Heightened Norepinephrine-Mediated Vasoconstriction in Type 2 Diabetes

Robert V. Hogikyan, Andrzej T. Galecki, Jeffrey B. Halter, and Mark A. Supiano

Adrenergic responsiveness (AR) appears to be increased in subjects with diabetes, but measurement of arterial AR in normotensive people with type 2 diabetes mellitus has not been previously reported. We sought to determine whether, compared with control subjects, there is increased arterial AR in type 2 diabetes mellitus and its relationship to the level of systemic sympathetic nervous system activity (SNSa). We studied 15 type 2 diabetic subjects aged 57 ± 3 years without hypertension or clinical signs of autonomic neuropathy and 13 age-matched control subjects aged 55 ± 2 years. We assessed vascular α-AR by measuring forearm blood flow (FABF) by venous occlusion plethysmography during intrabrachial artery norepinephrine (NE) and phentolamine infusions, as well as arterial plasma NE levels and the extravascular NE release rate (NE_2) derived from ^{3}H-NE kinetics, as estimates of systemic SNSa. The vasoconstricting effect of NE during intrabrachial artery NE infusion was greater in type 2 diabetes compared with control subjects ($P = .02$). The vasodilating effect of phentolamine was greater in type 2 diabetics compared with control subjects ($P = .05$), suggesting increased endogenous arterial α-adrenergic tone. Arterial plasma NE levels (control *v* type 2, 1.8 ± 0.10 *v* 1.84 ± 0.14 nmol/L, $P = .86$) and NE_2 (control *v* type 2, 11.8 ± 1.54 *v* 13.3 ± 0.89 nmol/min/m^2, $P = .39$) were similar in the two groups. In summary, in type 2 diabetes compared with control subjects, (1) the vasoconstriction response to intraarterial NE is greater, (2) plasma NE and NE_2 are similar, suggesting similar levels of systemic SNSa, and (3) arterial α-adrenergic tone is greater. We conclude that subjects with type 2 diabetes demonstrate inappropriately increased α-AR for their level of systemic SNSa.

THE REGULATION OF vascular tone involves the coordinated integration of multiple systems including the sympathetic nervous system (SNS). In individuals with diabetes mellitus, the regulation of vascular tone may be altered and may contribute to long-term sequelae such as vascular disease, including hypertension. Also, in insulin-resistant persons with type 2 diabetes, high insulin levels have been associated with vascular disease.[1]

Studies of SNS function in diabetes have largely focused on type 1 diabetes patients with autonomic neuropathy. Studies of SNS activity ([SNSa] estimating the release of norepinephrine [NE] from nerve terminals) have demonstrated decreased plasma NE levels and NE spillover into the circulation, consistent with neuropathic damage to peripheral sympathetic nerves.[2,3] Vascular α-adrenergic responsiveness ([α-AR] the effector-cell response to NE) has been reported to be increased in such patients, consistent with upregulation in response to decreased SNSa.[4] The increase in vascular α-AR in diabetes could also be explained by endothelial dysfunction or resistance to the vascular effects of insulin, since both nitric oxide[5] and insulin[6] have been demonstrated to impair α-adrenergic responses. Although there is some evidence that elevated SNSa may be present in individuals with elevated insulin levels,[7,8] little information is available about the relationship between SNSa and AR in otherwise healthy humans with type 2 diabetes.

The present study was designed to determine the relationship between SNSa and arterial NE-mediated vasoconstriction in normotensive subjects with type 2 diabetes compared with normotensive control subjects. We hypothesized that NE-mediated vasoconstriction is increased in people with type 2 diabetes.

SUBJECTS AND METHODS

Subjects

Thirteen control subjects and 15 subjects with type 2 diabetes in otherwise good general health were recruited through newspaper advertisement and the Human Subjects Core of the Geriatrics Center at the University of Michigan. Subjects were screened before study entry by a medical history, physical examination, and laboratory tests including a complete blood cell count and routine chemistries. Diabetic subjects were classified as type 2 by their primary care providers. All had adult-onset diabetes and no history of ketoacidosis.

