2006

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

Sheri R. Colberg
*Old Dominion University*, scolberg@odu.edu

Henri K. Parson

Tanja Nunnold
*Old Dominion University*

D. Robb Holton
*Old Dominion University*

Aaron I. Vinik



## Original Publication Citation

Colberg, S. R., Parson, H. K., Nunnold, T., Holton, D. R., & Vinik, A. I. (2006). Effect of a single bout of prior moderate exercise on cutaneous perfusion in type 2 diabetes. *Diabetes Care, 29*(10), 2316-2318. doi:10.2337/dc-06-1440

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

SHERI R. COLBERG, PHD[1]
HENRI K. PARSON, PHD[2]
TANJA NUNNOLD, MSED[1]
D. ROBB HOLTON, MSED[1]
AARON I. VINIK, MD, PHD[2]

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

From the [1]Exercise Science, Sport, Physical Education, and Recreation Department, Old Dominion University, Norfolk, Virginia; and [2]The Strelitz Diabetes Institutes at Eastern Virginia Medical School, Norfolk, Virginia.

Address correspondence and reprint requests to Sheri Colberg, PhD, ESPER Department, Old Dominion University, Norfolk, VA 23529. E-mail: scolberg@odu.edu.

Received for publication 10 July 2006 and accepted in revised form 14 July 2006.

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

DOI: 10.2337/dc-06-1440

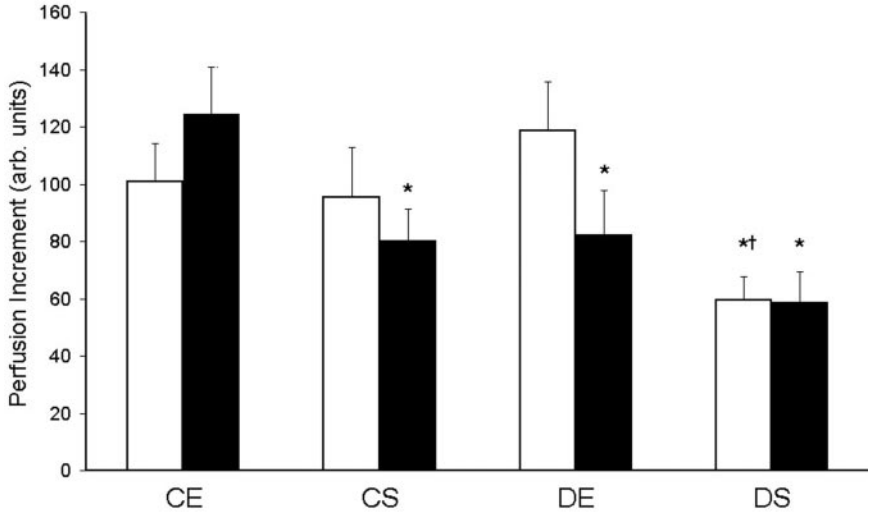


**Figure 1**—*Perfusion responsiveness to heating by group. □, pre-exercise group; ■, post-exercise group. CE, control exercisers; CS, control sedentary; DE, diabetic exercisers; DS, diabetic sedentary. *P < 0.05 vs. control exercisers at same time; †P < 0.05 vs. diabetic exercisers at same time.*

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.

