# Acute Effects of Adrenergic-Mediated Ischemia on Nerve Conduction in Subjects With Type 2 Diabetes

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**Several lines of evidence support peripheral nerve ischemia as a contributing factor in the etiology of human diabetic neuropathy. We questioned whether diabetic subjects with relatively normal nerve function in the baseline state would be more likely than healthy control subjects to show either improvement of ulnar nerve function with acute intraarterial infusion of nitroprusside (vasodilation) or be more sensitive than control subjects to worsening of nerve function with acute intraarterial infusion of norepinephrine (vasoconstriction). We measured forearm blood flow (FABF) using venous occlusion plethysmography and assessed ulnar nerve function at baseline and during two intrabrachial artery infusions. Six nondiabetic control subjects (mean age, 56 years) and 11 subjects with type 2 diabetes (mean age, 58 years) in good general health participated. Only three type 2 diabetic subjects had peripheral sensory neuropathy, which was mild. Among control subjects, there was no significant change in sensory distal latency, motor distal latency, motor proximal latency, or sensory or motor conduction velocity during norepinephrine infusion. In contrast, among type 2 diabetic subjects, there was a significant increase in sensory (baseline *v* norepinephrine, 2.73 ± 0.10 *v* 2.94 ± 0.10 milliseconds [MS], $P \leq .01$) and motor distal latencies (baseline *v* norepinephrine, 2.90 ± 0.06 *v* 3.18 ± 0.1 ms, $P \leq .001$) and motor proximal latency (baseline *v* norepinephrine, 7.15 ± 0.18 *v* 7.60 ± 0.23 ms, $P < .01$) and a decrease in sensory conduction velocity (baseline *v* norepinephrine, 52.1 ± 2.0 *v* 47.7 ± 1.6 m/s, $P < .01$) during norepinephrine infusion. There were no consistent changes in nerve function during nitroprusside infusion in either group. In summary, we found that subjects with type 2 diabetes, but not control subjects, demonstrate a decrement in nerve function with vasoconstriction during intraarterial infusion of norepinephrine, but no consistent change during nitroprusside-induced vasodilation. These findings suggest there may be enhanced sensitivity of nerve function to ischemia in type 2 diabetic subjects with mild or absent clinical neuropathy.**


SEVERAL LINES OF EVIDENCE support peripheral nerve ischemia as a contributing factor in the etiology of human diabetic neuropathy.[1,2] Ischemia may result from either inadequate oxygenation of the blood reaching diabetic nerves or inadequate blood flow to them. Nerve blood flow has been shown to decrease soon after the development of diabetes in rats. At 1 week, this decrease in endoneurial blood flow is accompanied by a reduction in conduction velocity.[3] Treatment with a variety of vasodilators has been shown in some instances to reverse nerve conduction and blood flow deficits in rats.[2]

Using an acute model of ischemia, resistance to ischemia-mediated nerve conduction impairment has been described in both animals and humans with diabetes.[4-6] One proposed explanation for these findings is that diabetic nerves convert to anaerobic metabolism as an energy source in the setting of inadequate insulin and/or insulin action.[7] In animal models, this resistance to ischemia was prevented when glucose levels were well controlled.[8,9] Inadequate glucose control may contribute to ischemia through osmotic effects leading to fluid shifts, possibly resulting in hyperviscosity,[7] ultimately decreasing the blood flow. In these studies, ischemia has been accomplished by external compression. Intraarterial norepinephrine at pharmacologic doses is another means to reduce blood flow to test the effects of ischemia on nerve function.

There is indirect support for a vascular component to peripheral nerve dysfunction in human diabetes.[2] We tested whether nerve function in subjects with type 2 diabetes would be more dependent on changes in blood flow than in control subjects. We postulated that peripheral nerves of diabetic subjects without overt severe neuropathy may be more sensitive to acute vasoconstriction resulting from intraarterial norepinephrine than control nerves. We also questioned whether such patients would be more likely than healthy control subjects to show improvement of nerve function with acute vasodilation. To test this hypothesis, we used a forearm blood flow (FABF) model and assessment of ulnar nerve function during intrabrachial artery infusion of nitroprusside to produce vasodilation and during intrabrachial artery infusion of norepinephrine to produce vasoconstriction.

