Acute Effects of Blood Pressure Elevation on Insulin Clearance in Normotensive Healthy Subjects

Christopher J. O’Callaghan, Karla Komersova, William J. Louis

Abstract—Reduced clearance of insulin from plasma contributes to the hyperinsulinemia associated with essential hypertension (EH); however, the association between impaired insulin clearance and EH remains unexplained. Whether elevated blood pressure (BP) affects insulin clearance is unknown; therefore, we used the hyperinsulinemic euglycemic clamp to determine the effects of BP elevation on insulin clearance and sensitivity in eight healthy volunteers. Placebo infusion increased mean BP by 2.6±1.6 mm Hg, which was significantly less than rises produced by phenylephrine, an α₁-adrenergic agonist (+11±1.8 mm Hg, P<.05), or by angiotensin II (+13±1.3 mm Hg, P<.01). Although β-adrenergic stimulation with isoproterenol did not change mean BP (+3.6 mm Hg, P=NS), it significantly increased systolic pressure (+23±2.8 mm Hg versus +2.3±4.6 mm Hg with placebo P<.01). Insulin secretion (ie, C-peptide concentrations) was not affected by any of the treatments; however, phenylephrine significantly reduced the metabolic clearance rate of insulin (MCRinsulin) (16.6±1.0 mL/kg per minute with placebo versus 13.6±0.7 mL/kg per minute with phenylephrine, P<.01) and thereby increased plasma insulin concentrations (66±5.1 μU/mL with placebo versus 79±4.1 μU/mL with phenylephrine, P<.05). Phenylephrine also increased glucose utilization (42±5.8 μmol/kg per minute during placebo versus 58±4.8 μmol/kg per minute during phenylephrine, P<.05); however, this was proportional to the increased insulin concentrations; therefore, insulin sensitivity was unchanged. MCRinsulin and plasma insulin concentrations were not affected by angiotensin II; however, glucose utilization increased to 51±2.7 μmol/kg per minute (P<.01 versus placebo), indicating insulin sensitivity was increased. MCRinsulin was unaffected by isoproterenol. Thus, α-adrenergic stimulation but not increased BP per se is a potent regulator of insulin clearance and plasma insulin concentrations.

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Key Words: insulin ◼ hypertension, essential ◼ sympathetic nervous system ◼ renin-angiotensin system ◼ metabolism

Although EH is associated with impaired insulin-mediated glucose uptake (ie, insulin resistance), glucose homeostasis is maintained by elevation of plasma insulin concentrations. However, this shift in steady state is not without cost. In addition to its effects on glucose metabolism, insulin can also modify plasma lipid concentrations, renal electrolyte handling, sympathetic nervous system activity, and vascular smooth muscle cell growth. Given these actions, it is hardly surprising that hyperinsulinemia is an independent risk factor for the development of coronary and carotid atherosclerotic disease. Hence, in insulin-resistant states, euglycemia appears to be maintained at the expense of increased risk of cardiovascular disease.

The plasma insulin concentration is ultimately determined by a balance between the rate of pancreatic beta cell secretion of insulin and the rate of insulin removal from plasma. Whether insulin secretion is increased in EH remains unclear; however, several studies have found that patients with EH have impaired ability to clear insulin from plasma. Insulin is predominantly cleared by metabolic degradation via a receptor-mediated process, and until lately it was thought that the defect in insulin clearance in EH may have been another manifestation of the primary defect responsible for impaired insulin-mediated glucose uptake. However, Lender et al have recently reported that the association between impaired insulin clearance and EH is independent of the effect of insulin on glucose metabolism.