**Acknowledgments**— This work was fully supported by a clinical research grant from the American Diabetes Association.

**References**

1. Colberg SR, Stansberry KB, McNitt PM, Vinik AI: Chronic exercise is associated with enhanced cutaneous blood flow in type 2 diabetes. *J Diabetes Complications* 16:139–145, 2002
2. Stansberry KB, Scanelli JA, McNitt PM, Vinik AI: Nitric oxide production mediates neurogenic vasodilation in human skin but is not impaired in type 2 diabetes (Abstract). *Diabetes* 49 (Suppl. 1):A33, 2000
3. Colberg SR, Parson HK, Holton DR, Nunnold T, Vinik AI: Cutaneous blood flow in type 2 diabetic individuals following an acute bout of maximal exercise. *Diabetes Care* 26:1883–1888, 2003
4. Stansberry KB, Hill M, McNitt PM, Bhatt BA, Vinik AI: Skin blood flow reactivity and neuropathy (Abstract). *Diabetes* 43 (Suppl. 1):107A, 1994
5. Stansberry KB, Hill MA, Shapiro SA, McNitt PM, Bhatt BA, Vinik AI: Impairment of peripheral blood flow responses in diabetes resembles an enhanced aging effect. *Diabetes Care* 20:1711–1716, 1997
6. Wardell K, Braverman IM, Silverman DG, Nilsson GE: Spatial heterogeneity in normal skin perfusion recorded with laser Doppler imaging and flowmetry. *Microvasc Res* 48:26–38, 1994
7. Tenland T, Salerud EG, Nilsson GE, Oberg PA: Spatial and temporal variations in human skin blood flow. *Int J Microcirc Clin Exp* 2:81–90, 1983
8. Vinik AI, Erbas T, Park TS, Pierce KK, Stansberry KB: Methods for evaluation of peripheral neurovascular dysfunction. *Diabetes Technol Ther* 3:29–50, 2001
9. Vallance P, Patton S, Bhagat K, MacAllister R, Radomski M, Moncada S, Malinski T: Direct measurement of nitric oxide in human beings. *Lancet* 346:153–154, 1995
10. Pergola PE, Kellogg DL, Johnson JM, Kosiba WA, Solomon DE: Role of sympathetic nerves in the vascular effects of local temperature in human forearm skin. *Am J Physiol* 265:H785–H792, 1995
11. Boulton AJ, Scarpello JH, Ward JD: Venous oxygenation in the diabetic neuropathic foot: evidence for arterio-venous shunting? *Diabetologia* 22:6–8, 1982
12. Ward JD, Simms JM, Knight G, Boulton AJ, Sandler DA: Venous distension of the diabetic neuropathic foot (physical sign of arteriovenous shunting). *J R Soc Med* 76: 1011–1014, 1983
13. Rendell M, Bamisedun O: Diabetic cutaneous microangiopathy. *Am J Med* 93: 611–618, 1993
14. Kilo S, Berghoff M, Hilz M, Freeman R: Neural and endothelial control of microcirculation in diabetic peripheral neuropathy. *Neurology* 54:1246–1252, 2000
15. Williams SB, Cusco JA, Roddy MA, Johnstone MT, Creager MA: Impaired nitric oxide-mediated vasodilation in patients

with non-insulin-dependent diabetes mellitus. *J Am Coll Cardiol* 27:567–574, 1996
16. Tooke JE: Peripheral microvascular disease in diabetes. *Diabetes Res Clin Pract* 30 (Suppl.):S61–S65, 1996
17. Wang JS: Effects of exercise training and detraining on cutaneous microvascular function in man: the regulatory role of endothelium-dependent dilation in skin vasculature. *Eur J Appl Physiol* 93:429–434, 2005
18. Kvernmo HD, Stefanovska A, Kirkeboen KA, Osterud B, Kvernebo K: Enhanced endothelium-dependent vasodilatation in human skin vasculature induced by physical conditioning. *Eur J Appl Physiol Occup Physiol* 79:30–36, 1998
19. Colberg SR, Parson HK, Nunnold T, Holton DR, Swain DP, Vinik AI: Change in cutaneous perfusion following ten weeks of aerobic training in type 2 diabetes. *J Diabetes Complications* 19:276–283, 2005
20. Colberg SR, Parson HK, Nunnold T, Herriott MT, Vinik AI: Effect of an 8-week resistance training program on cutaneous perfusion in type 2 diabetes. *Microvasc Res* 71:121–127, 2006
21. Leighton B, Foot A: The role of sensory peptide calcitonin gene-related peptide(s) in skeletal muscle carbohydrate metabolism: effects of capsaicin and resiniferatoxin. *Biochem J* 307:707–712, 1995
22. Guzik TJ, West NE, Pillai R, Taggart DP, Channon KM: Nitric oxide modulates superoxide release and peroxynitrite formation in human blood vessels. *Hypertension* 39:1088–1094, 2002
23. Hink U, Li H, Mollnau H, Oelze M, Matheis E, Hartmann M, Skatchkov M, Thaiss F, Stahl RAK, Warnholtz A, Meinertz T, Griendling K, Harrisson DG, Forstermann U, Munzel T: Mechanisms underlying endothelial dysfunction in diabetes mellitus. *Circ Res* 88:E14–E22, 2001
24. Turk Z, Misur I, Turk N, Benko B: Rat tissue collagen modified by advanced glycation: correlation with duration of diabetes and glycemic control. *Clin Chem Lab Med* 37:813–820, 1999
25. Ullal J, Mason M, Stansberry K, Barlow P, Vinik A: Losartan causes acute increase in SkBF and increase in NO stimulated cGMP in type 2 diabetes as compared to lisinopril or a combination (Abstract). *Diabetes* 52 (Suppl. 1):A457–A458, 2003
26. Vallejo S, Angulo J, Peiro C, Cercas E, Sanchez-Ferrer A, Nevado J, Llergo JL, Rodriguez-Manas L, Sanchez-Ferrer CF: Treatment with acarbose may improve endothelial dysfunction in streptozotocin-induced diabetic rats. *J Cardiovasc Pharmacol* 36:255–262, 2000
27. Forsgren S, Bergh A, Carlsson E, Thornell LE: Calcitonin gene-related peptide expression at endplates of different fibre types in muscles in rat hind limbs. *Cell Tissue Res* 274:439–446, 1993