## SUBJECTS AND METHODS

### *Subjects*

Six nondiabetic control subjects (mean age, 56 years; range, 33 to 75; three men and three women) and 11 subjects with type 2 diabetes (mean age, 58 years; range, 37 to 75; nine men and two women) in good general health were recruited through newspaper advertisement and from the Human Subjects Core of the University of Michigan Geriatrics Center. Subjects were screened before study entry with a medical history, physical examination, and laboratory tests, including complete blood cell count, urinalysis, and routine chemistries. Subjects were classified as type 2 diabetics by their primary care providers. All had

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adult onset of diabetes and no history of ketoacidosis. Subjects were excluded from participation if they exceeded 150% of their ideal body weight (Metropolitan Life Insurance Tables, 1983), had a resting seated blood pressure greater than 160 mm Hg systolic or greater than 90 mm Hg diastolic, were taking any medication that might affect blood flow or nerve function (which could not be withheld for 3 days prior to study), or had evidence from either the history, physical examination, or laboratory results of significant underlying illness.

Three subjects with type 2 diabetes were on replacement therapy for hypothyroidism with a thyroid-stimulating hormone level in the normal range. With regard to treatment for diabetes, four were treated with diet alone, four with a sulfonylurea, and three with insulin. With regard to the duration of diabetes, four were newly diagnosed during screening for this project, four reported a diabetes duration of 5 years or less, one 10 years or less, and two greater than 10 years. Although none of the subjects with diabetes underwent typical cardiovascular autonomic function testing, in addition to having no clinical symptoms or signs of autonomic dysfunction, arterial plasma norepinephrine levels were obtained at baseline on the morning of study to provide a measure of sympathetic nervous system activity. The nerve conduction studies performed as part of this study were used to characterize large fiber sensory function. Among the control subjects, one had an isolated prolonged ulnar sensory latency. Among the diabetic subjects, three had mild sensory neuropathy using the Diabetes Control and Complications Trial criteria of a positive neurologic examination and abnormalities of two nerve conductions,[10] and two had an isolated prolonged ulnar sensory latency. Otherwise, they were without large fiber sensory neuropathy. Each subject provided written informed consent that was approved by the University of Michigan Institutional Review Board.

### *Study Protocol*

The subjects reported to the General Clinical Research Center of the University of Michigan Hospitals at 7:30 AM on the day of study. They were instructed to fast from 10:00 PM the night before and not to take their afternoon insulin the day before study nor insulin on the morning of study. Subjects taking an oral agent withheld it for 3 days prior to study. The subjects were studied in the supine position in a quiet room maintained at a constant temperature of 23° to 25°C to facilitate adequate baseline FABF.

Forearm volume (FAV) was measured using water displacement[11,12] (Table 1). A 20-gauge 1.25-inch Angiocath catheter was placed in the brachial artery of the nondominant arm. The catheter was connected to a pressure transducer (1290A quartz transducer; Hewlett-Packard, Andover, MA). Mean arterial pressure (MAP) was determined from the electronically integrated area under the intraarterial blood pressure curve from the Marquette telemetry system (Electronics Series 7700; Marquette Electronics, Milwaukee, WI) just before each FABF measurement. One of the three basic electrocardiographic limb leads was monitored.

**Table 1. Characteristics of the Control Subjects and Subjects With Type 2 Diabetes**

| Characteristic | Control | Type 2 Diabetes | *P* |
|---|---|---|---|
| Age (yr) | 56.5 ± 7.3 | 58.8 ± 3.8 | .76 |
| Gender (n) | 3M/3F | 9M/2F | |
| Body mass index (kg/m$^2$) | 24.1 ± 1.2 | 29.5 ± 1.1 | <.01 |
| Body fat (%) | 27.1 ± 2.6 | 28.9 ± 2.0 | .61 |
| MAP (mm Hg) | 95.3 ± 2.8 | 101.3 ± 1.9 | .09 |
| Glycosylated hemoglobin (%) | 5.7 ± 0.2 | 10.0 ± 1.0 | <.01 |
| Baseline palm temperature (°C) | 32.2 ± 0.9 | 33.5 ± 0.2 | .07 |
| Plasma norepinephrine (pg/mL) | 292 ± 35 | 360 ± 27 | .15 |

NOTE. Results are the mean ± SE.
Abbreviations: M, male; F, female.

