Insulin Does Not Reduce Forearm \(\alpha\)-Vasoreactivity in Obese Hypertensive or Lean Normotensive Men

J. Michael Neahring, Konrad Stepniakowski, Andrew S. Greene, Brent M. Egan

Evidence supports the hypothesis that an impaired capacity of insulin to antagonize norepinephrine-induced vasoconstriction increases \(\alpha\)-adrenergic tone in overweight young men with insulin resistance and mild hypertension. Therefore, the effects of regionally infused insulin at 100 \(\mu\)U/mL on forearm blood flow (milliliters per deciliter per minute) and responses to norepinephrine were measured in seven obese hypertensive and eight lean normotensive men younger than 45 years old. The obese hypertensive men were hyperinsulinemic and insulin resistant compared with the normotensive men, as evidenced by abnormal values for fasting insulin (15.5 ± 1.6 versus 7.2 ± 0.8 \(\mu\)U/mL, \(P<.001\)), the insulin area under the curve in response to a 2-hour oral glucose tolerance test (12.0 ± 1.5 versus 6.7 ± 1.1 \(\mu\)U/min/dL, \(P<.01\)), and the disappearance rate of glucose during a 15-minute insulin tolerance test (2.7 ± 0.3 versus 4.1 ± 0.3 mg%/min, \(P<.05\)). The logarithm of the norepinephrine EC\(_{50}\) was not significantly different in obese hypertensive men (mean, 95% confidence interval: \(-8.15, -8.42\) to \(-7.87\)) versus lean normotensive men (\(-7.91, -8.23\) to \(-7.59\)). The 2-hour regional insulin infusion at 100 \(\mu\)U/mL did not significantly alter the EC\(_{50}\) for norepinephrine in either group. Insulin at this concentration induced significant and similar increases of forearm blood flow in the hypertensive and normotensive groups (1.7 ± 0.4 versus 1.7 ± 0.6 mL/100 mL per minute, \(P=NS\)). At approximately 100 \(\mu\)U/mL, insulin does not antagonize norepinephrine-induced vasoconstriction in the forearm circulation of either obese hypertensive or lean normotensive men. At this dose, the direct forearm vasodilator actions of insulin, in contrast to indexes of insulin-mediated glucose disposal, are comparatively well preserved in obese young men with mild hypertension. Thus, abnormalities of the regional vascular actions of insulin do not explain the previously reported elevation of forearm vascular \(\alpha\)-adrenergic tone in obese, mildly hypertensive young men. (Hypertension. 1993;22:584-590.)

KEY WORDS • obesity • hypertension, obesity-induced • insulin • vascular resistance • receptors, \(\alpha\)-adrenergic, alpha

Although being overweight is associated with a greater prevalence of hypertension in all age and gender subgroups, the strongest relation between obesity and hypertension is observed in men younger than 45 years old. Overweight men younger than 45 years old have not only threefold more hypertension but also a fivefold greater prevalence of fasting insulin values greater than 11 \(\mu\)U/mL compared with lean men of similar age. Euglycemic hyperinsulinemia stimulates sympathetic activity more in younger versus older men, which implicates a neurogenic link between excess hyperinsulinemia and hypertension in obese younger men. Along this line, insulin-induced sympathetic activation is preserved among obese men younger than 45 years old, despite their resistance to insulin-mediated glucose disposal. Thus, hyperinsulinemia may contribute to evidence for greater sympathetic drive, increased forearm vascular \(\alpha\)-adrenergic tone, and elevated blood pressure in obese young men. However, insulin also antagonizes \(\alpha\)-adrenergic vasoconstriction. Given these opposing actions, if disordered insulin metabolism contributes to an elevated blood pressure, then the pressor effects of insulin must outweigh the depressor actions. In fact, mildly hypertensive Zucker obese rats are resistant to the inhibitory effect of insulin on phenylephrine-induced vasoconstriction. This study was designed principally to test the hypothesis that obese, mildly hypertensive young men are resistant to the action of insulin to blunt \(\alpha\)-adrenergic vasoconstriction.