Mechanisms of blood pressure regulation that have been linked to the pathogenesis of EH include activation of the sympathetic nervous system and/or the renin-angiotensin system. In addition to modulating blood pressure, both the sympathetic nervous system and the renin-angiotensin system have metabolic actions including effects on insulin sensitivity. Moreover, elevation of blood pressure with either α-adrenergic agonist or angiotensin receptor stimulation has increased insulin concentrations during euglycemic hyperinsulinemia. Thus, an alternative hypothesis to explain the association between impaired insulin clearance and EH could be that clearance of insulin is directly reduced by elevated blood pressure or by mechanisms that increase blood pressure. In the present study, we have measured the acute effects of α-adrenergic stimulation (with phenylephrine), β-adrenergic stimulation (with isoproterenol), and angiotensin receptor stimulation (with Ang II) on insulin clearance in normotensive
nondiabetic subjects. In these experiments, drug doses were titrated against changes in blood pressure and/or heart rate.

**Methods**

Eight healthy male subjects (aged 23±0.8 years, BMI of 22.9±0.9 kg/m² and resting blood pressure of 125±4.4/68±3.0 mm Hg) participated in this double-blind, placebo-controlled, random-order study. Each individual was studied on four separate days at 1- or 2-week intervals. All studies were preceded by a 12-hour fast and by abstinence from coffee, tea, and alcohol for 24 hours. Between the study days, the subjects maintained their usual daily routine and diets. The study protocol was approved by the Austin Hospital Ethics and Research Committee, and informed written consent was obtained from each participant.

The hyperinsulinemic euglycemic clamp was used to measure acute changes in MCR of insulin (MCR_{insulin}) and insulin sensitivity. On the patient’s arrival at the clinic, cannulas were inserted into veins in the cubital fossa of the right arm (and used for all infusions) and retrogradely into a left wrist vein (which was placed in a water bath heated to 42°C for sampling of arterialized blood). During the euglycemic clamp, blood pressure was continuously measured from the middle finger of the right hand using the Finapres device (Ohmeda) and each 10 minutes from the left arm (Dinamap, Critikon).

After measurement of baseline blood glucose concentrations (Reflux, S. Boehringer Mannheim BmbH), a primed constant infusion of insulin was given at 40 mU/m² per minute (Actrapid, Novo Nordisk Pharmaceutical). While insulin was infused, blood glucose concentrations were measured each 5 minutes, and 20% glucose was infused to maintain euglycemia. The MCR_{insulin} and insulin sensitivity were measured for the first time in the period between 60 and 90 minutes after the insulin infusion was begun, and this period was defined as “pretreatment.” Infusions of placebo (ie, saline), phenylephrine (160 ng·kg⁻¹·min⁻¹), isoproterenol (1.25 ng·kg⁻¹·min⁻¹) or Ang II (0.25 ng·kg⁻¹·min⁻¹) commenced 90 minutes after the insulin infusion was begun. The infusion rates of the pressor agents were adjusted every 5 minutes until finger diastolic blood pressure had increased by 10 mm Hg, pulse rate had increased by 10 beats per minute, and/or 30 minutes had elapsed. Because phenylephrine caused pulse rate to fall in some subjects, the rate of phenylephrine infusion was decreased to the previous level if the pulse rate fell below 40 beats per minute. The next period, beginning 120 minutes after commencement of hyperinsulinemia and continuing until the end of the experiment, was defined as the “treatment” period and was 30 minutes in duration. In this period the infusion rates of the pressor agents were kept constant, and a second measurement of MCR_{insulin} and insulin sensitivity was made. Because it is recognized that steady state is never satisfactorily achieved using this experimental technique, the treatment period was extended for a further 30 minutes in a subgroup of subjects (n=5) to establish that changes in MCR_{insulin} and insulin sensitivity produced by the pressor agents were maintained.

Blood samples were taken each 5 minutes immediately before hyperinsulinemia was begun (n=3) and each 10 minutes from the 60th minute of hyperinsulinemia until completion of the experiment. The blood was kept on ice until the plasma was separated by centrifugation. The plasma was stored at −20°C until insulin and C-peptide concentrations were measured by radioimmunoassay (Phadeseph, Kabji Pharmacia, and Byk-Sangtec Diagnostica, respectively).

