Insulin Stimulates Both Endothelin and Nitric Oxide Activity in the Human Forearm

Carmine Cardillo, MD; Sridhar S. Nambi, MD; Crescence M. Kilcoyne, RN, MS; Wassim K. Choucair, MD; Arie Katz, MD; Michael J. Quon, MD, PhD; Julio A. Panza, MD

Background—The mechanism of the hemodynamic effect of insulin in the skeletal muscle circulation has not been fully elucidated. The purpose of this study was to assess whether the hemodynamic response to insulin involves the concurrent release of endothelin (ET-1) and nitric oxide (NO), 2 substances with opposing vasoactive properties.

Methods and Results—Bioactivity of ET-1 and NO was assessed without insulin and during insulin infusion in the forearm circulation of healthy subjects by use of blockers of ET-1 receptors and by NO synthesis inhibition. In the absence of hyperinsulinemia, ET-1 receptor blockade did not result in any significant change in forearm blood flow from baseline \( P=0.29 \). Intra-arterial insulin administration did not significantly modify forearm blood flow \( P=0.88 \). However, in the presence of hyperinsulinemia, ET-1 receptor antagonism was associated with a significant vasodilator response \( P<0.001 \). In the presence of ET-1 receptor blockade, the vasoconstrictor response to NO inhibition by \( \text{L-L-NMMA} \) was significantly higher after insulin infusion than in the absence of hyperinsulinemia \( P=0.006 \).

Conclusions—These findings suggest that in the skeletal muscle circulation, insulin stimulates both ET-1 and NO activity. An imbalance between the release of these 2 substances may be involved in the pathophysiology of hypertension and atherosclerosis in insulin-resistant states associated with endothelial dysfunction. (Circulation. 1999;100:820-825.)

Key Words: insulin ■ endothelin ■ nitric oxide ■ vasodilation ■ receptors

In recent years, the hemodynamic properties of insulin have received growing attention, mostly because the effects of the hormone on muscle blood flow seem to modulate its ability to stimulate glucose uptake.\(^1\)–\(^4\) The precise mechanisms involved in the hemodynamic action of insulin, however, have not been fully elucidated. Some investigators have reported that the vasodilator response to insulin in the limb circulation of healthy humans is related to local release of nitric oxide (NO), because NO synthesis inhibition by \( \text{N}^0\)-monomethyl-L-arginine (L-NMMA) blunts the vasodilator effect of the hormone.\(^5\)–\(^6\) These findings, however, are at odds with those of other investigations in which no vasodilation was observed in response to insulin.\(^7\)–\(^8\) These discrepancies suggest that an increased insulin-stimulated NO activity may be counteracted by the concurrent release of other substances with vasoconstrictor properties so that the overall hemodynamic effect is neutral. Also, because of the antihypertensive and antiatherogenic effects of NO,\(^9\) the imposition of vasoconstrictive and proatherosclerotic mechanisms may help to explain the association commonly reported between insulin-resistant hyperinsulinemic states and hypertension or atherosclerosis.\(^7\)

A substance with vasoconstrictive and mitogenic properties that might be involved in these phenomena is the peptide endothelin (ET-1). Studies performed in cell cultures have demonstrated increased ET-1 immunoreactivity after exposure to insulin.\(^10\)–\(^11\) Also, after administration of insulin, increased plasma levels of ET-1 have been observed in healthy subjects\(^12\) and in patients with non–insulin-dependent diabetes mellitus (NIDDM) or obesity.\(^13\)–\(^14\) However, the relevance of circulating ET-1 levels in reflecting its vasoconstrictor activity is questionable, because the peptide acts predominantly in an autocrine and paracrine manner, and its secretion by endothelial cells is polarized toward the underlying vascular smooth muscle.\(^15\) Consequently, plasma ET-1 levels may not necessarily reflect endothelial cell production of the peptide or its biological effect on smooth muscle cells. Pharmacological agents that block the receptors through which ET-1 exerts its hemodynamic effects have been developed recently. The use of those agents may allow a better assessment of the contribution of ET-1 to the regulation of vascular tone.

The present study was designed to investigate the role of insulin in modulating the bioactivity of ET-1 and NO in the forearm circulation of healthy subjects. For this purpose, we compared vascular responses to ET-1 receptor blockers and NO synthesis inhibition in the absence or presence of local hyperinsulinemia.

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Clinical Characteristics of the Study Population

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<th>Study 1</th>
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Data are mean±SEM except for sex and race.

Methods

Study Population

Nine healthy volunteers with no family history of diabetes or hypertension, whose clinical and metabolic characteristics are reported in the Table, were selected for this study. Subjects were screened by clinical history, physical examination, routine chemical analyses, electrocardiography, and chest radiography. Exclusion criteria were a history or evidence of present or past hypertension, hypercholesterolemia, diabetes mellitus, cardiac disease, peripheral vascular disease, coagulopathy, or any other disease predisposing them to vasculitis or Raynaud phenomenon. All subjects were on an isocaloric diet with an approximate caloric distribution of 50% carbohydrate, 30% fat, and 20% protein. None of the volunteers were taking any medication or vitamin supplements. The study protocol was approved by the National Heart, Lung, and Blood Institute Investigational Review Board. Participants gave written informed consent for all procedures.