Insulin may also act as a direct vasodilator in the forearm, although agreement is not uniform. Impairment of the direct vasodilating action of insulin could contribute to elevated vascular resistance in obese, hypertensive young men. The secondary aims of this study were to determine if insulin directly increases forearm blood flow (FABF) and to document if this action is impaired in obese men younger than 45 years old with mild hypertension.
Methods

Human Volunteers

Fifteen paid male volunteers, aged 34 to 45 years, were recruited from the Hypertension Clinic and by advertisement. Each subject signed a written informed consent document approved by the Human Research Review Committee. All volunteers underwent a history, physical, and laboratory examination to exclude health problems except for obesity and hypertension. Medications were discontinued a minimum of 3 weeks before the study diet was begun. Seven white men were categorized as obese hypertensive, defined as a body mass index greater than 27 kg/m², blood pressure greater than 140 mm Hg systolic and/or greater than 90 mm Hg diastolic, and a history of hypertension. Eight men (seven white, one black) were categorized as lean normotensive, with a body mass index greater than 25.5 kg/m², blood pressure less than 140/90 mm Hg, and no history of hypertension.

Physiological Measurements

Blood pressures at screening were measured in triplicate with a mercury sphygmomanometer after subjects rested for 5 minutes in a seated position. In the laboratory, mean arterial pressure was measured directly from the brachial artery by electronic integration of the arterial pulse waveform. FABF (in milliliters per 100 mL forearm volume per minute) was obtained by mercury-in-Silastic strain-gauge venous occlusion plethysmography using the Hokanson EC-4.2 Cuff on the arm was inflated to 50 mm Hg for 15 seconds and deflated 5 seconds over four cycles using the Hokanson E-20 rapid cuff inflator. A separate cuff around the wrist was inflated to 50 mm Hg and deflated simultaneously with the arm cuff to prevent venous return from the hand circulation during the FABF measurement. Forearm vascular resistance was calculated as mean arterial pressure/FABF. Hyperemic FABF was measured after 10 minutes of ischemic forearm exercise. Stroke volume (in milliliters) was measured by thoracic impedance plethysmography using the Hokanson EC-4.5 cuff on the arm and in a vein of the contralateral forearm for 10 minutes of ischemic exercise. Ensemble averaging of 10 cardiac cycles was used to reduce variability of stroke volume caused by respiration. Cardiac output (in liters per minute) was calculated as heart rate x stroke volume/1000.

Biochemical Measurements

Serum insulin was measured by radioimmunoassay (Coat-A-Count Insulin, Diagnostic Products Corp, Los Angeles, Calif) with a sensitivity of 1 μU/mL and a coefficient of variation of 6.5% at insulin values of 1 to 20 μU/mL and 3.7% at 100 to 300 μU/mL. Glucose was measured with a glucose analyzer (Beckman Instruments, Brea, Calif). Plasma norepinephrine was measured by single-isotope radioenzymatic assay, with intra-assay and interassay coefficients of variation of 5% and 8%, respectively. Plasma renin activity was determined by radioimmunoassay.

Anthropometric Measurements and Calculations

Height and weight were measured in lightly clothed subjects without shoes. Triceps, biceps, subscapular, and iliac skinfold thicknesses were obtained with Lange calipers (Cambridge Scientific Instruments, Cambridge, Mass). Percent body fat was calculated from the skinfold data. Waist and hip circumferences were measured with subjects in the standing position, and the waist-to-hip ratio was calculated.