**Calculations**

C-peptide is cosecreted in equimolar concentrations with insulin; therefore, plasma concentration of C-peptide was used as an index of insulin secretion (IS). When insulin secretion is suppressed, the MCR_{insulin} is equal to the steady state plasma insulin concentration divided by the insulin infusion rate. The IS index was calculated by dividing the glucose infusion rate by the plasma insulin concentration. All values obtained during the “baseline” period (the 15 minutes preceding hyperinsulinemia), the pretreatment period, and the first 30 minutes of the treatment period were averaged for each subject. Values recorded during the second 30 minutes of the treatment period were also averaged, and these values were compared with the first 30 minutes of the treatment period using the paired t test (Table 1). Since no significant differences were detected between the first and second halves of the treatment period, all values recorded during this time were averaged so as to obtain a single treatment value for all subjects.

**Statistics**

All data are presented as mean±SEM. The difference between pretreatment and treatment values was taken as a measure of the effects of treatment, and the paired sample t test (using the Bonferroni correction) was used to make between-day comparisons of placebo with phenylephrine, isoproterenol, and Ang II; within-day comparisons were also made between pretreatment and treatment values.

**Results**

**Blood Pressure and Pulse Rate**

As expected, Finapres and Dinamap measurements of mean and diastolic blood pressures were similar. However, the finger systolic blood pressure included a component of the reflected pulse wave; therefore, Finapres systolic blood pressure tended to be higher than the Dinamap measurement. Despite these differences, the pattern of change in finger blood pressure during the treatments was similar to the concurrently recorded arm blood pressure pattern.

Blood pressure and pulse rate in the pretreatment period did not differ between the study days (Table 2). The infusions of the active agents rapidly increased blood pressure: within 15 minutes of commencement, the infusion rates were within ±1-dose increments of the final infusion rate in all subjects. The average infusion rates of phenylephrine, isoproterenol, and Ang II during the treatment period were 800±160, 11.9±1.8, and 5.6±2.1 ng·kg⁻¹·min⁻¹, respectively. Mean and diastolic blood pressures were significantly increased by the phenylephrine and Ang II infusions (Table 1), and systolic blood pressure was increased by all treatments. Isoproterenol also increased the pulse rate, whereas phenylephrine infusion caused the pulse rate to fall. The target pulse rate or diastolic blood pressure was always reached during the isoproterenol and Ang II infusions; however, phenylephrine caused bradycardia in three subjects, which prevented further dose increments.

**Euglycemic Clamp Data**

On the placebo day, the baseline blood glucose and plasma insulin concentrations were 4.7±0.2 mmol/L and 7.4±0.7 μU/mL, respectively, and these values did not differ from corresponding baseline values recorded on the other days (ie, 4.5±0.1 mmol/L and 7.1±0.7 μU/mL with phenylephrine, 4.6±0.1 mmol/L and 6.8±0.7 μU/mL with isoproterenol, and 4.7±0.1 mmol/L and 8.3±1.7 μU/mL with Ang II). As expected, infusion of insulin increased the pretreatment insulin

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**Selected Abbreviations and Acronyms**

- Ang II = angiotensin II
- BMI = body mass index
- EH = essential hypertension
- MCR = metabolic clearance rate
TABLE 1. Plasma Insulin Concentration and Glucose Infusion Rate Required to Maintain Euglycemia Before and During Infusion of Active Agents

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Pretreatment</th>
<th>0-30 Min</th>
<th>30-60 Min</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[Insulin]_{plasma} (\mu U/mL)</td>
<td>64±6.6</td>
<td>67±7.3</td>
<td>62±5.8</td>
<td>.148</td>
</tr>
<tr>
<td>GIR, (\mu mol \cdot kg^{-1} \cdot min^{-1})</td>
<td>45±6.4</td>
<td>51±4.7</td>
<td>50±6.3</td>
<td>.830</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[Insulin]_{plasma} (\mu U/mL)</td>
<td>60±4.8</td>
<td>79±4.5</td>
<td>77±5.0</td>
<td>.683</td>
</tr>
<tr>
<td>GIR, (\mu mol \cdot kg^{-1} \cdot min^{-1})</td>
<td>45±4.1</td>
<td>58±1.8</td>
<td>61±4.5</td>
<td>.124</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[Insulin]_{plasma} (\mu U/mL)</td>
<td>59±7.1</td>
<td>61±5.7</td>
<td>54±1.5</td>
<td>.226</td>
</tr>
<tr>
<td>GIR, (\mu mol \cdot kg^{-1} \cdot min^{-1})</td>
<td>46±4.7</td>
<td>51±6.9</td>
<td>45±6.5</td>
<td>.682</td>
</tr>
<tr>
<td>Ang II</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[Insulin]_{plasma} (\mu U/mL)</td>
<td>58±2.0</td>
<td>64±2.7</td>
<td>69±3.1</td>
<td>.101</td>
</tr>
<tr>
<td>GIR, (\mu mol \cdot kg^{-1} \cdot min^{-1})</td>
<td>45±0.9</td>
<td>55±2.2</td>
<td>61±3.4</td>
<td>.500</td>
</tr>
</tbody>
</table>