### *Bioelectrical Impedance*

Body composition was estimated by bioelectrical impedance using an RJL instrument (model BIA-103 B; RJL Systems, Mt. Clemens, MI).

### *FABF Protocol*

FABF was measured using venous occlusion plethysmography during an intrabrachial artery infusion protocol we have previously described.[13] This method permits a local effect on FABF to be studied without significant systemic hemodynamic effects.[14] To establish a stable baseline, FABF readings were taken until three consecutive readings representing similar FABF were obtained. An arterial blood sample for catecholamines was then obtained. The vasodilator nitroprusside (Nitropress; Abbott Laboratories, North Chicago, IL) was diluted in 5% dextrose to achieve an infusion dose of 0.64 μg/dL FAV/min administered via the brachial artery catheter by an infusion pump (model 970T: Harvard Apparatus, South Natick, MA). Infusion of this dose was continued until completion of the FABF measurement and nerve conduction study (approximately 20 minutes), when the infusion was stopped.

Following a 10-minute washout period, norepinephrine infusion was performed. Norepinephrine (Levophed bitartrate; Sterling Drug, New York, NY) was diluted in 5% dextrose to achieve an infusion dose of 24 μg/dL FAV/min. Intraarterial infusion of this dose was continued until completion of the FABF measurement and nerve conduction study (approximately 20 minutes), when the infusion was stopped. The doses for nitroprusside and norepinephrine were chosen based on past studies that demonstrated significant changes in local FABF without systemic hemodynamic changes.[13,15,16]

### *Neurophysiologic Studies*

Measurements of nerve conduction at baseline, during nitroprusside, and then during norepinephrine infusion were performed, following the FABF measurement that began after 4 minutes of infusion, using surface electrodes and a standard electromyograph (TD 20; Teca, Pleasantville, NY) in the nondominant arm. Palmar surface temperature was measured (YSI Tele-Thermometer; Yellow Springs Instruments, Yellow Springs, OH) just prior to the nerve conduction study (approximately 6 minutes into the infusion). Ulnar sensory evoked responses were measured from the fifth digit (averaging three responses), stimulating the ulnar nerve supramaximally at the wrist. Ulnar motor evoked responses were measured from the abductor digit quinti (hand) after stimulation at the wrist and elbow. Recording electrodes were left in place throughout the evaluation, and stimulation sites were marked and used to evoke each response, keeping distances identical. Measurements of motor and sensory conduction velocity and distal latency onset during nitroprusside and norepinephrine were corrected for temperature variation before comparison to baseline measurements by the method of Denys.[17] The change in temperature between the baseline measurement and the measurement during vasoactive infusate administration was used. To avoid unintentional bias in the interpretation of nerve studies, the interpreter was blinded as to whether the study was from a diabetic subject and as to whether the study was performed during a vasoactive infusion or before any infusions.

### *Analytical Methods*

The percent glycosylated hemoglobin was determined in the Core Laboratory of the University of Michigan Diabetes Research and Training Center using the Isolab Glyc-Affin Ghb rest kit (Isolab, Akron, OH).

Arterial blood samples were collected into chilled plastic tubes containing EGTA and reduced glutathione. The tubes were kept on ice

until centrifugation at 4°C. Plasma samples were stored at −70°C until assayed. Plasma norepinephrine was quantified by a single-isotope radioenzymatic assay.[18] The intraassay coefficient of variation for norepinephrine in this assay is 5%.