Dietary Control

Volunteers were interviewed by the Clinical Research Center (CRC) dietitian to determine their usual diet. An isocaloric diet was calculated for each subject using the NUTRITIONIST III DIET ANALYSIS software (N-Squared Computing, Salem, Ore). The diet was controlled for Na⁺ (500 mg/d), K⁺ (2500 mg/d), Ca²⁺ (800 mg/d), and Mg²⁺ (300 mg/d). The caloric composition of the diet was 45% to 50% carbohydrate, 35% to 40% fat, and 15% protein. The diet was supplemented with 18 600-mg NaCl tablets daily (approximately 184 mEq). Subjects came to the CRC on alternate days during the week before the lab study to be weighed and to obtain all food and beverages, which were prepared by trained metabolic cooks in the CRC kitchen under the direction of the dietitian. The caloric intake was adjusted to maintain body weight within 1.5% of baseline. Compliance with the diet was verified by 24-hour urinary Na⁺.

Protocol 1

Seven obese hypertensive and eight lean normotensive subjects completed this protocol. The subject began a urine collection at 7 AM after 6 days on the study diet, reported to the CRC at 7 AM the following morning, and closed the urine collection. Forearm volume by water displacement and body weight were measured. Electrodes were positioned for impedance cardiography. The brachial artery catheter was placed under sterile conditions. Intravenous catheters were inserted retrogradely into a deep vein of the study (ipsilateral) forearm and in a vein of the contralateral forearm for blood sampling. Room temperature was controlled to maintain stable baseline FABF. After 30 minutes of supine rest, FABF was measured in both arms. Once three consecutive measurements of FABF were within ±10%, blood samples for glucose, insulin, catecholamines, and plasma renin activity were obtained.

Norepinephrine was infused regionally in seven sequential ascending doses of 3 x 10⁻¹⁰, 10⁻⁹, 3 x 10⁻⁸, 10⁻⁷, and 3 x 10⁻⁷ mol/L for 5 minutes each. FABF was measured during the final 90 seconds of each infusion. The norepinephrine infusion rate for each dose was calculated based on FABF ([milliliter per deciliter per minute] x [forearm + hand volume (deciliters)]).

After the norepinephrine infusion was completed, baseline FABF was generally reestablished within 40 minutes. During this time, insulin was diluted to 25 000 μU/mL in 95 mL 0.9% NaCl with 5 mL of 5% albumin. FABF was measured every 10 minutes and the infusion rate adjusted to maintain a regional insulin concentration 100 μU/mL above basal levels for 2 hours. Venous glucose and insulin samples were obtained from both forearms at 30-minute intervals. After 2 hours, the insulin infusion was continued while norepinephrine was repeated. The norepinephrine and insulin were calculated for each dose based on the preceding FABF value. FABF was then measured after 10 minutes of ischemic exercise.

Subprotocol 1a. In five obese hypertensive and three lean normotensive subjects, the diet and study were repeated. However, 0.9% NaCl plus albumin (vehicle) without insulin was given (sham procedure) for 2 hours after the sequential norepinephrine infusion and continued while norepinephrine was repeated. Studies in the same subject requiring brachial artery catheterization were separated by at least 3 weeks.
Subprotocol 1b. Four volunteers (three lean, one obese) followed the study diet for 7 days. They received a brachial artery infusion of methoxamine at $10^{-4}$ to $3 \times 10^{-6}$ mol/L. After a second baseline measurement, insulin was infused at $100 \mu U/mL$ FABF for 2 hours and continued while methoxamine was repeated.

Subprotocol 1c. Four lean volunteers followed the study diet for 7 days and underwent a regional hemodynamic study in which the FABF response to regional norepinephrine ($3 \times 10^{-10}$ to $3 \times 10^{-7}$ mol/L) was obtained. After a second baseline measurement, $3 \times 10^{-9}$ mol/L nitroprusside per milliliter FABF was infused and continued while norepinephrine was repeated.

