.0 ± 2.4	22.2 ± 1.5	24.7 ± 2.6	19.9 ± 1.0
RPE	18.2 ± 0.6	17.9 ± 0.5	17.4 ± 0.5	17.0 ± 0.6
RER	0.98 ± 0.02	1.02 ± 0.03	0.98 ± 0.01	1.03 ± 0.02
HR (bpm)	154.6 ± 5.2	155.6 ± 3.8	150.7 ± 4.9	141.9 ± 6.3
Lactate (mmol/l)	4.4 ± 0.5	4.4 ± 0.4	3.8 ± 0.3	3.9 ± 0.3
SBP (mmHg)	180 ± 6	184 ± 5	190 ± 5	198 ± 6
DBP (mmHg)	90 ± 2	92 ± 2	93 ± 2	97 ± 3

Data are means ± SE. DBP, diastolic blood pressure; HR, heart rate; RER, respiratory exchange ratio; RPE, rating of perceived exertion; SBP, systolic blood pressure.

postexercise insulin resistance, which was significantly higher in both diabetic groups than in either control group.

Table 3 shows the measured dorsal foot skin blood flow in the nonprobed foot and interstitial NO levels in the probed foot during baseline conditions and local heating to 44°C. No significant difference in baseline blood flow among groups was observed before or after exercise, and DE subjects alone demonstrated significantly enhanced baseline blood flow ( $P < 0.05$ ) after exercise. No group differences in blood flow were noted for IRP or cold pressor responses (data not shown). Maximal NO levels during local heating did not differ significantly among groups at either time.

Figure 1 demonstrates the response to local heating after an acute bout of maximal exercise; CE subjects had significantly higher blood flow than DS subjects alone during the final minutes of heating ( $P < 0.05$ ). As shown in Table 3, no subject group experienced a significant change in maximal blood flow with

local heating when comparing each group's pre- and postexercise values. With groups combined by diabetes status, however, control subjects exhibited a higher maximal response to local heating to 44°C than diabetic subjects ( $99.92 \pm 7.57$  vs.  $74.67 \pm 6.83$  perfusion units,  $P < 0.05$ ) preexercise, with only a trend toward higher heated flow after exercise ( $P = 0.07$ ). Figure 2 additionally demonstrates that the magnitude of increases in blood flow in response to heating was significantly lessened in both diabetic groups preexercise compared with CE subjects, but only in DS subjects postexercise.

Using multivariate correlational analysis, resting insulin resistance (HOMA method) was found to correlate significantly with both resting systolic ( $r = 0.37$ ,  $P < 0.01$ ) and diastolic ( $r = 0.31$ ,  $P < 0.05$ ) blood pressures. Both HbA<sub>1c</sub> and fasting glucose levels were weakly inversely correlated with blood flow during heating (but not during baseline condi-

tions) both before and after exercise ( $r = -0.32$  for each,  $P < 0.05$ ).

**CONCLUSIONS**— The current study examined dorsal foot skin blood flow before and after an acute bout of maximal cycle ergometer exercise in diabetic and control subjects. Baseline (nonstimulated) blood flow was enhanced by prior exercise in the more physically active diabetic subjects compared with control subjects. With local heating to 44°C, blood flow responsiveness was significantly lower in both diabetic groups compared with active control subjects preexercise, but only less in sedentary individuals with diabetes after maximal exercise.