### *Data and Statistical Analysis*

Baseline subject characteristics were compared using unpaired *t* tests. To control for potential differences in baseline FABF within and between the control and diabetic groups, FABF data for nitroprusside and norepinephrine were analyzed as the change in FABF from the baseline value obtained before the baseline measurement of nerve function. The change in FABF and the FABF values achieved during nitroprusside in control versus type 2 diabetic groups were analyzed by unpaired *t* test.

The change in conduction characteristics and the temperature measured prior to each nerve conduction measurement were compared between control and diabetic groups using unpaired *t* tests. Differences in conduction velocity and latency in both sensory and motor ulnar nerves were compared within groups using paired *t* tests. Values are presented as the mean ± SE. Statistical analysis was performed using Statview 4.5 (Abacus Concepts, Berkeley, CA). *P* values less than .05 were considered statistically significant.

## RESULTS

### *Subject Characteristics*

Characteristics of the control and type 2 diabetic subjects are compared in Table 1. The two groups were not statistically different with respect to age or percent body fat, but diabetic subjects had a higher body mass index. The diabetic group tended to have higher MAP, baseline FABF, and plasma norepinephrine than the control group and lower palmar skin temperature, although these differences were not statistically significant. Plasma glucose on the morning of study was 151 ± 11 mg/dL (range, 100 to 193) among diabetic subjects and 93 ± 3 mg/dL (range, 79 to 100) among control subjects. Glycosylated hemoglobin was elevated in the diabetic subjects, with a range of 6.5% to 14.7% (normal, 4% to 8%). Serum creatinine was within the normal range for all subjects (normal, 0.9 to 1.3 mg/dL).

### *FABF During Vasoactive Intraarterial Infusions*

The increase in FABF from baseline (control *v* type 2, 3.53 ± 0.28 *v* 5.36 ± 0.76 mL/dL FAV/min, $P = .10$) to the level achieved during intraarterial infusion of nitroprusside was greater among control subjects compared with type 2 diabetics (control *v* type 2, ΔFABF, 10.8 ± 0.90 *v* 7.40 ± 0.98 mL/dL FAV/min, $P = .04$). However, there was no significant difference between control and type 2 diabetic subjects in the absolute FABF achieved during local intraarterial infusion of nitroprusside (control *v* type 2, 14.3 ± 0.9 *v* 12.8 ± 1.2 mL/dL FAV/min, $P = .39$). The decrease in FABF from baseline to the FABF achieved during intraarterial infusion of norepinephrine was greater among diabetic subjects (control *v* type 2 ΔFABF, −1.3 ± 0.4 *v* −3.5 ± 0.7 mL/dL FAV/min, $P = .05$). However, there was no significant difference between control and diabetic groups in the absolute FABF achieved during local intraarterial infusion of norepinephrine (control *v* type 2, 2.2 ± 0.5 *v* 1.8 ± 0.3 mL/dL FAV/min, $P = .51$).

### *Temperature During Vasoactive Intraarterial Infusions*

Palmar temperature was measured during each infusion just before each nerve conduction measurement. Temperatures (°C) measured during the nitroprusside (control *v* type 2, 34.0 ± 0.4 *v* 34.0 ± 0.2; $P = .8$) and norepinephrine (control *v* type 2, 32.7 ± 0.6 *v* 33.0 ± 0.2, $P = .6$) infusions were not statistically different between groups.

### *Ulnar Sensory and Motor Nerve Conduction Studies During Nitroprusside*

*Ulnar sensory and motor distal latency.* Ulnar sensory distal latency from the wrist to the fifth digit was obtained on all six controls and all 11 subjects with type 2 diabetes at baseline, and on eight of 11 diabetic subjects during nitroprusside. Ulnar motor distal latency from the wrist to hypothenar was obtained on all subjects at baseline and during nitroprusside. Neither baseline sensory (control *v* type 2, 2.77 ± 0.19, 2.73 ± 0.10 ms, $P = .84$) nor motor (control *v* type 2, 2.85 ± 0.11 *v* 2.90 ± 0.06 ms, $P = .66$) distal latencies differed significantly between groups. Among control subjects, there were no significant changes in ulnar sensory wrist to fifth digit or ulnar motor wrist to hypothenar distal latencies during nitroprusside. In contrast, among the diabetic subjects, there was an increase in ulnar sensory distal latency but no consistent change in ulnar motor distal latency during nitroprusside infusion (Table 2).

