Vasoconstriction With Norepinephrine Causes Less Forearm Insulin Resistance Than a Reflex Sympathetic Vasoconstriction

Kenneth A. Jamerson, Shawna D. Smith, John V. Amerena, Eric Grant, Stevo Julius

Abstract We used the insulin-perfused human forearm model to assess the effects of vasoconstriction induced with norepinephrine on the extraction of glucose in the forearm in two groups of healthy young volunteers. The norepinephrine findings were compared with a previously studied group in which vasoconstriction had been caused by reflex activation of the sympathetic nervous system. The aim of the study was to determine the relative importance of hemodynamic and receptor-mediated mechanisms of insulin resistance. Plasma insulin, arterial and venous glucose samples, and forearm blood flow were measured at 10-minute intervals during a 30-minute baseline, a 60-minute intra-arterial insulin infusion, and during 30 minutes of insulin infusion plus vasoconstriction. Group 1 (n=14) had physiological vasoconstriction induced by inflation of bilateral thigh cuffs to 40 mm Hg to cause pooling of blood in the lower extremities and reflex vasoconstriction in the forearm; group 2 (n=8) had intra-arterial infusion of norepinephrine to achieve the same degree of vasoconstriction as seen with inflation of thigh cuffs in group 1. Subjects in group 3 (n=7) had infusion of intra-arterial norepinephrine to achieve a twofold increase in physiological vasoconstriction. With a physiological decrease in forearm blood flow (group 1), there was a 19% decrease in forearm blood flow resulting in a 23% reduction in glucose uptake in the forearm (P<.03). The same degree of reduction in forearm blood flow with a predominantly a-adrenergic agonist, norepinephrine (group 2), causes much less insulin resistance (a decrease in utilization of 13%) (P<.04). When forearm blood flow is decreased twofold over the physiological vasoconstriction (group 3), there is a 42% reduction in glucose uptake (P<.005). The larger degree of insulin resistance with mild (25%) reflex vasoconstriction when compared with an equal degree of vasoconstriction induced by norepinephrine may be due to activation of ß-receptors during the reflex or to differences in the microcirculatory patterns with different modalities of vasoconstriction. (Hypertension. 1994;23[part 2];1006-1011.)

Key Words • insulin resistance • sympathetic nervous system • forearm • norepinephrine

A frequent association of tissue insulin insensitivity and blood pressure in humans has been observed in several clinical surveys.1-7 Recent investigations have focused on a possible pressor effect of insulin through sympathetic nervous system tone,8-11 an increase in the intravascular volume,12,13 or through the effect of insulin on vascular smooth muscle.14-15 It has been speculated that high insulin in insulin-resistant states may cause the increase of blood pressure in hypertension through these various pressor mechanisms.16 In contrast to the insulinogenic hypothesis of the blood pressure elevation, the infusion of insulin into humans has been repeatedly associated with vasodilation or attenuation of vasoconstrictive stimuli instead of a pressor effect.11,17-19

In a recent review we offered an alternative explanation for the frequent association between elevated blood pressure and insulin resistance.20,21 We proposed that vascular changes in the microcirculation secondary to long-standing elevations in blood pressure may alter the delivery of insulin and glucose to tissues and may thereby, in part, cause insulin resistance. Our hypothesis suggests that the primary defect may be vascular in nature, from elevation in blood pressure, and not in tissue sensitivity to the effects of insulin. A first step in testing the validity of this hypothesis was to show that in normal individuals an acute change in blood flow could cause changes in glucose utilization in vivo. We used bilateral inflation of thigh cuffs to cause a pooling of blood in the lower extremities and a subsequent decrease in venous return.22 From previous work23,24 it has been shown that this hemodynamic change results in unloading of cardiopulmonary receptors and a centrally mediated increase in sympathetic outflow that manifests as a decrease in forearm blood flow (FABF).25

With inflation of thigh cuffs, we were able to achieve on average a 19% reduction in FABF.22 This decrease in flow was considered to be physiological vasoconstriction and was accompanied by a 23% decrease in forearm glucose utilization.22 The results demonstrate that acute activation of the sympathetic nervous system causes acute insulin resistance, but the study design did not allow us to distinguish whether the insulin resistance was secondary to activation of adrenergic receptors or the decrease in FABF.