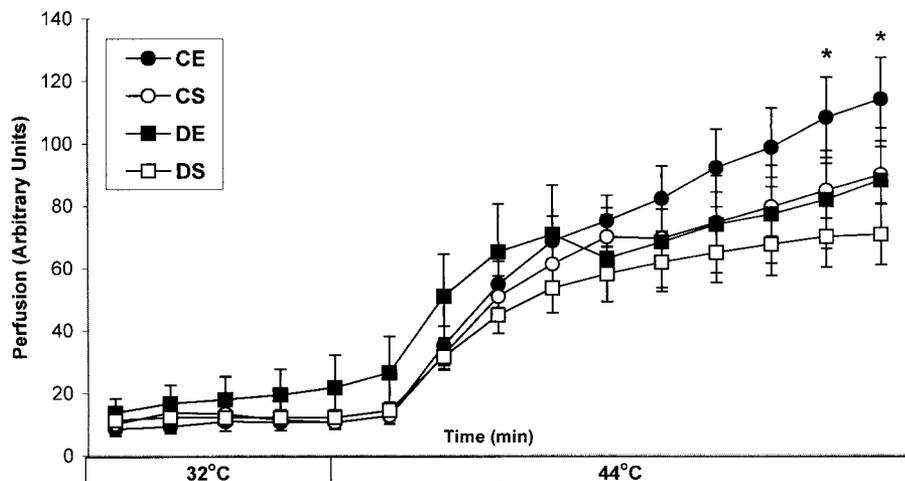
During rest and exercise, the regulation of microvascular blood flow to the skin is undeniably complex and multifaceted. Although 75% of the blood flow response to heating is regulated by small C-fiber nociceptors (4), potent local vasodilator compounds such as NO, prostacyclin, and bradykinin can also increase capillary blood flow (1,3), whereas angiotensin II, endothelin, and norepinephrine can cause vasoconstriction (2,3). Blood flow may be shunted away from the skin in the diabetic state because of the loss of neural control over arteriovenous shunts (5–7). In the forearm skin of type 2 diabetic subjects, significant C-fiber impairment along with an attenuated NO-mediated skin vasodilation has been previously shown (8).

In the present study, baseline (nonstimulated) dorsal foot blood flow before exercise was not significantly different in any subject group, but basal flow was significantly enhanced after exercise in DE subjects. This hyperemic baseline blood flow response to prior maximal exercise, not previously demonstrated in a diabetic population and not evident in control subjects, was interestingly heightened by chronic exercise participation, even though this group was not highly trained compared with control subjects; we can only speculate that even greater changes would be present if active subjects had a higher VO<sub>2peak</sub> relative to sedentary subjects. These data conflict with previous findings of blood flow decrements in a diabetic population during resting conditions (6,8), but they concur with our previous findings of enhanced cutaneous blood flow under certain flow conditions

Table 3—Cutaneous blood flow and NO in the foot dorsum

	CE	CS	DE	DS
Blood flow (perfusion units)				
Baseline				
Preexercise	6.43 ± 1.18	6.67 ± 0.84	6.92 ± 0.70	9.32 ± 2.05
Postexercise	8.81 ± 2.42	8.17 ± 1.15	14.08 ± 2.92*	12.18 ± 3.02
Local heat (44°C)				
Preexercise	108.54 ± 17.67	91.29 ± 9.05	75.20 ± 6.35†	74.96 ± 6.41†
Postexercise	114.27 ± 13.37	89.99 ± 9.08	88.30 ± 16.78	70.90 ± 9.71‡
Nitric Oxide (nmol/l)				
Local heat (44°C)				
Preexercise	149.52 ± 22.20	128.87 ± 23.84	152.83 ± 17.08	160.09 ± 17.08
Postexercise	106.24 ± 15.07	126.81 ± 29.00	133.49 ± 16.74	137.08 ± 16.88

All data are means ± SE. \* $P < 0.05$  vs. preexercise value; † $P < 0.05$  DE and DS combined vs. CE and CS combined; ‡ $P < 0.05$  vs. CE during same condition.



**Figure 1**—Dorsal foot blood flow after maximal exercise during local heating. \* $P < 0.05$  CE vs. DS.

in diabetic individuals who are chronic exercisers (14).

Furthermore, local warming of the skin to 42°C over 20–40 min has been shown to cause maximal vasodilation (22), and our current findings support our previous discovery of a lower baseline blood flow response to local heating in sedentary diabetic subjects (14). After maximal exercise is performed, cutaneous blood flow appears to also be regulated differently in diabetic subjects than active control subjects; both diabetic groups exhibited a blunted responsiveness to local heat preexercise, which persisted in the sedentary group only after maximal exercise. Thus, these data sug-