GIR indicates glucose infusion rate. Comparison was made in 5 subjects between the first 30 minutes (0-30 min) and the second 30 minutes (30-60 min) of a 60-minute period during which the rates of infusion of the active drugs were kept at a constant rate (see “Methods” for details). Probability values have not been adjusted for multiple comparisons.

concentrations (to 66±5.2 \(\mu U/mL\) on the placebo day, 64±4.5 \(\mu U/mL\) prior to phenylephrine, 64±4.1 \(\mu U/mL\) prior to isoproterenol, and 63±5.3 \(\mu U/mL\) prior to Ang II); however, blood glucose concentrations remained similar to the baseline concentrations (ie, 4.8±0.2 mmol/L with placebo, 4.6±0.2 mmol/L with phenylephrine, 4.5±0.1 mmol/L with isoproterenol, and 4.6±0.1 mmol/L with Ang II). In comparison to fasting concentrations of C-peptide (ie, 435±138 pmol/L), pretreatment–C-peptide values were low, consistent with suppressed insulin secretion,\(^3\) and did not differ between the study days (Fig 1).

Administration of placebo during the treatment period did not affect glucose, insulin, or C-peptide concentrations (Fig 1). In contrast, phenylephrine infusion increased plasma insulin concentrations (by 24%, \(P<.01\) compared with placebo); however, this was not explained by increased secretion of

**TABLE 2. Arm and Finger Measurements of Blood Pressure and Pulse Rates Before Start of Insulin Infusions (Baseline), Between 60 and 90 Minutes After Commencing Hyperinsulinemia (Pretreatment) and During the Final 30 to 60 Minutes of the Insulin Infusion (Treatment)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Pulse rate, bpm</th>
<th>Systolic, mm Hg</th>
<th>Mean, mm Hg</th>
<th>Diastolic, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Arm</td>
<td>Finger</td>
<td>Arm</td>
<td>Finger</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>63±3.7</td>
<td>63±3.5</td>
<td>121±5.2</td>
<td>130±7.0</td>
</tr>
<tr>
<td>Pretreatment</td>
<td>61±2.3</td>
<td>63±2.6</td>
<td>125±4.9</td>
<td>136±6.8</td>
</tr>
<tr>
<td>Treatment</td>
<td>62±3.3</td>
<td>63±2.8</td>
<td>127±5.0</td>
<td>137±5.2</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>63±5.1</td>
<td>64±4.9</td>
<td>121±3.8</td>
<td>123±6.2</td>
</tr>
<tr>
<td>Pretreatment</td>
<td>60±4.7</td>
<td>63±4.5</td>
<td>127±3.8</td>
<td>137±4.9</td>
</tr>
<tr>
<td>Treatment</td>
<td>52±3.8*</td>
<td>55±3.9†</td>
<td>141±2.7*</td>
<td>144±5.3</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>61±4.5</td>
<td>64±5.2</td>
<td>119±2.8</td>
<td>124±6.0</td>
</tr>
<tr>
<td>Pretreatment</td>
<td>61±3.7</td>
<td>65±4.0</td>
<td>120±2.4</td>
<td>135±4.7</td>
</tr>
<tr>
<td>Treatment</td>
<td>79±4.2†</td>
<td>82±3.4‡</td>
<td>143±3.8†</td>
<td>147±4.6‡</td>
</tr>
<tr>
<td>Ang II</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>62±4.3</td>
<td>65±3.7</td>
<td>120±4.5</td>
<td>133±3.0</td>
</tr>
<tr>
<td>Pretreatment</td>
<td>61±3.1</td>
<td>64±3.3</td>
<td>123±4.2</td>
<td>147±2.9</td>
</tr>
<tr>
<td>Treatment</td>
<td>61±5.0</td>
<td>64±4.7</td>
<td>135±3.1¶</td>
<td>161±4.2*</td>
</tr>
</tbody>
</table>