In the present study, we attempt to further evaluate the effects of activation of adrenergic receptors versus hemodynamically induced changes of glucose utilization in the forearm. We used the insulin-perfused isolated forearm technique to investigate the effect of vasoconstriction on glucose utilization by comparing results of pharmacologic a-adrenergic vasoconstriction with previous results of physiological vasoconstriction on the extraction of glucose in the intact human forearm of healthy subjects. Whereas a-adrenergic receptor block-
ers have been shown to improve insulin sensitivity in clinical trials, an effect of α-receptors on glucose utilization in peripheral skeletal muscles has not been previously described.

Methods

Subjects and Protocol

Subjects were recruited by advertisement in local newspapers. The protocol was reviewed and approved by the Committee to Review Grants for Clinical Research and Investigation Involving Human Beings at the University of Michigan Medical Center. Young healthy men and women were admitted to the General Clinical Research Center after a 12-hour fast. Subjects taking prescription or nonprescription medications were excluded from the study. Women on oral contraceptive pills were studied at the end of the 5 days of their cycle when they were on estrogen withdrawal. After informed consent and a medical history were obtained, anthropometric data were collected. Subjects were placed in a recumbent position before the placement of a brachial arterial line and retrograde cannulation of a deep forearm vein in the antecubital fossa. The placement of catheters to isolate the forearm has been previously described.

Electrocardiogram and intra-arterial blood pressure were monitored continuously for the duration of the procedure. After placement of the catheters, subjects had a 15-minute rest followed by a 30-minute baseline period where FABF was measured at 10-minute intervals; arterial and venous samples for plasma glucose and blood gases were obtained every 15 minutes. One baseline plasma insulin specimen was obtained at the end of the 30 minutes. After a 30-minute baseline period, an intra-arterial infusion of insulin was begun using a Harvard pump with a stock concentration of insulin (Humulin) of 0.01 mU/μL in 1% albumin at a rate calculated to raise plasma insulin concentrations to 100 μU/mL over baseline fasting plasma insulin values. During the 60-minute insulin infusion period, FABF was measured at 10-minute intervals; plasma insulin and arterial and venous samples for glucose and blood gases were obtained at 40, 50, and 60 minutes of insulin infusion.

After 60 minutes of insulin infusion, vasoconstriction was induced in one of two ways: (1) infusion of norepinephrine into the brachial artery at a dose intended to reduce FABF by 25% or (2) infusion of norepinephrine to reduce FABF by 50%. Recently published results on the effect of physiological vasoconstriction by infusion of bilateral thigh cuffs are used for comparison. The dose of norepinephrine was selected from a dose titration study done by Egan et al. Norepinephrine was infused for 3 minutes, and FABF was measured during minute 4. Based on the average of three blood flow measurements made at the end of the 4-minute norepinephrine infusion, subjects were assigned to groups of 25% or 50% reduction in blood flow (groups 2 and 3, respectively). Local norepinephrine infusion was continued for 30 minutes. Blood flow, arterial and venous glucose, and plasma insulin were measured at 10-minute intervals during this infusion period.

Plasma glucose and insulin samples were immediately centrifuged at 3000 rpm and analyzed at the Michigan Diabetes Research and Training Center. Glucose was measured by hexokinase reaction and insulin by radioimmunoassay. Complete blood gas analyses were performed with an Instrumentation Laboratory System 1302 and a 282 CO2 Analyzer.