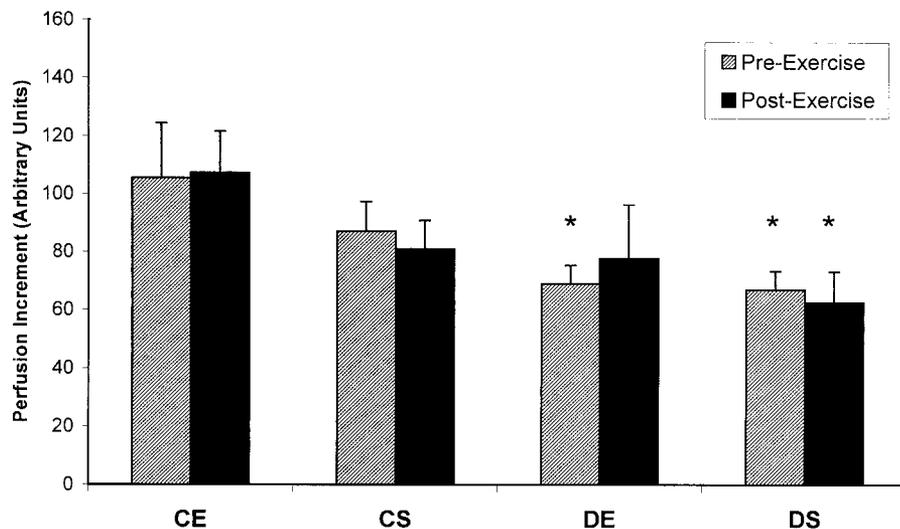
gest that the presence of diabetes alone negatively alters the blood flow response to local heating to 44°C before and after an acute bout of maximal exercise, but that chronic activity may ameliorate this effect.

Exercise training is known to enhance thermoregulatory control, allowing higher cutaneous flow at a given core body temperature and, accordingly, greater heat dissipation (23). Although Kellogg et al. (24) demonstrated that NO appears to play a role in cutaneous vasodilation during local heating to 41°C, whole-body heating did not increase NO levels in the forearm skin, suggesting that NO may serve only a permissive role dur-

ing and possibly after exercise (25). However, other studies have shown that physically trained athletes have chronically increased basal NO metabolism (14) as well as greater resting skin perfusion (26).

In the present study, all subjects experienced a significant increase in basal skin blood flow and NO in response to local heating to 44°C, and as shown in Fig. 1, blood flow continued to rise during extended heating, whereas, although not shown, NO levels actually leveled off early in the same heating period. We previously suggested that the defective blood flow response to local heating in diabetes may be due to a diminished local effectiveness of NO (14,15), but we were unable to substantiate this assertion with the current data. Thus, the subjects' equivalent rise in NO suggests that blunted cutaneous blood flow in response to local heating in diabetic subjects is likely mediated through non-NO mechanisms, such as an altered sensitivity to local neuropeptides (substance P, calcitonin gene-related peptide, and others), compounded by the concurrence of a sedentary lifestyle. However, without further research, we cannot definitively rule out the possibility that the bioavailability of NO may have been negatively affected by the production of superoxide from NO synthase (NOS) mediated through protein kinase C (27). Additionally, Jack et al. (28) recently reported that in diabetic rats, endothelium-derived hyperpolarizing factor (EDHF) may play a much larger role than NO in endothelium-dependent relaxation because diabetes itself markedly reduced the contribution of EDHF in the mesenteric vascular bed.

Finally, disordered neurogenic vasodilation in diabetes may also be partly related to long-term hyperglycemia; in poorly controlled streptozotocin-induced diabetes in rats, it has been associated with reduced NO synthesis and enhanced quenching of available NO (12). Advanced glycation end products (AGEs), also formed during hyperglycemic conditions (29), can quench NO and directly inhibit NOS activity (30). In a study by Vallejo et al. (31), endothelial dysfunction in diabetic rats was related to hyperglycemia and elevated HbA<sub>1c</sub> (but not plasma AGE levels) and to enhanced oxidative stress caused by hyperglycemia. In the current study, we observed an inverse relationship between both fasting glucose



**Figure 2**—Responsiveness of dorsal foot blood flow to local heat before and after maximal exercise. \* $P < 0.05$  vs. CE at the same time.

or HbA<sub>1c</sub> and the maximal cutaneous heated blood flow, but no relationship with maximal NO release, again suggesting that our findings are more likely attributable to a deficiency of sensory neuropeptides or EDHF, rather than the quenching of NO (32,33). The role of intracellular messengers or other non-NO mechanisms should be the focus of future studies because these are required for nociceptor responses (34,35).

In summary, based on the current data, both chronic activity and a prior acute bout of maximal exercise may be beneficial in preventing or reducing some of the impairment in cutaneous blood flow induced by diabetes itself. Regular physical training may have the capacity to offset some of its deleterious effects on cutaneous blood flow under certain flow conditions, and prior maximal exercise may temporarily enhance basal cutaneous blood flow and its responsiveness to local warming. As such, exercise may still prove to be an invaluable tool in the retention of effective skin vasodilation and prevention of foot ulcers.

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