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Effect of a Single Bout of Prior Moderate Exercise on Cutaneous Perfusion in Type 2 Diabetes

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In diabetic individuals, increased shunting of circulation away from the skin may exist, contributing to their greater risk for ulcerations and poor cutaneous healing. In a prospective study (1), we previously found a lower skin perfusion during local heating in the foot dorsum of sedentary type 2 diabetic individuals compared with active people without diabetes. This defect was present despite normal increases in skin interstitial nitric oxide (NO), suggesting that NO is either ineffective or not involved (2). A prior bout of maximal exercise also lessened the impaired responsiveness to local heating of the dorsal foot in active type 2 diabetic individuals but not in their sedentary counterparts (3). Thus, this study examined the effect of a single bout of prior moderate cycle exercise on dorsal foot cutaneous perfusion and interstitial NO.

RESEARCH DESIGN AND METHODS

— Thirty-two diabetic and 26 nondiabetic subjects of both sexes free of known cardiovascular disease, severe peripheral neuropathy, unstable proliferative retinopathy, end-stage renal disease, uncontrolled hypertension, insulin use, and angiotensin II receptor blocker or ACE inhibitor use participated in the study and were in one of the following groups: control exercisers ($n = 13$), control sedentary ($n = 13$), diabetic exercisers ($n = 15$), and diabetic sedentary ($n = 17$). By self-report, exercisers had participated in aerobic exercise for ≥30 min three times per week for ≥6 months.

Each subject underwent a graded, maximal exercise protocol on a cycle ergometer described previously (3). On another day, subjects returned to complete 20 min of moderate exercise at ~50% of the predetermined $V\dot{O}_{2peak}$.

Baseline and postmoderate exercise dorsal foot skin perfusion was measured noninvasively in both feet using continuous laser Doppler assessment (4,5). Probes were positioned in the midmetatarsal area where no vasculature was evident in a thermoneutral laboratory environment (6,7). After baseline assessment, a small area of skin (2 cm) was heated to 32°C for 5 min, followed by 44°C for 10 min to induce neurogenic vasodilation (1,8). Postexercise measures began ~10 min postexercise. A subcutaneous NO microsensor was placed to sample circulating cutaneal interstitial fluids, then removed during exercise and reinserted in the contralateral foot postexercise, as previously described (1,3,9).

ANOVA was used to test resting characteristics and acute exercise responses among subject groups. Repeated-measures ANOVA was utilized to compare groups before and after moderate exercise, with significance set at $P \leq 0.05$.

RESULTS

— Subjects differed by group only on measures of fasting serum glucose, HbA_{1c} (A1C), fasting insulin levels, insulin resistance, and HDL cholesterol, as expected (3). The control exercise subjects had significantly higher perfusion than diabetic sedentary subjects only during the final 5 min of heating ($P < 0.05$), but no group experienced changes in maximal skin perfusion attributable to prior exercise.

However, the perfusion responsiveness to heating to 44°C (Fig. 1) was significantly greater in all exercisers (control and diabetic exercise subjects) compared with diabetic sedentary subjects before exercise but was enhanced in control exercise subjects compared with diabetic sedentary subjects only following 20 min of moderate exercise. In addition, perfusion responsiveness to local heating was inversely related to A1C ($r = -0.33$) and fasting glucose ($r = -0.32$) postexercise ($P < 0.05$).

Interstitial NO levels did not differ during baseline conditions. Moreover, during maximal stimulatory conditions pre-exercise (control exercisers 109.0 ± 17.9, control sedentary 127.7 ± 17.7, diabetic exercisers 130.4 ± 17.0, and diabetic sedentary subjects 128.6 ± 19.3 nmol/l) and postexercise (control exercisers 96.4 ± 14.2, control sedentary 122.4 ± 21.7, diabetic exercisers 133.7 ± 25.6, and diabetic sedentary subjects 123.6 ± 16.8 nmol/l), NO levels were similar among groups despite differences in perfusion.

CONCLUSIONS

— The current study examined dorsal foot skin perfusion before and following an acute bout of moderate cycle ergometer exercise (20 min at ~50% $V\dot{O}_{2peak}$) in diabetic and control subjects. The response to localized heating is largely controlled by small C-fiber nociceptors (10), allowing neural control over arteriovenous shunts (11–13). In the skin of type 2 diabetic subjects, significant C-fiber impairment along with an attenuated NO-mediated skin vasodilation has been previously shown (14,15). In the present study, however, all measures of C-fiber and autonomic function were intact; thus, any differences seen between diabetic and control groups were not likely attributable to neuropathic changes.