Protocol 2

After 6 days on the study diet, all volunteers had fasting measurements of glucose and insulin on arterialized venous blood at baseline ($-20$, $-10$, and 0 minutes) and at 15, 30, 60, 90, and 120 minutes after a 75-g oral glucose load. The following morning, glucose and insulin measurements were obtained in triplicate in the fasting state and again 3, 6, 9, 12, and 15 minutes after an intravenous bolus of human insulin at 0.1 U/kg (insulin tolerance test).

Data Analysis

Data are reported as mean±SEM. Analyses were performed using ssrs 5.0 (Chicago, Ill). A comparison of descriptive variables in hypertensive and normotensive subjects was made with the Student’s unpaired $t$ test. The insulin and glucose areas under-the-curve (AUC) were calculated. The dose-response curves to norepinephrine, both with and without insulin, and to nitroprusside were assessed with repeated-measures analysis of variance for determination of the separate and interactive effects of diagnosis (hypertensive versus normotensive), dose or time, and insulin. The effective concentration of norepinephrine inducing 50% of the maximum response ($EC_{50}$) was calculated for each individual using GRAPHPAD 4.0 software (San Diego, Calif). The fit of the curve to the actual data without and with insulin, respectively, was $R^2=92.90$ and $93.04$. The $R^2$ for the normotensive subjects was $95.01$ and $96.03$ in hypertensive subjects. The mean and 95% confidence intervals for the norepinephrine $EC_{50}$ were calculated from the group data for hypertensive and normotensive subjects. Because the differences in venous glucose values between the two forearms during the regional insulin infusion were not normally distributed, these data were analyzed using the nonparametric Wilcoxon rank-sum test. Three consecutive FABF values were averaged at baseline and at 30-minute intervals during the 120-minute insulin infusion. For example, the 30-minute value represents the mean of FABF at 20, 30, and 40 minutes, etc. Analysis of covariance was used to assess the FABF response to insulin in obese hypertensive versus lean normotensive subjects, while controlling for differences in basal FABF.

Results

As summarized in Table 1, the hypertensive and normotensive groups were not significantly different for age or height. Based on the selection process, the hypertensive subjects had greater values than normotensive subjects for systolic and diastolic blood pressures as well as body mass index. Percent body fat and percent body fat were elevated in the hypertensive subjects. Although the glucose AUC values were not different during the 2-hour oral glucose tolerance test, the insulin AUC was not significantly different in the two groups.

Table 1. Baseline Values for Obese Hypertensive Patients and Lean Normotensive Volunteers

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotensive</th>
<th>Hypertensive</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>40±1</td>
<td>39±2</td>
<td>NS</td>
</tr>
<tr>
<td>Height, cm</td>
<td>180±2</td>
<td>176±3</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.3±0.3</td>
<td>39.0±2.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>18.3±1.2</td>
<td>30.7±1.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.85±0.01</td>
<td>0.99±0.02</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>120±3</td>
<td>147±6</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>76±2</td>
<td>95±2</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

BP indicates blood pressure. Values are mean±SEM.

Table 2. Baseline Laboratory Data In Obese Hypertensive and Lean Normotensive Men

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotensive</th>
<th>Hypertensive</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean BP, mm Hg</td>
<td>79±3</td>
<td>92±4</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>56±4</td>
<td>69±4</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>5.6±0.2</td>
<td>6.2±0.5</td>
<td>NS</td>
</tr>
<tr>
<td>$FABF_25$ (mL/100 mL)/min</td>
<td>2.7±0.2</td>
<td>5.5±0.8</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>$FABF_50$ (mL/100 mL)/min</td>
<td>55.8±6.6</td>
<td>40.6±4.6</td>
<td>NS</td>
</tr>
<tr>
<td>Femoral resistance (mmol/24 h)</td>
<td>1.7±0.2</td>
<td>2.7±0.3</td>
<td>&lt;.02</td>
</tr>
<tr>
<td>Hct,crit</td>
<td>40.6±0.01</td>
<td>40.2±0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Urine Na⁺, mmol/24 h</td>
<td>207±10</td>
<td>179±9</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma NE, pg/mL</td>
<td>305±11</td>
<td>240±27</td>
<td>NS</td>
</tr>
<tr>
<td>PRA, (ng Ang/l/mL)/h</td>
<td>0.95±0.15</td>
<td>1.64±0.19</td>
<td>&lt;.02</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; bpm, beats per minute; FABF, forearm blood flow; b, brachial; i, after 10 minutes of ischemia; FAVR, forearm vascular resistance; NE, norepinephrine; PRA, plasma renin activity; and Ang I, angiotensin I. Values are mean±SEM.
TABLE 3. Glucose and Insulin Metabolism in Obese Hypertensive and Lean Normotensive Men