Ulnar motor proximal latency from the elbow to hypothenar was obtained on all control subjects and 10 of 11 diabetic subjects at baseline and all control subjects and eight of 11 diabetic subjects during intraarterial infusion of nitroprusside.

**Table 2. Effects of Intraarterial Nitroprusside Infusion on Ulnar Nerve Function**

| Measurement | Control | | Type 2 Diabetes | |
|---|---|---|---|---|
| | Baseline (n = 6) | Nitroprusside (n = 6) | Baseline (n = 8) | Nitroprusside (n = 8) |
| Latency (ms) | | | | |
| Distal sensory wrist-5th† | 2.77 ± 0.19 | 2.87 ± 0.18 | 2.66 ± 0.12 | 2.80 ± 0.09* |
| Distal motor wrist-hypothenar | 2.85 ± 0.11 | 2.89 ± 0.14 | 2.89 ± 0.08 | 2.92 ± 0.12 |
| Proximal motor elbow-hypothenar | 6.55 ± 0.31 | 6.36 ± 0.25 | 7.36 ± 0.20‡ | 7.3 ± 0.17 |
| Conduction velocity (m/s) | | | | |
| Sensory wrist-5th† | 51.8 ± 3.4 | 52.9 ± 3.2 | 53.3 ± 2.4 | 51.2 ± 1.8 |
| Motor elbow-wrist | 58.5 ± 2.0 | 58.6 ± 1.7 | 55.2 ± 2.1‡ | 54.8 ± 2.0 |

NOTE. Results are the mean ± SE.

*$P < .05$, Baseline *v* nitroprusside.

†Fifth digit of hand.

‡n = 7.

Baseline motor proximal latency tended to be higher among the diabetic group (control *v* type 2, 6.55 ± 0.31 *v* 7.15 ± 0.18 ms, $P = .09$). Among both the control and diabetic groups, there was no significant change in motor proximal latency during vasodilation with nitroprusside (Table 2).

*Ulnar sensory and motor conduction velocity.* Ulnar sensory conduction velocity, from the wrist to the fifth digit was obtained on all control subjects at baseline and on eight of 11 diabetic subjects during nitroprusside. Ulnar motor conduction velocity, from the elbow to the wrist was obtained on 10 of 11 diabetic subjects at baseline and eight of 11 diabetic subjects during nitroprusside. Baseline sensory conduction velocity was not significantly different between groups (control *v* type 2, 51.8 ± 3.4 *v* 52.1 ± 2.0 m/s, $P = .93$). Motor conduction velocity tended to be lower in the diabetic group (control *v* type 2, 58.5 ± 2.0 *v* 56.6 ± 1.6 m/s, $P = .49$), but this difference was not statistically significant. Vasodilation during nitroprusside resulted in no significant change in sensory or motor conduction velocity in either the control or diabetes group (Table 2).

### *Ulnar Sensory and Motor Nerve Conduction Studies During Norepinephrine*

*Ulnar sensory and motor distal latency.* Ulnar sensory distal latency from the wrist to the fifth digit and motor distal latency from the wrist to hypothenar were obtained on all control and diabetic subjects at baseline and during intraarterial infusion of norepinephrine. Among the control subjects, there was no significant change in sensory distal latency or motor distal latency during norepinephrine. In contrast, among the diabetic subjects, there was a significant increase in both sensory and motor distal latency during norepinephrine infusion (Table 3).

Ulnar motor proximal latency, from the elbow to hypothenar was obtainable for all control subjects, 10 of 11 diabetic subjects at baseline, and all diabetic subjects during norepinephrine. Among the control subjects, there was no significant change in motor proximal latency during norepinephrine. However, among the diabetic subjects, there was a significant increase in motor proximal latency during norepinephrine infusion (Table 3).