Glucose Balance

The forearm balance of glucose was expressed in two ways: (1) as arteriovenous (A-V) gradient (A-V difference in glucose) or (2) as glucose utilization, the product of the A-V difference and simultaneous ipsilateral measurement of FABF (strain-gauge plethysmography, Hokanson).

Analysis

All data are expressed as mean ± SEM. The values were averaged for each condition (baseline, insulin infusion, and insulin infusion plus vasoconstriction). Student's t test for paired values was used to compare results between conditions.

Results

Table 1 shows the anthropometric and hemodynamic data on each group of subjects during the 30-minute baseline period. Subjects were predominantly male, as difficulties in placing catheters in women led to frequent technical failure. On average, subjects were not obese and had fasting insulin values well within normal limits.

The infusion of insulin resulted in local hyperinsulinemia in the forearm with an increase in insulin in the range of physiological postprandial levels in each group.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1 (n=14)</th>
<th>Group 2 (n=8)</th>
<th>Group 3 (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>28.1±1.8</td>
<td>35.5±1.8</td>
<td>28.1±1.6</td>
</tr>
<tr>
<td>Race, white/black</td>
<td>10/4</td>
<td>7/1</td>
<td>7/0</td>
</tr>
<tr>
<td>Height, cm</td>
<td>179.6±2</td>
<td>175.3±4</td>
<td>180±2</td>
</tr>
<tr>
<td>FABF, mL/dL per minute</td>
<td>3.76±0.26</td>
<td>3.97±0.52</td>
<td>4.83±0.93</td>
</tr>
<tr>
<td>Glucose utilization, mg/dL per minute per 100 cm³ of forearm volume</td>
<td>16.4±3.1</td>
<td>9.6±5.3</td>
<td>18.0±4.7</td>
</tr>
<tr>
<td>Plasma insulin, μU/mL</td>
<td>10.8±1.4</td>
<td>12.1±1.2</td>
<td>12.1±1.2</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>83.5±3.3</td>
<td>88.0±5.4</td>
<td>79.4±5.6</td>
</tr>
<tr>
<td>MBP, mm Hg</td>
<td>91.1±1.0</td>
<td>98.6±4.3</td>
<td>94.3±4.3</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>61.5±1.6</td>
<td>63.6±1.6</td>
<td>62.7±3.5</td>
</tr>
</tbody>
</table>

FABF indicates forearm blood flow; MBP, mean blood pressure; and bpm, beats per minute. Values are mean ±SEM. Groups are distinguished by type of vasoconstriction. In group 1, FABF was reduced 19% by sympathetic reflex from inflation of bilateral thigh cuffs. Groups 2 and 3 had a 25% and 50% reduction in FABF, respectively, by intra-arterial norepinephrine.

Table 1. Baseline Characteristics of Subjects
### TABLE 2. Hemodynamic Effects of Intra-arterial Insulin Infusion Alone and Insulin Plus Vasoconstriction in the Forearm of Healthy Subjects

<table>
<thead>
<tr>
<th>Hemodynamic Parameter</th>
<th>Group 1 (Cuffs)</th>
<th>Group 2 (25% NE)</th>
<th>Group 3 (50% NE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FABF, cm²/dL per forearm volume per minute</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>5.07±0.40</td>
<td>4.72±0.64</td>
<td>5.53±0.92</td>
</tr>
<tr>
<td>Vasoconstriction</td>
<td>4.13±0.31</td>
<td>3.64±0.45</td>
<td>2.28±0.7</td>
</tr>
<tr>
<td>Change</td>
<td>-19%*</td>
<td>-23%†</td>
<td>-58‡</td>
</tr>
<tr>
<td>MABP, mm Hg</td>
<td>92±1</td>
<td>98.6±4.3</td>
<td>95±2.5</td>
</tr>
<tr>
<td>Insulin</td>
<td>92±1.9</td>
<td>102±4.9</td>
<td>98±3.8</td>
</tr>
<tr>
<td>Vasoconstriction</td>
<td>0%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>61.5±1.2</td>
<td>64±1.9</td>
<td>66±2.8</td>
</tr>
<tr>
<td>Insulin</td>
<td>66.1±2.7</td>
<td>66±3.2</td>
<td>67±3.0</td>
</tr>
<tr>
<td>Vasoconstriction</td>
<td>10%</td>
<td>3%</td>
<td>1.5%</td>
</tr>
</tbody>
</table>