We specifically targeted a group of subjects with limited heterogeneity with respect to body weight and blood pressure. Subjects were excluded from participation if they exceeded 150% of their ideal body weight (Metropolitan Life Insurance Tables, 1983), had a history of hypertension or a resting seated blood pressure greater than 160 mm Hg systolic or greater than 90 mm Hg diastolic, or had evidence from either the history, physical examination, or laboratory results of other significant underlying illness. Subjects were excluded if they were taking vasoactive medications (eg, calcium-channel blocker, angiotension-converting enzyme inhibitor, β-blocker, etc.). One of the subjects with diabetes was African-American and the remainder were Caucasian. Three subjects with type 2 diabetes were on replacement therapy for hypothyroidism with a thyrotropin level in the normal range. Two diabetic subjects were taking a diuretic for lower-extremity edema. Diabetes treatment regimens included diet alone (n = 4), a sulfonylurea (n = 6), insulin (n = 3), a sulfonylurea plus insulin (n = 1), and metformin (n = 1). With regard to the duration of diabetes, four subjects were newly diagnosed, four reported a diabetes duration of 5 years or less, three reported a diabetes duration of 10 years or less, three reported a diabetes duration greater than 10 years, and one was

From the Division of Geriatric Medicine, Department of Internal Medicine, and Institute of Gerontology, University of Michigan; and the Geriatric Research, Education, and Clinical Center, Department of Veterans Affairs Medical Center, Ann Arbor, MI.

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Address reprint requests to Robert V. Hogikyan, MD, GRECC (11G), VA Medical Center, 2215 Fuller Rd, Ann Arbor, MI 48105.

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unknown. Each provided written informed consent that was approved by the University of Michigan Institutional Review Board.

Study Protocol

All subjects reported to the General Clinical Research Center of the University of Michigan Hospitals at 7:30 AM on each of the 2 days of study. They were instructed to fast from 10:00 PM the night before each of the study days and to abstain from cigarettes, caffeine, and other known modulators of catecholamines for 12 hours before each study. Subjects were studied in the supine position in a quiet room maintained at a constant temperature of 23° to 25°C. In subjects with type 2 diabetes, oral hypoglycemics were discontinued 3 days prior to study, diuretics were discontinued 7 days prior to study, and insulin was withheld beginning with the afternoon dose on the day before study.

[^{3}H]NE Kinetics Protocol

Forearm volume (FAV) was measured using water displacement.[9,10] A 20-gauge, 1.25-inch Angiocath catheter (Becton Dickinson Vascular Access, UT) was placed into the brachial artery of the nondominant arm. The catheter was connected to a pressure transducer (Hewlett-Packard 1290A quartz transducer; Hewlett-Packard, Andover, MA). An intravenous (IV) line was placed in the contralateral arm for infusion of [^{3}H]NE. The [^{3}H]NE kinetics protocol was performed as previously described[11] with sampling from the brachial arterial catheter. One of the three basic electrocardiogram limb leads was monitored.

Forearm Blood Flow Protocol

Forearm blood flow (FABF) was measured using venous occlusion plethysmography during an intraarterial infusion protocol that we have previously described.[12] This protocol began following the tracer [^{3}H]NE infusion protocol (ie, at least 110 minutes after arterial catheter placement). FABF measurements during intraarterial infusions of acetylcholine and then nitroprusside were conducted initially. The results are reported elsewhere.[13] Intrabrachial artery infusion of NE has been used to characterize α-AR by a number of investigators,[9,14] including our laboratory.[12,15] NE infusion began following a washout period of a minimum of 15 minutes after the last dose of nitroprusside. To establish a stable baseline, FABF readings were taken until three consecutive readings representing similar FABF values were obtained. To determine the effect of intraarterial infusions of NE on FABF, NE (Levophed bitartrate; Sterline Drug, New York, NY) was diluted in 5% dextrose to achieve stepwise increasing infusion doses of 7.4, 30, 118, 473, and 1,420 pmol/100 mL FAV/min. Each NE dose was administered by an infusion pump (Harvard model 970T; Harvard Apparatus, South Natick, MA) for 4 minutes prior to recording FABF during the fifth minute of each infusion. Following FABF measurement at the 1,420-pmol dose, the NE infusion was stopped.