Local warming of the skin to 42°C over 20–40 min has been shown to cause maximal vasodilation (16). We previously found a lesser perfusion response to

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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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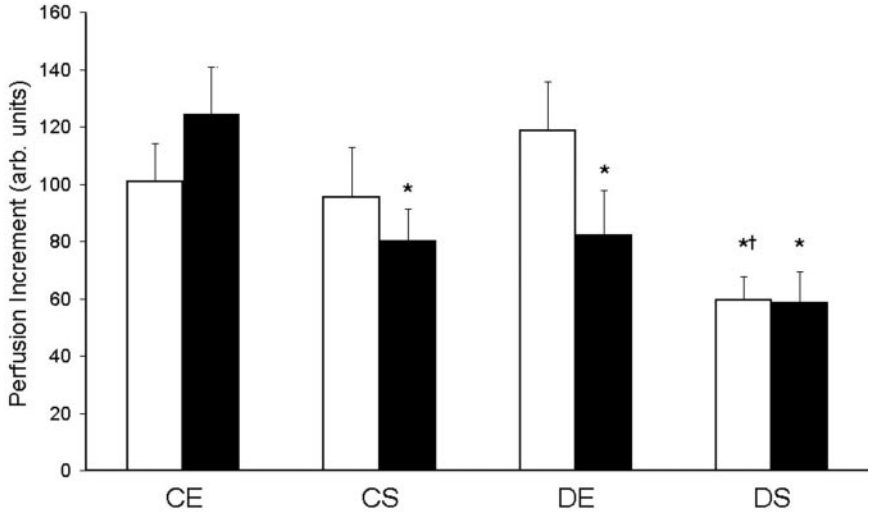

Figure 1—*Perfusion responsiveness to heating by group. □, pre-exercise group; ■, post-exercise group. CE, control exercisers; CS, control sedentary; DE, diabetic exercisers; DS, diabetic sedentary. *P < 0.05 vs. control exercisers at same time; †P < 0.05 vs. diabetic exercisers at same time.*

local heating in sedentary diabetic subjects at rest (1) and following an acute bout of maximal cycle exercise (3). Similarly, following moderate exercise, cutaneous perfusion was blunted in diabetic sedentary subjects under heat-stimulated conditions, suggesting that the combination of diabetic and sedentary states together has a greater effect.

Endothelium-dependent dilation in skin vasculature is enhanced by moderate exercise training and reversed by detraining (17), and trained athletes have enhanced endothelium-dependent vasodilatation in skin vasculature at rest (18). These studies suggest that exercise modifies the responsiveness of the cutaneous endothelium, although we found such differences in our subjects to be abolished by a bout of maximal exercise (3). Likewise, differences in stimulated perfusion increments between diabetic exercisers and diabetic sedentary subjects were no longer evident after exercise in this study. Thus, an acute bout of moderate exercise may modify pre-exercise differences, albeit possibly only temporarily.

All subject groups in the present study experienced significant increases in basal skin perfusion and NO in response to local heating to 44°C, even without a sustained increase in NO, suggesting that the defective response often observed in diabetes is not likely caused by a diminished local effectiveness of NO (1,2). These NO findings are similar to our findings for prior maximal exercise (3), aerobic training (19), and resistance training (20).

Moreover, the equivalent rise in NO suggests that cutaneous perfusion with local heating is more likely mediated through a non-NO mechanism, such as an altered sensitivity to local neuropeptides like substance P and calcitonin gene–related peptide (21). While the bioavailability of NO may have been negatively affected by the production of reactive oxygen species (22,23), advanced glycation end products (24), or failure to activate cyclic guanosine monophosphate, our studies showing normal NO-stimulated calcitonin gene–related peptide release in type 2 diabetes make these outcomes unlikely (25).

Finally, in the current study, a significant inverse relationship between both fasting glucose and A1C and the responsiveness to local heating after exercise existed. Such a relationship may be attributable either to a deficiency of sensory neuropeptides (26,27), to the quenching of NO by hyperglycemia (24), or to both and warrants further investigation.

In summary, following 20 min of moderate exercise, cutaneous perfusion in nondiabetic exercisers alone exhibits a greater responsiveness to local heating, suggesting that it is negatively affected by both diabetes and inactivity, independent of NO production in the skin.

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