Insulin indicates 60-minute intra-arterial insulin infusion; vasoconstriction, 30-minute insulin infusion with vasoconstriction for each group of subjects; NE, norepinephrine; FABF, forearm blood flow; MABP, mean arterial blood pressure; and bpm, beats per minute. Values are given as mean±SEM and percent change from study conditions. In group 1, FABF was reduced 19% by sympathetic reflex from inflation of bilateral thigh cuff. Groups 2 and 3 had a 25% and 50% reduction in FABF, respectively, by intra-arterial norepinephrine.

Within-group comparison from insulin to insulin plus vasoconstriction: *P<.001, †P<.05, ‡P<.008.

### TABLE 3. Forearm Metabolism of Glucose With Intra-arterial Insulin Infusion Alone and Insulin Plus Vasoconstriction

<table>
<thead>
<tr>
<th>Metabolic Parameter</th>
<th>Group 1 (Cuffs)</th>
<th>Group 2 (25% NE)</th>
<th>Group 3 (50% NE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma insulin, µU/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>133±25</td>
<td>88±13</td>
<td>148±39</td>
</tr>
<tr>
<td>Vasoconstriction</td>
<td>170±36</td>
<td>109±15</td>
<td>212±37</td>
</tr>
<tr>
<td>Change</td>
<td>28%</td>
<td>23%*</td>
<td>42‡</td>
</tr>
<tr>
<td>Glucose utilization, mg/dL per minute per 100 cm² of forearm volume</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>86±15</td>
<td>76±8.2</td>
<td>125±28</td>
</tr>
<tr>
<td>Vasoconstriction</td>
<td>66±13</td>
<td>66±11</td>
<td>73±23</td>
</tr>
<tr>
<td>Change</td>
<td>-23%†</td>
<td>-14‡</td>
<td>-42%*</td>
</tr>
<tr>
<td>A-V glucose gradient, mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>17.2±2.7</td>
<td>18±3</td>
<td>25±6</td>
</tr>
<tr>
<td>Vasoconstriction</td>
<td>13.8±2.4</td>
<td>19±3</td>
<td>30±6</td>
</tr>
<tr>
<td>Change</td>
<td>-20%</td>
<td>7%</td>
<td>19%</td>
</tr>
</tbody>
</table>

Insulin indicates 60-minute intra-arterial insulin infusion; vasoconstriction, 30-minute insulin infusion with vasoconstriction for each group of subjects; NE, norepinephrine; and A-V, arteriovenous. Values are given as mean±SEM and percent change from study conditions. In group 1, forearm blood flow (FABF) was reduced 19% by sympathetic reflex from inflation of bilateral thigh cuff. Groups 2 and 3 had a 25% and 50% reduction in FABF, respectively, by intra-arterial norepinephrine.

Within-group comparison from insulin to insulin plus vasoconstriction: *P<.004, †P<.03, ‡P<.008.
FABF were unchanged (Table 2). Two indices of forearm glucose extraction were calculated, the A-V glucose gradient and glucose utilization (product of the A-V difference and forearm blood flow, bottom) from insulin infusion alone to insulin infusion plus vasoconstriction by: cuffs (n=14); reflex vasoconstriction, norepinephrine (NE) 25% (n=8); 25% reduction in forearm blood flow (FABF) from infusion of norepinephrine into the brachial artery, norepinephrine 50% (n=7); and 50% reduction in FABF from norepinephrine infusion.