Following a washout period of at least 10 minutes, a repeat measurement of baseline FABF was performed. As a measure of endogenous arterial α-adrenergic tone (the net balance between SNSa and adrenergic response), the α-antagonist phentolamine was then infused to determine the increase in FABF above baseline.[9] Phentolamine (Regitine mesylate; Ciba-Geigy, Summit, NJ) was diluted in 0.9% normal saline and infused at a single dose of 0.043 μmol/100 mL FAV/min, and FABF was measured during the tenth minute of phentolamine infusion.

Frequently Sampled Intravenous Glucose Tolerance Test

On the day following the FABF protocol, after another overnight fast, the frequently sampled intravenous glucose tolerance test (FSIVGTT) was performed as described by Bergman.[16] It was performed as previously described by us[17] with augmentation by tolbutamide (137 mg/m^2 body surface area, control subjects) or insulin (0.05 U/kg, type 2 diabetic subjects).[18-21]

Analytical Methods

Mean arterial pressure (MAP) was determined from the electronically integrated area under the intraarterial blood pressure curve with the Marquette telemetry system (Series 7700; Marquette Electronics, Milwaukee, WI) just prior to each FABF measurement. Body composition was estimated by bioelectric impedance using an RJL instrument (model BIA-103 B; RJL Systems, Mt. Clemens, MI).

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 NE and epinephrine were quantified by a single-isotope radioenzymatic assay, with all samples from a given subject analyzed in the same assay.[22] The intraassay coefficient of variation for NE in this assay is 5%. Alumina extraction of plasma samples and measurement of [^{3}H]NE levels were performed as previously described.[11,23]

Baseline values reported from the FSIVGTT represent the mean of three measurements prior to glucose administration for each variable. Blood samples for plasma glucose and insulin were collected into chilled glass tubes containing sodium heparin, stored on ice, and separated immediately following each study. Plasma was stored at −70°C until assay. Plasma glucose was measured by the Autoanalyzer (Roche Diagnostic Systems, Somerville, NJ) glucose oxidase method and plasma insulin by radioimmunoassay at the Core Laboratory of the Michigan Diabetes Research and Training Center. Glycosylated hemoglobin was determined in the Core Laboratory of the Michigan Diabetes Research and Training Center using the Isolab Glyc-Affin GHb test kit (Isolab, Akron, OH).

The insulin sensitivity index (S_I) and a measure of glucose effectiveness (S_G) were calculated from a least-squares fitting of the temporal pattern of glucose and insulin throughout the FSIVGTT using the MINMOD program.[16] The acute insulin response to IV glucose (AIR_G) was calculated as the mean increase in plasma insulin above baseline at 3, 4, and 5 minutes after IV glucose administration. K_G, a measure of glucose tolerance, is the rate of plasma glucose disappearance calculated as the least-square slope of the natural logarithm of the absolute glucose concentration between 5 and 20 minutes after the glucose bolus (a normal value for K_G is >1%/min).

Data and Statistical Analysis

Values are presented as the mean ± SE. *P* values less than .05 are considered statistically significant. Statistical analysis was performed using Statview 4.5 (Abacus Concepts, Berkeley, CA) and SAS/PROC MIXED.[24]

Compartmental analysis of NE kinetics was performed using the previously described minimal two-compartment model.[11] The quantity of NE in each compartment (NE mass in the intravascular compartment, Q_1, and in the extravascular compartment, Q_2), the rate of NE appearance into each compartment (R_{12} into compartment 1 and NE_2 into compartment 2), the NE metabolic clearance rate from compartment 1 (MCR_1), the NE spillover fraction (NE_{SF}), and the volume of distribution of NE in compartment 1 (V_1) were calculated from the two-compartment model as a function of the estimated transfer rate coefficients as previously described.[11]

Baseline subject characteristics and results of the [^{3}H]NE kinetics and FSIVGTT were compared between study groups using Student's *t* tests. Gender mix was compared between groups with a Fisher's exact test. FABF responses to multiple doses of NE and a single dose of phentolamine were analyzed using the percent change in FABF from the preceding baseline FABF. The percent change FABF data were analyzed by comparing groups with repeated-measures ANOVA for the five doses of NE. The Mann-Whitney nonparametric test was used to compare the percent change FABF response with the single phentolamine dose between groups. In addition, separate linear mixed effects (LME) models[25] were developed to describe the effects of several

