Insulin resistance has recently been found to be a common feature of essential hypertension. We have tested the hypothesis that reduced skeletal muscle blood flow in response to insulin may at least partially account for the wide range of insulin sensitivity observed in normotensive subjects. To this end, we studied 19 lean (body mass index ≤27) subjects exhibiting basal mean arterial pressures ranging from 58 to 110 mm Hg. All subjects were normotensive with the exception of one. Each subject was studied at baseline and during a hyperinsulinemic (600 milliunits/m² per minute) euglycemic clamp to quantitate insulin sensitivity. Mean arterial pressure was monitored invasively, and both leg (muscle) blood flow and cardiac output were measured by indicator dilution techniques, allowing the determination of both systemic and leg (or muscle) vascular resistance. In response to hyperinsulinemia, both cardiac output and leg blood flow increased approximately 37% and 80% (p<0.01), respectively. Rates of insulin-mediated glucose uptake were inversely correlated with the baseline mean arterial pressure (r=—0.62, p<0.01). The individual increment in leg blood flow above baseline in response to insulin was inversely proportional to the height of the baseline mean arterial pressure (r=—0.59, p<0.01). Mean arterial pressure and insulin-mediated glucose uptake were not correlated with either age or body fat content. The femoral arteriovenous glucose difference during hyperinsulinemia was not correlated with either basal mean arterial pressure or the rate of insulin-mediated glucose uptake. In summary, among normotensive subjects, 1) the rate of insulin-mediated glucose uptake is inversely proportional to the basal mean arterial pressure, 2) the increase in insulin-mediated muscle blood flow is inversely related to the basal mean arterial pressure, and 3) muscle glucose extraction is not related to the basal mean arterial pressure or the rate of insulin-mediated glucose uptake. In conclusion, attenuated insulin-mediated skeletal muscle blood flow appears to be a major cause of insulin resistance in subjects with elevated mean arterial pressure. Our data in normotensive subjects do not exclude the coexistence of other defects in glucose uptake and metabolism; nevertheless, they strongly support a hemodynamic basis for the insulin resistance observed in patients with hypertension. (Hypertension 1993;21:129—135)

KEY WORDS • blood flow • insulin resistance • glucose clamp technique • cardiac output • vascular resistance • lactate • hypertension, essential
from constitutive reductions in capillary density as proposed by Lillioja et al.\textsuperscript{13} in obese Pima Indians or by a dynamic defect in insulin-mediated capillary recruitment as we have previously proposed.\textsuperscript{4-5} Altered insulin and glucose delivery has been attractive as a potential mechanism of insulin resistance in hypertension. This is particularly so because insulin increases muscle blood flow by a selective reduction in skeletal muscle vascular resistance,\textsuperscript{14} and hypertension is characterized by elevated vascular resistance.\textsuperscript{15} Moreover, essential hypertension in rats is associated with skeletal muscle capillary rarefaction,\textsuperscript{16} resulting in reduced capillary density.

To explore the idea that reductions in IMGU associated with elevated arterial pressure may be, at least in part, the result of decreased skeletal muscle blood flow, we studied a group of 19 nondiabetic lean subjects (body mass index $\leq 27$) exhibiting a large range of mean arterial pressure (MAP). Insulin sensitivity was quantitated by the combination of the hyperinsulinemic euglycemic clamp and the leg balance techniques. Leg blood flow, cardiac output, MAP, and leg (muscle) and systemic vascular resistances were measured at baseline and during an insulin infusion designed to achieve maximally effective insulin concentrations.

**Methods**

**Subjects**

The characteristics of the study group are shown in Table 1. All subjects had a body mass index $\leq 27$ (weight [kg]/height$^2$ [m$^2$]), had normal glucose tolerance to a 75-g oral glucose load,\textsuperscript{17} and no family history of diabetes. All subjects were normotensive (except one subject whose MAP was 110 mm Hg), were chemically euthyroid, and were not ingesting any medications. Subjects exhibited a wide range of activity profiles, ranging from regular endurance training (runners) to relatively sedentary lifestyles. Volunteers gave informed consent and were hospitalized 2 days before the study at the General Clinical Research Center at Indiana University Hospital. Studies were approved by the Indiana University Human Subjects Review Board.