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**Discussion**

Insulin resistance in hypertensive subjects has been previously described as a postreceptor mechanism in which the major defect is related to storage of intracellular glucose as glycogen, predominately in skeletal muscles.29-31 This mechanism is inferred as intracellular glucose as glycogen, predominately in skeletal muscles.29-31 This mechanism is inferred as intracellular glucose as glycogen, predominately in skeletal muscles.29-31 This mechanism is inferred as intracellular glucose as glycogen, predominately in skeletal muscles.29-31 This mechanism is inferred as intracellular glucose as glycogen, predominately in skeletal muscles.29-31 This mechanism is inferred as intracellular glucose as glycogen, predominately in skeletal muscles.29-31 This mechanism is inferred as intracellular glucose as glycogen, predominately in skeletal muscles.29-31 This mechanism is inferred as intracellular glucose as glycogen, predominately in skeletal muscles.29-31 This mechanism is inferred as 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β-blockable lactate release in perfused skeletal muscle or in incubated tissues.42

An alternative explanation of the effect on glucose utilization of the physiologic versus norepinephrine-induced vasoconstriction is also feasible. Baron’s group (Laakso et al)43,44 proposed that, in addition to its direct effect on the glucose transporter, insulin’s effect on glucose uptake may be due in part to its vasodilatation and the recruitment of new capillaries. We extended these observations to suggest that functional or structural loss of capillaries may negatively affect the glucose utilization in the skeletal muscle of patients with hypertension.20,21 Insulin concentrations show a gradient from nutritional capillaries to the interstitium,45 and it has been suggested that this may be a rate-limiting factor for insulin’s action. The disparate effects of physiological versus pharmacologic sympathetic activation may depend on the pattern of vasoconstriction along the various segments of the vascular tree. Recently, Rattigan et al46 demonstrated a decrease of glucose utilization in perfused rat hindlimbs with local infusion of serotonin in doses that in other experiments caused a considerable amount of vascular shunting in the skeletal muscle.47 The effect of serotonin on the glucose utilization was flow-related, as serotonin had no effect on glucose utilization of the incubated muscle. The observation in our study can be explained also by such hemodynamic factors. It is conceivable that in comparison to exogenous infusion of norepinephrine, a physiological postsynaptic α-stimulation causes a larger function shunting of the blood from skeletal muscle cells.

Data presented in this study suggest that sympathetic activation can induce various degrees of insulin insensitivity in humans. The importance of receptor- versus flow-mediated insulin resistance in hypertension has been documented.48 A possible role for hemodynamic factors is suggested by the observation that vasodilators with various mechanisms of action improve insulin sensitivity.49 The forearm flow in normal humans is related to vascular resistance, as serotonin had no effect on glucose utilization of the incubated muscle. The observation in our study can be explained also by such hemodynamic factors. It is conceivable that in comparison to exogenous infusion of norepinephrine, a physiological postsynaptic α-stimulation causes a larger function shunting of the blood from skeletal muscle cells.

In summary, we find that insulin resistance can be induced in the forearm of healthy volunteers by acute activation of the sympathetic nervous system or by infusion of norepinephrine. Activation of the sympathetic nervous system causes more insulin resistance than does vasoconstriction alone. One possible explanation is that activation of the sympathetic nervous system may have caused a β-receptor-mediated decrease in glucose uptake. With the higher dose of norepinephrine and a significant decrease in FABF, the insulin resistance that ensues is in proportion to the decrease in FABF. Furthermore, the insulin resistance persists for as long as there is vasoconstriction (30 minutes in this study). Thus, it is also possible that, in addition to the receptor-mediated resistance, there is a decrease in the uptake of glucose in human skeletal muscle mediated by the α-adrenergic reduction of blood flow. The relative importance of receptor- versus flow-mediated insulin resistance deserves further investigation.

Acknowledgments

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References


Vasoconstriction with norepinephrine causes less forearm insulin resistance than a reflex sympathetic vasoconstriction.

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