Table 1. Characteristics of Type 2 Diabetes and Control Subjects (mean ± SE)

Characteristic	Control (n = 13)	Type 2 Diabetes (n = 15)	P
Age (yr)	55 ± 2	57 ± 3	.66
Sex (male/female)	7/6	11/4	.25
BMI (kg/m^2)	26.0 ± 0.6	28.3 ± 1.0	.08
Body fat (%)	25.9 ± 2.3	26.7 ± 1.7	.78
MAP (mm Hg)	95.1 ± 2.6	95.9 ± 2.5	.82
Glycosylated hemoglobin (%)	5.7 ± 0.1	9.8 ± 0.7	<.01
Fasting total cholesterol (mg/dL)	200 ± 9	197 ± 11	.83

covariates on FABF data for the five doses of NE and a single dose of phentolamine. Baseline FABF, age, gender, body mass index (BMI), percent body fat, MAP, glycosylated hemoglobin, fasting glucose and insulin, S_I, S_G, AIR_G, K_G, and NE_2 and their interactions with stimulus dose and with study group were incorporated into the LME analysis. To develop the best LME models for NE and phentolamine responses, several models were considered for each infusate. To accommodate a nonlinear dose-response relationship, logarithmic transformation was applied to the FABF measurements. The NE model takes into account that several measures were repeated on the same individual. To describe variance heterogeneity and correlation of individual measurements, the optimal covariance structure for the NE and phentolamine models was selected using Akaike's information criterion.[26] The likelihood ratio test was used to select an optimal model. To check the goodness of fit of the models developed, residuals were inspected by plotting them against predicted values and against available covariates (not presented).

RESULTS

Subject Characteristics and FSIVGTT Results

Characteristics of the control subjects and those with type 2 diabetes are compared in Table 1. The groups were similar with respect to age, gender, percent body fat, MAP, and fasting total cholesterol. The BMI tended to be higher in subjects with type 2 diabetes relative to the control subjects. Only one diabetic subject had clinical signs and symptoms of peripheral sensory neuropathy, and none reported symptoms of autonomic neuropathy. As expected, subjects with type 2 diabetes differed from control subjects in all parameters of glucose metabolism measured in the fasting state and during the FSIVGTT (Table 2). Data were not obtained for one type 2 diabetes subject who had insulin antibodies. Glycosylated hemoglobin values for subjects with type 2 diabetes were 5.0% to 14.5% (normal, 4% to 8%).

NE Kinetics and Plasma Catecholamines

There were no significant differences in arterial plasma NE (control *v* type 2, 1.8 ± 0.10 *v* 1.84 ± 0.14 nmol/L, $P = .86$) or epinephrine (control *v* type 2, 0.32 ± 0.02 *v* 0.33 ± 0.03 nmol/L, $P = .74$) levels between groups. Results of the NE kinetic studies are summarized in Table 3. There were no statistically significant differences in NE kinetic parameters when comparing control and diabetic subjects; the volume of distribution (V_1) tended to be higher among diabetic subjects ($P = .07$). The mean value for NE_2 (the estimate of extravascular NE release) was higher rather than lower in diabetic subjects compared with the control subjects, and values for Q_2 (NE mass in compartment 2) and R_{12} (NE spillover into the vascular compartment) were virtually identical in the two groups.

Table 2. FSIVGTT Results for Type 2 Diabetes and Control Subjects (mean ± SE)

Parameter	Control (n = 13)	Type 2 Diabetes (n = 14)	P
Fasting glucose (mmol/L)	5.27 ± 0.11	10.0 ± 0.78	<.01
Fasting insulin (pmol/L)	64 ± 5.8	152 ± 23.4	<.01
S_I ($\times 10^{-5} \cdot min^{-1}$/pmol/L)	6.36 ± 1.1	0.11 ± 0.20	<.01
S_G (min^{-1})	0.019 ± 0.001	0.014 ± 0.001	.01
AIR_G (pmol/L)	526.3 ± 70	46.8 ± 17.5	<.01
K_G (%/min)	2.1 ± 0.2	1.3 ± 0.1	<.01