Infusions of placebo, phenylephrine, isoproterenol, or Ang II were begun after 90 minutes of hyperinsulinemia. Data presented as mean±SEM, \(n=8\) subjects for each value.

* \(P<.05\); † \(P<.01\); ‡ \(P<.001\) compared with placebo.

¶ \(P<.05\) compared with pretreatment.
insulin because there was no change in plasma C-peptide (Fig 1). Thus, compared with placebo, phenylephrine infusion significantly reduced the MCRinsulin (Table 3). Consistent with the rise in plasma insulin concentrations, phenylephrine infusion also increased the rate of glucose utilization (by 30%, \( P < .05 \) compared with placebo; Fig 1); however, the increase in glucose utilization was approximately proportional to the increase in the plasma insulin concentration, thus the insulin sensitivity index was unchanged (Fig 1).

Infusion of Ang II did not significantly affect plasma insulin or C-peptide concentrations; hence the MCRinsulin was unchanged (Table 3). Although plasma insulin concentrations remained stable, the rate of glucose utilization increased by 37% (\( P < .01 \) compared with placebo). Therefore, Ang II infusion apparently increased insulin sensitivity (Fig 1).

Despite having significant effects on blood pressure and pulse rate, isoproterenol infusion did not affect any of the euglycemic clamp variables (Fig 1). Although C-peptide concentrations appeared to increase, this rise was not statistically significant (\( P = .34 \)) and was only from 66±13 pmol/L to 95±24 pmol/L, which is very small in absolute terms, ie, fasting C-peptide concentrations in our subjects were 435±138 pmol/L, and C-peptide concentration may increase to over 2500 pmol/L following oral glucose ingestion.\(^{27}\) Therefore, these data indicate that \( \beta \)-adrenergic stimulation did not change insulin secretion or the MCRinsulin.

### Discussion

#### Insulin Clearance

To investigate the association between EH and abnormalities in insulin and glucose metabolism, we used the hyperinsulinemic euglycemic clamp to measure the acute effects of \( \alpha \)-adrenoceptor, \( \beta \)-adrenoceptor, and angiotensin receptor stimulation on insulin clearance. In this technique, steady state hyperinsulinemia is achieved by infusing insulin at a constant rate, and hypoglycemia is prevented by infusing glucose. This method does not allow the precise quantification of endogenous secretion of insulin unless an exorbitant period is allowed for plasma C-peptide concentrations to reach steady state (ie, the plasma half-life of C-peptide is 40 minutes).\(^{24,30}\) However, C-peptide concentrations observed in the present study did confirm that endogenous insulin secretion was practically negligible during the pretreatment period\(^{30}\) and was not increased by any of the treatments that we used. Therefore, under these conditions the MCRinsulin was equal to the steady state plasma insulin concentration divided by the insulin infusion rate.\(^{27,28}\)

The particularly novel finding of this study was that phenylephrine, a selective \( \alpha \)-adrenoceptor agonist, increased plasma insulin concentrations by 24%. However, since phenylephrine did not affect insulin secretion, the rise in plasma insulin concentrations must have been caused by reduced clearance of insulin from plasma. This observation is corroborated by and apparently explains the finding of Lager et al,\(^{31}\) who observed a 25% increase in plasma insulin concentrations when propranolol was used to unmask the \( \alpha \)-adrenoceptor stimulating properties of epinephrine during euglycemic hyperinsulinemia. In the present study, the decrease in the MCRinsulin during phenylephrine infusion was substantial (ie, \(-20\%)\) and was produced by a dose that increased mean blood pressure by only 9.4 mm Hg more than placebo. Thus, it appears that the MCRinsulin (and consequently plasma insulin concentrations) is very sensitive to acute changes in \( \alpha \)-adrenergic activity.