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotensive</th>
<th>Hypertensive</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting plasma insulin, μU/mL</td>
<td>7.2±0.8</td>
<td>1.5±1.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Fasting plasma glucose, mg/dL</td>
<td>86±1</td>
<td>95±2</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Insulin AUCOGTT, μU×min/mL</td>
<td>6 678±1 124</td>
<td>11 980±1 536</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Glucose AUCOGTT, mg×min/dL</td>
<td>17 203±703</td>
<td>18 601±1 048</td>
<td>NS</td>
</tr>
<tr>
<td>Kntt, mg%/min</td>
<td>4.1±0.3</td>
<td>2.7±0.3</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Insulin AUCITT, μU×min/mL</td>
<td>5 777±663</td>
<td>7 439±370</td>
<td>NS</td>
</tr>
<tr>
<td>Glucose AUCITT, mg×min/dL</td>
<td>1 196±26</td>
<td>1 312±39</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Gluvaso-Gluvas*, mg/dL</td>
<td>9.7±3.0</td>
<td>0.0±0.7</td>
<td>&lt;.03</td>
</tr>
</tbody>
</table>

AUC indicates area under the curve; OGTT, oral glucose tolerance test; K, disappearance rate constant for glucose during insulin tolerance test (ITT); and Gluvaso-Gluvas*, venous glucose concentrations in the contralateral minus ipsilateral forearm during 2-hour regional insulin infusion. Values are mean±SEM.

greater in hypertensive subjects. During the 15-minute insulin tolerance test, the disappearance rate of plasma glucose was significantly slower in hypertensive subjects, despite a tendency to a higher insulin AUC. The difference between the contralateral and ipsilateral forearm venous glucose concentration was significantly greater in normotensive versus hypertensive subjects during the final 60 minutes of the regional insulin infusion.

Effects of Regional Hyperinsulinemia on Forearm Vascular Reactivity to Norepinephrine

The absolute norepinephrine-induced reduction in FABF was greater in hypertensive than normotensive subjects, whereas the relative (log) flow responses were parallel (Fig 1). As shown, the logarithm of the norepinephrine EC50 was not significantly different in the obese hypertensive (mean, 95% confidence interval: -8.15, -8.42 to -7.87) versus the lean normotensive (-7.91, -8.34 to -7.59) groups. Insulin did not significantly alter the norepinephrine EC50 either within or between the hypertensive (-8.08, -8.34 to -7.82) and normotensive (-8.01, -8.43 to -7.58) groups. Insulin did not antagonize methoxamine-mediated constrictr responses (Fig 2). In fact, insulin augmented (significantly steeper slope) the absolute but not the relative (log) norepinephrine-induced decline of FABF. This apparent enhancement of forearm vascular responsiveness to α-agonists was likely a nonspecific effect of the higher initial FABF, because nitroprusside also significantly increased the slope of the FABF response to norepinephrine.