Table 3. NE Kinetic Parameters in Control and Type 2 Diabetic Groups

Parameter	Control (n = 13)	Type 2 Diabetes (n = 15)	P
NE_2 (nmol · $min^{-1} \cdot m^{-2}$)	11.8 ± 1.54	13.3 ± 0.89	.39
Q_1 (nmol/m^2)	2.13 ± 0.12	2.42 ± 0.24	.30
Q_2 (nmol/m^2)	280.1 ± 34.3	273.0 ± 19.7	.85
R_{12} (nmol · $min^{-1} \cdot m^{-2}$)	2.24 ± 0.12	2.24 ± 0.12	.92
MCR_1 (L · $min^{-1} \cdot m^{-2}$)	1.04 ± 0.06	1.08 ± 0.04	.59
V_1 (L/m^2)	2.19 ± 0.15	2.64 ± 0.18	.07

NOTE. Values are the mean ± SE.

Abbreviations: NE_2, extravascular NE release rate; Q_1 and Q_2, mass of NE in compartments 1 and 2; R_{12}, rate of NE appearance into compartment 1; MCR_1, rate of NE clearance from compartment 1; V_1, NE volume of distribution in compartment 1.

FABF During Vasoactive Intraarterial Infusions

NE. FABF prior to the NE infusion protocol was comparable between groups (control *v* type 2, 4.2 ± 0.4 *v* 4.7 ± 0.4 mL/100 mL FAV/min, $P = .40$). Dose-response curves representing the percent decrease from baseline FABF during intraarterial infusions of NE for control and type 2 diabetes subjects are shown in Fig 1. The dose-response curve of the type 2 diabetes group was significantly shifted to the left compared with the curve of the control subjects (ANOVA $P = .02$), indicating increased sensitivity to NE-mediated vasoconstriction.

A LME model was developed to estimate the difference between study groups considering the covariates baseline

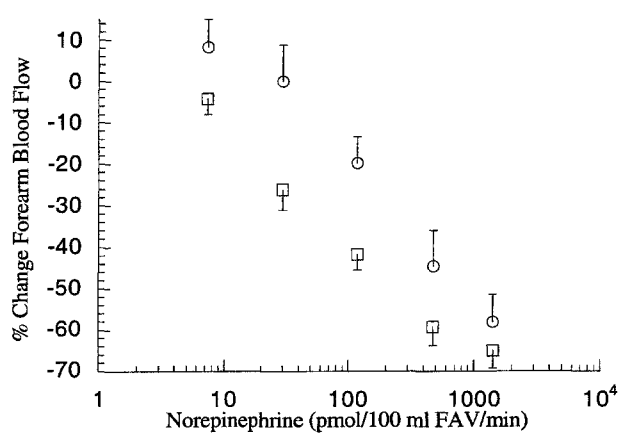

Fig 1. Group data (mean ± SEM) for percent change in FABF from baseline in response to intraarterial infusion of NE among control (○, n = 13) and type 2 diabetes subjects (□, n = 15) ANOVA, $P = .02$.

FABF, age, gender, BMI, percent body fat, MAP, glycosylated hemoglobin, fasting glucose and insulin, S_I, S_G, AIR_G, K_G, and NE_2. The best model included only baseline pre-NE FABF and did not identify a significant effect of the other covariates, except that when S_I was included, the study group effect was no longer significant, suggesting the very close link between S_I and type 2 diabetes. The model also revealed that the overall difference in the FABF response to NE between study groups remained significant ($\chi^2 = 7.82$, $df = 2$, $P = .02$). Glycosylated hemoglobin tended to enter into the best model ($P = .08$) in a positive direction, where a higher glycosylated hemoglobin was present in subjects with heightened vasoconstriction to NE.

Phentolamine. Nine control and seven type 2 diabetes subjects received phentolamine infusion. Baseline pre-phentolamine FABF tended to be higher in the control group, but this difference was not statistically significant (control *v* type 2, 6.0 ± 1.0 *v* 4.3 ± 0.5 mL/100 mL FAV/min, $P = .19$). Diabetic subjects showed a greater percent increase in FABF compared with control subjects (control *v* type 2, 71% ± 13% *v* 117% ± 19% increase, $P = .05$) (Fig 2).