*Ulnar sensory and motor conduction velocity.* Ulnar sensory conduction velocity, from the wrist to the fifth digit and ulnar motor conduction velocity, from the elbow to the wrist were obtained in all subjects. Among the control subjects, there was no significant change in sensory or motor conduction velocity during norepinephrine. In contrast, among the diabetic subjects, there was a significant decrease in sensory conduction velocity but no significant change in motor conduction velocity during norepinephrine infusion (Table 3).

## DISCUSSION

Decreased FABF during intraarterial norepinephrine infusion was associated with decreased peripheral sensory nerve conduction velocity but no significant change in motor nerve conduction velocity in subjects with diabetes. Correspondingly, distal latency was found to increase significantly with norepinephrine infusion in subjects with diabetes. Increased FABF during intraarterial nitroprusside infusion was associated with no change in conduction velocity in either subject group. These results are similar to previous findings in various animal models of diabetes[19] and consistent with the hypothesis that vascular components may contribute to the development or progression of impaired nerve conduction in individuals with diabetes.

These results seem contrary to the literature that characterizes the resistance of diabetic nerves to ischemic conduction block.[20] In both animals and humans, diabetic nerves have shown resistance to ischemic compression block. A number of different mechanisms have been proposed to account for the resistance of diabetic nerves to ischemic compression.[21] Among these is the induction of anaerobic metabolism in the diabetic nerve. This resistance to ischemic conduction failure is lessened, if not eliminated, with normalized glycemic control[9] or during decreased sympathetic neurovascular tone in experimental animals.[3,22]

This model of decreased FABF during intraarterial norepinephrine may result in a uniform reduction of FABF, whereas ischemic compression causes a compartmentalized decrease of blood flow. If this is true, it is possible that intraarterial norepinephrine causes more complete acute nerve ischemia by decreasing blood flow at the level of the vasonervorum versus ischemic compression at the macrovascular level of the brachial artery, although resistance to ischemia has been shown during hypoxia, as well, in diabetic rats.[23] In this study, we measured the change in FABF, not the change in nerve blood flow. Our interpretation of the data assumes that the two are at least correlated, if not similar. If this relationship is different between diabetic and control subjects, it may explain, in part, the differences noted. Although we believe it is unlikely, there is also the possibility that norepinephrine has a direct adrenergic

**Table 3. Effect of Intraarterial Norepinephrine Infusion on Ulnar Nerve Function**

| Measurement | Control | | Type 2 Diabetes | |
|---|---|---|---|---|
| | Baseline (n = 6) | Norepinephrine (n = 6) | Baseline (n = 11) | Norepinephrine (n = 11) |
| Latency (ms) | | | | |
| Distal sensory wrist-5th | 2.77 ± 0.19 | 2.76 ± 0.21 | 2.73 ± 0.10 | 2.94 ± 0.10* |
| Distal motor wrist-hypothenar | 2.85 ± 0.11 | 2.91 ± 0.20 | 2.90 ± 0.06 | 3.18 ± 0.10† |
| Proximal motor elbow-hypothenar | 6.55 ± 0.31 | 6.52 ± 0.32 | 7.15 ± 0.18‡ | 7.60 ± 0.23* |
| Conduction velocity (m/s) | | | | |
| Sensory wrist-5th | 51.8 ± 3.4 | 52.4 ± 3.3 | 52.1 ± 2.0 | 47.7 ± 1.6† |
| Motor elbow-wrist | 58.5 ± 2.0 | 58.6 ± 2.5 | 56.6 ± 1.6‡ | 55.1 ± 2.0 |

NOTE. Results are the mean ± SE.

*$P \leq .01$, baseline *v* norepinephrine.

†$P \leq .003$, baseline *v* norepinephrine.

‡n = 10.

effect on nerve function, not mediated by vasoconstriction, that is greater in diabetic versus control subjects.

In this study, the populations were well matched for age and percent body fat and reasonably well matched for blood pressure. As might be expected, the diabetic subjects had a higher body mass index than the control subjects. With regard to neuropathy, baseline large fiber sensory function was normal in these subjects, with only a mild sensory neuropathy identified in three diabetic subjects. Mean arterial plasma norepinephrine levels were higher, not lower, among the diabetic subjects, making significant autonomic neuropathy unlikely. There tended to be a higher proportion of men in the diabetic group, but prior study has not found evidence for gender differences in the nerve functions this study addressed. For the most important hypotheses, subjects served as their own controls.