**Diet.** The caloric content of the diets while subjects were hospitalized was standardized to be distributed as 50% carbohydrate, 30% fat, and 20% protein; the diet was designed to be weight maintaining. Subjects were studied in the supine position after an overnight 14-hour fast.

**Protocol**

**Glucose clamp studies.** Each subject underwent a euglycemic hyperinsulinemic clamp at an insulin infusion rate of 600 milliunits/m$^2$ per minute. After basal measurements were obtained, insulin was infused in a square-wave fashion, and a 20% dextrose solution was infused at a variable rate to keep the serum glucose concentration at the baseline level according to arterial serum glucose determinations performed at approximately 5-minute intervals. The clamp studies were carried out for 200 minutes to achieve steady-state glucose infusion rates, and IMGU rates were calculated on the basis of data obtained over the last 40 minutes of each study. During each clamp, K$_2$HPO$_4$ (approximately 0.0038 meq/kg per minute) was infused to prevent hypokalemia and hypophosphatemia.

During insulin infusions at 600 milliunits/m$^2$ per minute, endogenous rates of glucose appearance have been shown to be completely suppressed,\textsuperscript{4} so glucose uptake rates were calculated from the glucose infusion rates at steady state. Basal rates of whole-body glucose uptake were not measured in most subjects and thus are not reported.

**Leg glucose balance studies.** Leg glucose uptake was calculated by the Fick Principle as the product of the femoral arteriovenous blood glucose difference ($\Delta$F AVG) and leg blood flow at baseline and during the last 30 minutes of each insulin infusion. The $\Delta$F AVG was calculated as the mean of seven determinations obtained at 5-minute intervals. Leg blood flow was measured by a thermodilution catheter inserted into a 5F sheath placed into the femoral vein, as previously described.\textsuperscript{18} Blood flow was calculated as the mean of 12 determinations obtained over approximately a 5-minute period. Arterial blood was obtained through a 16-gauge catheter inserted into the femoral artery.

**Hemodynamic Measurements**

**Cardiac output.** Cardiac output was measured by the dye dilution technique at baseline and over the last 30 minutes of each clamp study. A bolus of 5 mg indocyanine green dye (Cardiogreen, Becton Dickinson Microbiology Systems, Cockeysville, Md.) was injected into the central venous circulation via a 12-in. catheter.
(Intracath, Deseret Medical, Inc., Sandy, Utah) inserted into a left antecubital vein and threaded cephalad to lodge in a thoracic vein. After dye injection, arterial blood was continuously withdrawn via a Waters SW-367 withdrawal pump through a Waters DC-410 densitometer cuvette connected to a Waters CO-10 cardiac output computer (Waters Instruments, Inc., Rochester, Minn.), which integrates the dye dilution curves. Each dilution curve was recorded on a chart recorder and inspected for integrity. The mean of three measurements of cardiac output was taken as the representative value.

**Mean arterial pressure and heart rate.** MAP was continuously monitored via a transducer (Sorenson Transpac, Abbot Critical Care Systems, North Chicago) connected to a vital signs monitor (Physiocontrol VSM 1, Redmond, Wash.). The mean of five MAP values was taken as the representative MAP.

Heart rate was monitored via precordial leads connected to the vital signs monitor. The representative heart rate was the mean of five values.

**Vascular resistance.** Systemic and leg vascular resistances were calculated by dividing MAP (mm Hg) by mean cardiac output (l/min) and leg blood flow (l/min) and are expressed in arbitrary units.

**Analytical methods.** Blood for serum glucose determination was drawn, put in untreated polypropylene tubes, and centrifuged with an Eppendorf microcentrifuge (Brinkmann Instruments, Inc., Westbury, N.Y.). The glucose concentration of the supernatant was then measured by the glucose oxidase method with a glucose analyzer (model 23A, Yellow Springs Instrument Co., Yellow Springs, Ohio). Blood for determination of serum insulin concentrations was collected in tubes treated with aprotinin (500 kIU/ml) and was allowed to clot. The specimens were spun, and the supernatant was removed and stored at −20°C. Serum insulin levels were measured by double-antibody radioimmunoassay. Body composition was determined by the underwater weighing technique.