A LME model was developed for phentolamine that considered the covariates baseline FABF, age, gender, BMI, percent body fat, MAP, glycosylated hemoglobin, fasting glucose and insulin, S_I, S_G, AIR_G, K_G, and NE_2. The best model included baseline FABF and age as covariates, where older subjects exhibited less vasodilation with phentolamine. The model also showed that the overall difference in the FABF response to phentolamine between study groups remained significant ($\chi^2 = 6.6$, $df = 1$, $P = .01$).

DISCUSSION

This study provides evidence for increased forearm arterial α-adrenergic-mediated vasoconstriction as demonstrated by the FABF response to intraarterial NE in normotensive subjects with type 2 diabetes compared with age-matched control subjects. Heightened NE-mediated vasoconstriction in type 2 diabetes was identified in a setting of similar systemic SNSa, as estimated by the rate of extravascular NE release (NE_2). The combination of an increased forearm vasoconstriction response to NE despite a similar level of systemic SNSa suggests that overall arterial α-adrenergic tone is increased in these normotensive type 2 diabetes subjects. The increased FABF response to intraarterial phentolamine in the type 2 diabetes subjects is consistent with this finding.

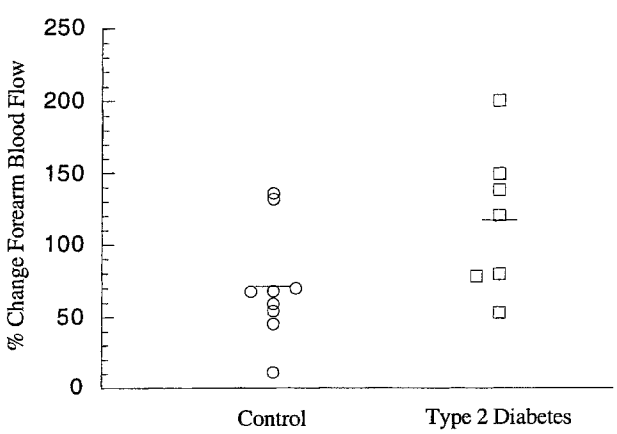

Fig 2. Individual data and mean values for percent change in FABF from baseline in response to intraarterial infusion of phentolamine among control and type 2 diabetes subjects. $P = .05$.

In addition to α-adrenergic receptors, β-adrenergic receptors, insulin, nitric oxide, and many other factors contribute to the control of arterial vascular tone. Studies have suggested that α_2-receptors on endothelial cells may regulate the release of nitric oxide.[27,28] The current study was not designed to examine the potential effect of intraarterial NE infusions on the release of nitric oxide. However, given the known interactions between the α-adrenergic system and the endothelium,[5] diabetes-associated endothelial dysfunction[13,29-31] might account for some of the increase in arterial α-AR observed in our study. The vasodilatory response to insulin has been demonstrated to be impaired in subjects with type 2 diabetes.[32] Insulin has also been shown to attenuate α-adrenergic-mediated vasoconstriction.[6] Therefore, heightened arterial α-AR may also be due in part to a state of vasomotor insulin resistance which has been characterized in subjects with type 2 diabetes.[32,33]

In this study, we used intraarterial infusions of NE to investigate differences between control subjects and subjects with type 2 diabetes in terms of vascular AR. Because intraarterial NE caused a dose-dependent decrease in FABF, we were able to quantify the sensitivity to this vasoconstrictor using brachial artery infusion methodology whereby FABF is varied without producing major systemic effects on heart rate or blood pressure that could confound interpretation of the results.[29] Our finding of increased NE-mediated vasoconstriction during intraarterial NE among the type 2 diabetes group is in general agreement with previous studies of adrenergic-mediated vasoconstriction in experimental animal models of diabetes.[34-44] However, other investigators have identified decreased or similar responses to adrenergic stimulation in experimental animal models of diabetes compared with nondiabetic control animals.[45-48] It has been suggested by others that some of this variation may be due to the type of model, duration of diabetes and extent of vessel innervation.[38,49]