Effects of Regional Hyperinsulinemia on Forearm Blood Flow and Comparison of Responses in Obese Hypertensive and Lean Normotensive Subjects

The regional insulin infusion produced mean venous plasma insulin concentrations in the ipsilateral forearm vein of 104±12 μU/mL in normotensive subjects and 100±10 μU/mL in hypertensive subjects. Blood flow increased within 30 minutes and was maintained for the duration of the 2-hour infusion in the ipsilateral but not the contralateral forearm of both groups (Fig 3). The regional insulin infusion tended to raise systemic insulin, as measured in the contralateral forearm, in hypertensive and normotensive subjects. However, this did not alter cardiac output, heart rate, or blood flow and glucose in the contralateral forearm (Fig 4). Although the sham procedure increased FABF, this was significantly less than the rise of FABF observed with insulin (Fig 4). Heart rate, mean arterial pressure, and cardiac output were not significantly different in the two groups (Fig 3). NE

FIG 1. Plots show forearm blood flow (FABF) responses and calculated group mean EC50 values in hypertensive and normotensive subjects to norepinephrine (NE) alone and with insulin. Left: Mean arterial pressure (MAP), heart rate (HR), cardiac output (CO), and absolute and natural log values for FABF at baseline and during regional NE infusion for hypertensive and normotensive subjects. Right: Same as left, but insulin was infused with NE. *P<.05 for indicated time point vs baseline value; + indicates the two series of data are different but parallel (no significant effect of dose×diagnosis); and †, the two curves are different and not parallel (significantly different effect, dose×diagnosis).
output did not change during the sham procedure. The absolute mean increase of FABF during the 2-hour regional infusion of insulin, although significant within each group, was similar in hypertensive versus normotensive subjects (1.7±0.4 versus 1.7±0.6 mL/100 mL per minute). The absence of significant differences in the FABF response to insulin in hypertensive versus normotensive subjects persisted when controlling for baseline FABF in covariate analysis.

Discussion

Effect of Regional Insulin on Forearm Vascular Reactivity to Norepinephrine

The primary objective of this study was to determine if an impairment of the capacity of insulin to antagonize reactivity to norepinephrine could contribute to the increased forearm vascular $\alpha$-adrenergic tone observed in our previous studies.\(^5\) The norepinephrine EC$_{50}$ was similar in obese hypertensive versus lean normotensive subjects (Fig 1). These findings are consistent with our earlier report that forearm vascular sensitivity to norepinephrine is similar in an overweight group of mildly hypertensive young men versus normotensive control subjects of similar age and weight.\(^5\) Regional insulin at approximately 100 $\mu$U/mL for 2 hours did not antago-
versus systemic infusions, physiological versus pharmaco-
vascular responses to a-agonists may be influenced by
jects, insulin levels do not exceed 100 µU/mL even after
multiple factors, including species and gender, regional
versus systemic infusions, physiological versus pharmaco-
logic doses, the presence or absence of endothelium, and
in vitro versus in vivo measurements. For example,
insulin antagonizes pressor responses to norepinephrine
in isolated tail arteries from male but not female rats.7
Insulin also blunts phenylephrine-mediated contractions
in deendothelialized rat aorta.8 Similarly, pharmacologic
doses of insulin antagonize reactivity to norepinephrine,
serotonin, and potassium in the rat mesenteric circula-
in vitro.8 However, physiological hyperinsulinemia
enhances rat mesenteric vascular reactivity to norepi-
neprhine but not angiotensin or serotonin.27 Euglycemic
hyperinsulinemia in humans similarly augments pressor
responses to norepinephrine but not angiotensin II.28
Thus, we cannot extrapolate from the forearm to other
regional beds or the systemic circulation.

Effects of Insulin on Forearm Blood Flow and
Comparison of the Flow Responses in Hypertensive
and Normotensive Subjects

In this study, insulin at 100 µU/mL with its vehicle
(saline plus albumin) was a direct vasodilator in the
regional forearm circulation, because blood flow in-
creased in the ipsilateral (infused) but not the contra-
lateral forearm (Fig 3). Moreover, the vasodilation
induced by insulin was greater than the response to the
sham procedure (Fig 4). Thus, insulin can increase
blood flow by local actions in the forearm.