**Statistical Analysis**

Student's paired t test was used to compare basal and insulin-stimulated data. Linear regression analysis was used to correlate various parameters shown in Table 4. Curvilinear analysis was applied for the drawing of some graphs when appropriate. All analyses were performed on a personal computer (Macintosh IIX) using the statistical software package STATVIEW II (Abacus Concepts, Inc., Berkeley, Calif.). Data are expressed as mean±SEM.

### Results

**Glucose Metabolism**

Rates of whole-body IMGU and leg glucose uptake are shown in Table 2. Leg glucose uptake increased approximately 25-fold during maximal insulin stimulation as a result of a 14-fold increase in ∆FAVG and an 80% increase in leg blood flow.

**Hemodynamics**

Hemodynamic parameters are shown in Table 3. Hyperinsulinemia resulted in approximately a 37% increase in cardiac output, which was due both to approximately a 14% increment in heart rate and approximately a 25% increase in stroke volume. Leg blood flow increased from 0.3±0.03 to 0.54±0.05 l/min (p<0.001). During euglycemic hyperinsulinemia, MAP fell approximately 6% from baseline (p<0.001). Systemic and leg vascular resistances declined approximately 31% and 48%, respectively (p<0.01).

**Correlation Analysis**

Table 4 shows the correlation analysis. The rate of whole-body IMGU was inversely related to basal MAP (r=−0.63, p<0.01) (Figure 1). Because whole-body IMGU occurs principally in skeletal muscle, it follows that examining the components of leg glucose uptake can reveal whether changes in glucose extraction (∆FAVG), blood flow, or both account for differences in IMGU between subjects exhibiting a wide range of basal MAP. The ∆FAVG was not correlated with either

### Table 3. Hemodynamic Parameters at Baseline and During Euglycemic Hyperinsulinemia

<table>
<thead>
<tr>
<th>CO (l/min)</th>
<th>SV (l)</th>
<th>HR (bpm)</th>
<th>LBF (l/min)</th>
<th>MAP (mm Hg)</th>
<th>SVR</th>
<th>LVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal</td>
<td>5.00±0.39</td>
<td>0.08±0.01</td>
<td>63.86±2.82</td>
<td>0.30±0.03</td>
<td>85.87±2.48</td>
<td>19.19±1.70</td>
</tr>
<tr>
<td>Hyperinsulinemia</td>
<td>6.83±0.48*</td>
<td>0.10±0.00*</td>
<td>72.58±2.39*</td>
<td>0.54±0.05*</td>
<td>80.81±2.98*</td>
<td>13.27±1.35*</td>
</tr>
</tbody>
</table>

CO, Cardiac output; SV, stroke volume; HR, heart rate; bpm, beats per minute; LBF, leg blood flow; MAP, mean arterial pressure; SVR, systemic vascular resistance; LVR, leg vascular resistance. Values are mean±SEM.

* p<0.01, hyperinsulinemia vs. baseline.

**Table 4. Correlational Analysis**

<table>
<thead>
<tr>
<th>IMGU</th>
<th>Basal MAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>r</td>
<td>p</td>
</tr>
<tr>
<td>IMGU</td>
<td>...</td>
</tr>
<tr>
<td>Basal MAP</td>
<td>0.63</td>
</tr>
<tr>
<td>∆FAVG</td>
<td>0.22</td>
</tr>
<tr>
<td>∆LBF (%)</td>
<td>0.44</td>
</tr>
<tr>
<td>∆LVR (%)</td>
<td>−0.50</td>
</tr>
<tr>
<td>∆SVR (%)</td>
<td>−0.48</td>
</tr>
<tr>
<td>LGU</td>
<td>0.52</td>
</tr>
<tr>
<td>Fat (%)</td>
<td>−0.22</td>
</tr>
<tr>
<td>Basal arterial lactate</td>
<td>−0.40</td>
</tr>
<tr>
<td>Basal arterial insulin</td>
<td>−0.60</td>
</tr>
</tbody>
</table>