During norepinephrine infusion, there was a greater decrease in FABF among diabetic compared with control subjects. This finding among subjects with diabetes may be due, in part, to the increased arterial adrenergic responsiveness in diabetes that has been previously described.[24-26] The study design does not permit exclusion of the possibility that had the control subjects been exposed to the same degree of decrease in FABF experienced by subjects with diabetes during norepinephrine, they, too, may have shown a decline in nerve function. However, this seems unlikely, since the range of decreases in FABF achieved during norepinephrine overlapped between groups and the absolute blood flow achieved during norepinephrine was virtually the same in both groups.

There was a trend for higher limb temperature (at baseline) in diabetic compared with control subjects. The average temperature changes noted were minimal, and were taken into account by adjusting the conduction velocities and latencies for temperature. This variability was greatest for nitroprusside, yet little change in nerve conduction velocity or distal latency was observed during nitroprusside. We measured surface (palm) temperature rather than nerve or core body temperature. It is possible that the temperature change throughout the length of the nerve was not as great as the change measured at the palmar surface. Since tissue temperature is dependent on flow and nerves may not regulate blood flow well, changes in FABF may not parallel changes in nerve blood flow. When all temperature correction was eliminated in a post hoc analysis, the findings during vasoconstriction did not change.

The general finding that vasodilatation during intraarterial nitroprusside did not lead to alterations in nerve function as characterized in this study may be a result of the short duration of exposure. However, as discussed earlier, in subjects who had clinically normal nerve function at baseline, it may be that a more prolonged increase in blood flow could result in improvement in nerve function where an increase of shorter duration did not. The design of the current study did not allow us to address this question. The only suggestion of a change in nerve function during nitroprusside infusion was an unexpected increase in distal sensory latency among the diabetes group. However, the magnitude of this increase was less than that observed during norepinephrine infusion and was of borderline significance, suggesting that it may be a false-positive result. However, we cannot exclude the possibility that this may be an independent effect of nitroprusside on nerve function, in addition to its effect on blood flow.

Our finding of impaired nerve function induced by intraarterial norepinephrine infusion in diabetic subjects is compatible with a possible link between metabolic and vascular defects contributing to diabetic neuropathy. In diabetes, glucose flux through the polyol pathway results in the conversion of glucose to sorbitol by the enzyme aldose reductase with concomitant oxidation of NADPH to $NADP^+$. With continued glucose flux through the polyol pathway, available NADPH reserves are depleted. Depletion of NADPH alters the normal redox equilibrium of the cell, which adversely affects the cell's ability to detoxify reactive oxygen species. Ischemia similar to that observed in the current study with intraarterial norepinephrine infusion promotes oxidative stress. Thus, it is possible that nerves from subjects with diabetes have reduced free radical scavenger ability that results in increased ischemia-induced oxidative damage, contributing to the slowed conduction velocities. In parallel, NADPH is also an obligate cofactor for nitric oxide (NO) synthase for production of the potent vasodilator NO from L-arginine. Decreased NO production due to NADPH depletion results in a decrease in nerve blood flow and conduction velocity.[27] These same limitations on NO production could exist in our study population, limiting the ability of compensatory NO-mediated vasodilation in the face of intraarterial norepinephrine-mediated vasoconstriction.

In summary, we found that subjects with type 2 diabetes, but not control subjects, demonstrate a decline in nerve function during vasoconstriction produced by intraarterial infusion of norepinephrine, and no change, generally, during short-term vasodilation by intraarterial infusion of nitroprusside. Consistent with prior study,[1] these findings support evaluation of the peripheral blood supply in subjects with type 2 diabetes who experience diabetic neuropathy. Future studies should be considered to address the possible contribution of heightened adrenergic vascular tone in subjects with type 2 diabetes and its possible role in the development or worsening of diabetic neuropathy.

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