Our findings of an increased in vivo vasoconstriction response to intraarterial NE in normotensive human subjects with type 2 diabetes complement and extend other human studies. In isolated subcutaneous skin arteries from human subjects with type 2 diabetes, NE sensitivity has been found to be augmented relative to control subjects.[5] No difference in the venoconstriction response to NE infusion into the dorsal hand vein was observed in otherwise healthy type 1 diabetes versus control subjects.[4] Other in vivo studies in humans with diabetes mellitus have relied on the blood pressure response to systemic NE, a nonspecific approach involving the integration of many regulatory processes. The majority, though not all,[50-53] of these studies identified an exaggerated pressor response to NE in subjects with diabetes relative to control subjects.

To estimate systemic SNSa, we studied the kinetics of NE release and removal in these subjects. In previous studies, SNSa in subjects with diabetes mellitus has been estimated using plasma levels of NE and rates of NE spillover into the circulation. These studies have found similar,[50,52] elevated,[7] or lower[54] plasma NE levels in diabetic groups compared with a healthy control group. Systemic and forearm NE spillover rates

were found to be similar between control and uncomplicated type 2 diabetes subjects.[55] In studies of diabetic subjects with neuropathy, estimates of systemic SNSa have been low relative to healthy control subjects.[2,3] In the present study, plasma NE levels and a more proximate estimate of systemic SNSa, the rate of NE release into an extravascular compartment, NE_2, clearly were not decreased in these diabetic subjects relative to control subjects, consistent with the lack of clinical signs of autonomic neuropathy among these subjects with type 2 diabetes. Thus, the heightened NE-mediated vasoconstriction that we observed does not appear to represent an upregulation response to diminished SNSa.

We used intraarterial infusion of phentolamine to investigate differences between control subjects and subjects with type 2 diabetes in overall vascular α-adrenergic tone.[9] The dose of phentolamine we administered has been previously shown to provide nearly complete arterial α-receptor blockade.[10] The greater mean increase in FABF during phentolamine infusion among the diabetic subjects relative to the control subjects is consistent with the other findings in this study of increased arterial AR and no difference in systemic SNSa. The finding that the FABF response to phentolamine varied negatively with age was unexpected. We have previously shown no age effect in the FABF response to phentolamine in subjects without diabetes.[15]

Among the potential contributors to the control of the level of NE-mediated vasoconstriction we measured, poorer glucose control as represented by a higher glycosylated hemoglobin tended to predict a greater response to NE. This suggests that the level of glucose control may be related to the regulation of NE-mediated vasoconstriction. The LME analysis suggests that a number of characteristics of the subjects in this study that were not controlled for in the study design, including BMI and the other parameters of glucose metabolism, did not account for the observed group difference in the FABF response to NE or phentolamine.

We acknowledge that our study design presents some limitations in the interpretation of the results. Since we did not measure the FABF response to a nonadrenergic vasoconstrictor (eg, angiotensin II), the possibility that there is generalized enhancement of vasoconstrictor sensitivity among type 2 diabetes subjects and not a specific adrenergic enhancement cannot be excluded. In this study, we have historical information about clinical signs or symptoms of autonomic neuropathy, but no specific test of autonomic function was performed. Estimates of systemic SNSa in this study demonstrate no difference, and certainly not lower levels, among the diabetic subjects. However, since there may be regional differences of SNS activation, we cannot exclude differential regional levels of SNSa in subjects with type 2 diabetes.

In summary, in type 2 diabetes compared with control subjects, (1) arterial NE-mediated vasoconstriction is increased, (2) plasma NE levels and NE_2 are similar, suggesting similar levels of systemic SNSa, and (3) overall arterial α-adrenergic tone as estimated by the FABF response to intraarterial phentolamine is increased. We conclude that under supine resting conditions, normotensive insulin-resistant subjects with type 2 diabetes demonstrate increased NE-mediated vasoconstriction inappropriate for their level of systemic SNSa. Future studies will need to address the dynamic regulation of SNS function, including measures of regional SNSa, during perturbations of SNSa (eg, upright posture or exercise) in individuals with type 2 diabetes.

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