In previous studies, \( \beta \)-adrenergic stimulation has not modified insulin concentrations during euglycemic hyperinsulinemia.\(^{19,24}\) Outwardly, this implies that insulin clearance has not changed; however, under some conditions, \( \beta \)-adrenergic stimulation increases endogenous insulin secretion.\(^{31}\) Therefore, accurate measurement of the MCRinsulin during \( \beta \)-adrenergic stimulation required the simultaneous measurement of insulin secretion. In the present study, we found that infusion of

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**TABLE 3. Insulin Clearance Values Between 60 and 90 Minutes After Start of Hyperinsulinemia (Pretreatment) and During Infusions of Placebo, Ang II, or Phenylephrine (Treatment)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Insulin Clearance, ( \text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment</td>
<td>Treatment</td>
</tr>
<tr>
<td>Placebo</td>
<td>16.7±1.3</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>17.0±1.0</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>17.5±1.4</td>
</tr>
<tr>
<td>Ang II</td>
<td>17.6±1.3</td>
</tr>
</tbody>
</table>

Data presented as mean±SEM, \( n = 8 \) subjects.  
* \( P < .01 \) compared with placebo.
isoproterenol, a nonspecific β-agonist, did not modify either insulin secretion or the MCR$_{insulin}$. Since infusion of epinephrine (a β-adrenergic stimulant with weaker α-adrenoceptor stimulating properties) also does not modify insulin clearance, our data suggest that the metabolic effects of epinephrine are consistent with the reported predominance of β-adrenoceptor stimulation at the doses used in those studies.

Insulin clearance was also unaffected by Ang II at a dose that increased diastolic blood pressure to 89 mm Hg. In contrast, Buchanan et al$^{22}$ reported that higher doses of Ang II (ie, 20 ng · kg$^{-1}$ · min$^{-1}$ compared with the 5.6 ng · kg$^{-1}$ · min$^{-1}$ used in the present study) substantially increased plasma insulin concentrations during hyperinsulinemia. C-peptide concentrations were not measured in the Buchanan study; therefore, it remains unclear whether the effects of high-dose Ang II on insulin concentrations are due to reduced insulin clearance or increased insulin secretion. Regardless of how those very high doses modified insulin concentrations, it appears that this effect of Ang II is not produced by the more moderate doses that were used in the present study.

Mechanism of the Effect of Phenylephrine

These studies were not designed to test how insulin clearance was altered; therefore, we can only speculate on the mechanism of these changes. Because infused insulin is efficiently extracted from plasma by the liver (≈50%) and the kidneys (≈30%), insulin clearance is probably regulated by organ blood flow.$^{33}$ α-Adrenergic stimulation has decreased hepatic blood flow in animal models,$^{34}$ suggesting a hemodynamic explanation for the reduction in MCR$_{insulin}$ produced by phenylephrine. Ang II, a potent inhibitor of renal blood flow,$^{22}$ did not affect the MCR$_{insulin}$; thus suggesting that phenylephrine-mediated changes in insulin clearance were more likely to have been caused by a decrease in hepatic rather than renal blood flow.