IMGU, insulin-mediated glucose uptake rate; Basal MAP, basal mean arterial pressure; ∆FAVG, femoral arteriovenous glucose difference; ∆LBF, ∆SVR, ∆LVR, percent changes from baseline in leg blood flow and systemic and leg vascular resistances; LGU, leg glucose uptake; Fat (%), percent body adiposity.
basal MAP or the rate of IMGU (Figure 2). In contrast, the percent increment in leg blood flow in response to insulin was inversely related to basal MAP ($r = -0.59$, $p < 0.01$) (Figure 3) and positively correlated to the rate of IMGU ($r = 0.44$, $p < 0.05$) (Figure 4). During insulin infusion, the percent decrease in systemic vascular resistance was inversely related to the rate of IMGU ($r = 0.48$, $p < 0.05$) (Figure 5). Normalizing rates of whole-body IMGU to kilograms of body weight or body surface area did not alter any of the relations. The rate of IMGU or basal MAP was not correlated with percent adiposity or age. Basal arterial insulin levels were related inversely to the rate of IMGU and positively to basal MAP. Basal arterial lactate levels were positively correlated with basal MAP.

**Discussion**

The current data indicate that the rate of IMGU in response to maximally effective insulin concentrations is inversely related to the baseline MAP. Moreover, under the current experimental conditions, differences in rates of IMGU between normotensive individuals appear to be largely accounted for by the magnitude of change in muscle blood flow and not by differences in skeletal muscle glucose extraction ($\Delta$FAVG). Together, the data suggest that reduced rates of IMGU (insulin resistance) in subjects with elevated blood pressure observed in hypertensive patients has been hypothetically considered by a number of groups. To our knowledge, the current report is the first to support this hypothesis by documenting an inverse relation between the height of the blood pressure and the ability of insulin to stimulate skeletal muscle blood flow.

A number of other studies have reported an inverse relation between the arterial pressure and rates of IMGU as measured by the euglycemic hyperinsulinemic clamp. The current study differs from these previous reports in important ways. Whereas others, for the most part, have measured glucose uptake at submaximally effective insulin concentrations (approximately 80 microunits/ml), we have documented an inverse relation between MAP and IMGU at maximally effective insulin concentrations (>2,000 microunits/ml). This experimental condition provides insights into the mechanism of insulin resistance that are not revealed at lower insulin concentrations. Indeed, defects in non-rate-limiting steps of glucose uptake that are apparent at lower insulin levels may participate alone (e.g., elevated circulating free fatty acids) or in concert to reduce rates of IMGU. On the other hand, at maximally effective insulin concentrations, non-rate-limiting steps of insulin action are overcome, and thus, reductions in IMGU are likely to be the result of a defect in a rate-limiting step for overall IMGU, such as glucose and insulin delivery or glucose transport. In this regard, Natali et al and Capaldo et al have reported smaller arteriove-
Hypertensive glucose differences across the forearm of hypertensive patients in response to physiological insulin concentrations when compared with normotensive subjects. Although we did not study frankly hypertensive subjects, our data do not indicate a relation between MAP and skeletal muscle glucose extraction. These reports are not necessarily contradictory if one considers the possibility that glucose extraction defects apparent at lower insulin concentrations may have been overcome at higher insulin levels.

A unique finding of our study is the clear and continuous inverse relation between basal MAP and the ability of insulin to augment skeletal muscle blood flow. Indeed, even within a normotensive population, those with the highest MAP had the smallest increment in insulin-mediated blood flow. This is also evident if one arbitrarily separates the subjects into a “low” (MAP <85 mm Hg, n=8) and “high” (MAP >85 mm Hg, n=11) blood pressure group. Indeed, the low MAP group exhibited a 127±25% increase in leg blood flow, whereas the high MAP group displayed only a 67±14% increase (p<0.05, high vs. low). Because this relation was apparent at high insulin levels and blood flow increases in a dose-dependent fashion in response to insulin, it follows that reduced insulin-mediated augmentation in skeletal muscle blood flow is likely to be present also at lower, more physiological insulin concentrations. It should be noted that other studies using the forearm balance technique have not documented significant increments in blood flow in either normotensive or hypertensive subjects in response to insulin. These discrepancies are probably the result of methodological differences (plethysmography versus thermodilution, arm versus leg) but are not likely to be due to differences in insulin concentrations studied, because we and others have clearly documented significant increments in blood flow at insulin levels ranging from 20 to 60 microunits/ml.