Andres et al11 reported that locally infused insulin
dilated the forearm circulation in humans. They also
observed a nonspecific vasodilation during the regional
insulin infusion (Fig 3) probably does not reduce the
forearm vascular actions of insulin. In our experience,
very modest regional vasodilator response to regional
insulin in this study, after correcting for the nonspecific effect of the sham
procedure, was approximately 20%. The minimal de-
note that insulin does not increase
FABF.13,14 One explanation for the incongruity of the fore-
may be the relatively large variability of basal FABF and the relatively
modest local vasodilating action of insulin. In other words,
the vasodilator response to regional insulin in this study,
after correcting for the nonspecific effect of the sham
procedure, was approximately 20%. The minimal de-
note that insulin does not increase
FABF.13,14 One explanation for the incongruity of the fore-
may be the relatively large variability of basal FABF and the relatively
modest local vasodilating action of insulin. In other words,
the vasodilator response to regional insulin in this study,
after correcting for the nonspecific effect of the sham
procedure, was approximately 20%. The minimal de-
note that insulin does not increase
FABF.13,14 One explanation for the incongruity of the fore-
may be the relatively large variability of basal FABF and the relatively
modest local vasodilating action of insulin. In other words,
the vasodilator response to regional insulin in this study,
after correcting for the nonspecific effect of the sham
procedure, was approximately 20%. The minimal de-
note that insulin does not increase
FABF.13,14 One explanation for the incongruity of the fore-
may be the relatively large variability of basal FABF and the relatively
modest local vasodilating action of insulin. In other words,
the vasodilator response to regional insulin in this study,
after correcting for the nonspecific effect of the sham
procedure, was approximately 20%. The minimal de-
note that insulin does not increase
FABF.13,14 One explanation for the incongruity of the fore-
may be the relatively large variability of basal FABF and the relatively
modest local vasodilating action of insulin. In other words,
rate of glucose disappearance during an insulin tolerance test. Despite systemic evidence for insulin resistance, the absolute increase of FABF during the regional insulin infusion was similar in both groups. In view of the link between flow and metabolic responses to insulin in the leg, one explanation for our data is that the systemic evidence for insulin resistance in obese hypertensive subjects does not include their forearms. Arterial glucose values were not obtained during the regional insulin infusion because our pilot studies indicated that the arterial sampling with flushing of the catheter increased the nonspecific vasodilation, as noted in previous studies. However, venous glucose levels were measured in both forearms at 30-minute intervals during the regional insulin infusion. The difference between the contralateral and ipsilateral forearm glucose concentrations during the final 60 minutes of the 2-hour regional insulin infusion would predominantly reflect the effect of insulin in the ipsilateral forearm. Although this is not a classic regional metabolic "clamp" study and interpretation is limited, the findings were consistent with previous reports. Lean normotensive subjects had a greater difference between the contralateral minus ipsilateral venous glucose values compared with hypertensive subjects (Table 3). Despite indirect evidence for resistance to insulin-mediated glucose uptake in the forearm, insulin at 100 μU/mL induced similar absolute increases of FABF in obese hypertensive and lean normotensive subjects.

Acknowledgments

This work was supported by grant HL-R01-43164 from the National Institutes of Health: Clinical Investigator and Postdoctoral Fellowship awards from the American Heart Association, Wisconsin Affiliate; and General Clinical Research Center (GCRC) Grant M01-RR58 to the Medical College of Wisconsin. The authors thank the GCRC nursing and nutrition staff for superb support.

References

Insulin does not reduce forearm alpha-vasoreactivity in obese hypertensive or lean normotensive men.
J M Neahring, K Stepniakowski, A S Greene and B M Egan

Hypertension. 1993;22:584-590
doi: 10.1161/01.HYP.22.4.584

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1993 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/22/4/584

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org/subscriptions/