Another possible explanation for the effects of phenylephrine on the MCR$_{insulin}$ is that hepatic and/or renal insulin receptor binding affinity was altered. Insulin is removed from hepatic or portal blood after binding to hepatocyte receptors, which are subsequently internalized and degraded.$^{15,16}$ Although traditionally it has been thought that β- but not α-adrenoceptor stimulation reduces insulin receptor affinity,$^{35}$ Desoye et al$^{18}$ recently demonstrated decreased insulin receptor binding of rodent adipocytes after α$_2$-adrenergic stimulation. Similar effects are yet to be demonstrated in human tissue; however, α$_2$-adrenoceptors are present on both hepatocytes and renal cells$^{37}$ and are known to influence intracellular glucose metabolism of hepatocytes.$^{30}$

Implications of the Present Study

It would appear that the association between reduced insulin clearance and EH does not relate to increasing blood pressure per se. Although blood pressure was significantly elevated by each of the infusions that we used, only α-adrenergic stimulation affected the MCR$_{insulin}$. Thus, it appears that phenylephrine’s effect on insulin clearance was a specific effect of α-adrenergic stimulation. The magnitude of this effect was sufficient to suggest that the level of sympathetic nervous system activity could be an important determinant of in vivo plasma insulin concentrations. However, since β-adrenergic stimulation had no effect on insulin metabolism, the effect of sympathetic nervous system activation on insulin clearance may be dependent on the receptor subtype that is stimulated. Moreover, α$_2$-adrenoceptor stimulation inhibits pancreatic secretion of insulin$^{39,40}$; therefore, the net effect of sympathetic nervous system activity on plasma insulin concentrations may ultimately depend on the balance between changes in insulin secretion and clearance.

These findings might explain an unexpected metabolic effect produced by treating EH with α$_2$-adrenoceptor blockers. Pollare et al$^{23}$ reported that although prazosin substantially increased insulin sensitivity, the initial rise in plasma insulin concentrations produced by intravenous glucose administration was reduced. In contrast, other pharmacological measures that improve insulin sensitivity (eg, angiotensin-converting enzyme inhibition,$^{45}$ oral hypoglycemic treatment$^{47}$) usually augment first-phase insulin release. Pollare et al$^{29}$ explained their findings by suggesting that prazosin may have decreased insulin secretion by allowing unopposed α$_2$-adrenoceptor stimulation. However, the results of the present study predict that α$_2$-adrenergic blockade might augment insulin clearance and therefore could provide an alternative explanation for the reduction in plasma insulin concentrations.

These data also provide a potential mechanism by which EH could be linked with reduced insulin clearance. However, it is important to stress that there are problems in extrapolating from short-term physiological actions in healthy subjects to the longer term clinical situation. For example, it is unknown whether the acute reduction of insulin clearance produced by phenylephrine infusion would be sustained during prolonged periods of α-adrenergic stimulation or whether α-adrenergic activity is persistently elevated in hypertensive patients. Therefore, we would suggest that further studies are required before our observations can be invoked to explain the association of EH with impaired insulin clearance.

Insulin Sensitivity

One factor that appears to regulate the effect of insulin on glucose metabolism is the rate of delivery of insulin to skeletal muscle—the major site of insulin-mediated glucose uptake. Consequently, it has been hypothesized that insulin resistance is associated with EH because of reduced blood flow to skeletal muscle.$^{35,42}$ Based on this hypothesis, it might be predicted that elevating blood pressure with vasoconstricting agents would simultaneously impair insulin sensitivity because of an associated fall in skeletal muscle blood flow. However, in the present study, both Ang II and phenylephrine increased glucose utilization during euglycemic hyperinsulinemia, and at least in the case of Ang II, this rise in glucose utilization was mediated by an increase in insulin sensitivity. Other investigators have recently reported similar effects of Ang II infusions, and this action apparently reflects diversion of blood flow from insulin resistant tissues, such as the splanchnic circulation, to skeletal muscle.$^{22}$

Thus, at least in the short-term, it appears that systemic vasoconstriction does not necessarily impair insulin sensitivity. Moreover, if the acute action of Ang II on insulin sensitivity was sustained over the longer term, the increase in insulin...
sensitivity produced by long-term angiotensin-converting enzyme inhibition would be not be due to reduced production of Ang II but could be due to some other mechanism, such as an increase in bradykinin concentrations. Similarly, these data suggest that the increase in insulin sensitivity produced by α-adrenergic blocker treatment of EH may not be due to increased skeletal muscle blood flow as has been speculated by some investigators.

Acknowledgments
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References
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