It is important to emphasize that no relation could be demonstrated between MAP and ΔFAVG or between IMGU and ΔFAVG. Therefore, lower rates of IMGU associated with higher basal MAP appear to be the result of a hemodynamic impairment in the ability of insulin to increase blood flow (insulin and glucose delivery) to skeletal muscle and not to a tissue defect per se in glucose extraction. Together, the data further support the concept that at maximally effective insulin concentrations, rates of skeletal muscle blood flow may be rate limiting to overall rates of IMGU and can thus account for much of the differences in rates of IMGU among lean normotensive individuals.

By design, our study population was nonobese (body mass index ≤27, Table 1); however, subjects exhibited a wide range of adiposity (12–35%). Because obesity is a major determinant of insulin resistance and hypertension, it is possible that our findings could be explained on the basis of the adiposity status of our study group. In this regard, it is important to point out that we found no correlation between MAP or IMGU...
with fat mass or percent body fat (Table 4). Therefore, it can be concluded that body fat content was not a determinant of either MAP or IMGU in our study population. In addition, we found that age was not a determinant of either MAP or IMGU in our study population. In this regard, we found no relation between arterial lactate levels and rates of IMGU, suggesting that the association between MAP and insulin sensitivity in our study population is probably not readily explained on the basis of aerobic capacity alone.

It is noteworthy that both relative changes in leg and systemic vascular resistances in response to insulin were correlated with the rate of IMGU (Table 4 and Figure S). Because the relative fall in leg vascular resistance (muscle vascular resistance) was greater than the relative fall in systemic vascular resistance \( p = 0.01 \) and the relative fall in systemic vascular resistance includes leg vascular resistance, it follows that the insulin-mediated fall in systemic vascular resistance is largely secondary to a reduction in muscle vascular resistance. This preferential reduction in muscle vascular resistance by insulin results in a redistribution of cardiac output (increase in blood flow) to skeletal muscle. Indeed, during hyperinsulinemia, the percent increase in cardiac output was correlated to the percent increment in leg blood flow \( r = 0.60, p = 0.007 \), and the relative fall in systemic vascular resistance was highly related to the relative fall in leg vascular resistance \( r = 0.70, p = 0.0008 \).

It is interesting to note that in response to insulin the relative fall in leg vascular resistance but not systemic vascular resistance was related to basal MAP. These data suggest that elevated MAP is associated with a defect in the ability of insulin to reduce skeletal muscle vascular resistance but does not significantly alter the action of insulin to modulate systemic vascular resistance. These data suggest that the effect of insulin to reduce vascular resistance is perhaps restricted to skeletal muscle and that it may have either a neutral effect or even an effect to increase vascular resistance in nonmuscle vascular beds, such as the splanchnic or adipose vasculature. This defect in vasodilation may be part of a general defect in vasodilation rather than one restricted to insulin alone. The underlying mechanism responsible for this observation remains to be elucidated and deserves further study.

Finally, our data may have important clinical implications. The higher prevalence of hypertension in patients with insulin resistance and the emergence of the concept of a syndrome of insulin resistance that features a clustering of cardiovascular risk factors \( 22-26 \) have reinforced the need to devise antihypertensive regimens that do not adversely affect glucose (and lipid) homeostasis. Consistent with the idea that skeletal muscle blood flow may have a role in determining insulin sensitivity are the clinical observations that antihypertensive agents that tend to increase vascular resistance (diuretics and \( \beta \)-blockers) also tend to worsen insulin action \( 21 \); conversely, those agents that reduce vascular resistance (calcium channel blockers, converting enzyme inhibitors, and \( \alpha \)-blockers) show either no change or even improvements in insulin sensitivity. \( 21-23 \) Based on the current findings, one would predict that pharmacological maneuvers that specifically reduce muscle vascular resistance and increase muscle blood flow would lead to enhanced peripheral insulin action. This idea is supported by unpublished preliminary data from our laboratory indicating that a twofold increase in leg blood flow induced by intra-arterial infusion of vasodilating agents results in a 40% increase in leg IMGU.

In summary, we have found that there is a continuous inverse relation between basal MAP and the rate of IMGU in normotensive subjects. Moreover, reduced rates of skeletal muscle blood flow in subjects with higher MAP appear to play a major role in causing insulin resistance in these subjects. Although our data do not exclude the coexistence of other abnormalities in glucose uptake and metabolism, they strongly support a hemodynamic basis for the insulin resistance observed in patients with frank hypertension.

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