Study Protocol

All studies were performed in the morning, after subjects had fasted overnight, in a quiet room with a temperature of ~22°C. Participants were asked to refrain from drinking alcohol or beverages containing caffeine and from smoking for ≥24 hours before the studies. While the participants were supine, a 20-gauge Teflon catheter (Arrow Inc) was inserted into the brachial artery of the left arm for drug infusion and blood sampling. A 20-gauge catheter (Abbott Laboratories) was inserted into a deep antecubital vein of the same arm for blood sampling, and another 20-gauge catheter was inserted into a deep antecubital vein of the contralateral arm for blood sampling and glucose infusion. Measurements of forearm blood flow, plasma glucose, forearm glucose uptake, and insulin concentrations were performed by methods reported previously. Blood pressure was recorded directly from the intra-arterial catheter immediately after each flow measurement, and heart rate was continuously recorded by ECG.

Study 1

Each participant underwent assessment of vascular responses to ET-1 receptor blockade and NO synthesis inhibition in the absence or presence of hyperinsulinemia. Because of the prolonged time required to assess the hemodynamic action of the infused drugs and their relatively long-lasting effects, studies were performed on 2 separate days ≥1 week apart and in random sequence. Volumes infused throughout the studies were matched by administration of saline in variable amounts.

On 1 study day, after the forearm was instrumented, subjects received intra-arterial infusion of saline for 15 minutes at 1 mL/min, and baseline blood flow was measured. This was followed by intra-arterial infusion of BQ-123 and BQ-788. BQ-123 (Bachem) is a synthetic peptide with high potency of antagonism for the ET_A receptor. BQ-788 is a synthetic and highly selective antagonist of the ET_B receptor. BQ-123 (100 nmol/mL solution) was infused at 100 nmol/min (1 mL/min infusion rate) and BQ-788 (Peninsula; 50 nmol/mL solution) was given at 50 nmol/min (1 mL/min infusion rate). Doses of BQ-123 and BQ-788 were similar to those previously used by other investigators and by us and were originally chosen to allow an intravascular concentration ~10-fold higher than the pA2 (negative logarithm of the molar concentration of antagonist that causes a 2-fold parallel shift to the right of the concentration-response curve) at the ET_A and the ETB receptor, respectively. In a previous study, Verhaar et al observed similar degrees of vasodilation using BQ-123 at either 10 or 100 nmol/min. The degree of vasoconstriction observed after selective ET_A receptor antagonism in normal subjects was similar in the study by Verhaar et al, in which BQ-788 was given at 1 nmol/min and in a previous study from our group, in which BQ-788 was given at 50 nmol/min. On the basis of these observations, it is reasonable to assume that the doses of BQ-123 and BQ-788 used in the present study (100 and 50 nmol/min, respectively) would produce a maximum effect. BQ-123 and BQ-788 were infused for 2 hours, and forearm blood flow was measured every 10 minutes.

After 2 hours of ET-1 receptor blockade, intra-arterial infusion of L-NMMA (Calbiochem; 4 nmol/mL solution) was superimposed in each subject at 4 nmol/min (infusion rate 1 mL/min). L-NMMA is an arginine analogue that competitively antagonizes the synthesis of NO from L-arginine. Blood flow was again measured after 30 minutes of L-NMMA infusion.

On a different occasion, after baseline measurements were taken, subjects underwent intra-arterial infusion of regular insulin (Humulin; Eli Lilly) at 0.1 mU per kg of body weight per minute (1 mL/min infusion rate) for 2 hours. Throughout the study, to avoid any confounding effect related to changes in glycemia, plasma glucose levels were determined every 10 minutes during insulin administration, and an infusion of 20% dextrose into the contralateral arm vein was adjusted to maintain glucose levels in the instrumented arm at values similar to baseline. The doses of glucose needed to maintain glycemic levels were generally very small in all subjects. Hemodynamic measurements were recorded every 30 minutes throughout the insulin infusion.

Next, BQ-123 (1 mL/min) and BQ-788 (1 mL/min) infusions were superimposed for 2 hours, and forearm blood flow was measured every 10 minutes. After 2 hours of ET-1 receptor blockade (4 hours after insulin infusion was started), intra-arterial infusion of L-NMMA (1 mL/min) was added, and forearm blood flow measurements were taken 30 minutes later.

Study 2

To investigate the contribution of each ET-1 receptor subtype to the vasodilator response to ET-1 receptor blockade during hyperinsulinemia, on a different occasion, the same study participants underwent another experimental protocol in which they received selective ET_A receptor blockade in the presence of hyperinsulinemia. Because 2 of the participants were unwilling to return for additional studies, data were obtained in only 7 of the 9 subjects who participated in study 1.

After the forearm was instrumented and baseline measurements were taken, subjects received intra-arterial infusion of insulin for 2 hours, at the same doses as before. Then, BQ-123 (1 mL/min) infusion was superimposed for 2 hours, and forearm blood flow was measured every 10 minutes.

Study 3

To rule out the possibility that the hemodynamic response observed with ET-1 receptor blockade during hyperinsulinemia was related to a delayed onset of insulin-mediated vasodilation, on a different occasion, 4 of the 9 original study participants underwent another experimental protocol in which they received selective ET_A receptor blockade without blockade of ET-1 receptors. After the forearm was instrumented and baseline measurements were taken, subjects received intra-arterial infusion of insulin for 4 hours at the same doses as before, and hemodynamic measurements were recorded every 30 minutes.
Statistical Analysis
Sample size was calculated a priori for the primary hypothesis that nonselective ET-1 blockade would result in a vasodilator response in the presence but not the absence of hyperinsulinemia. These calculations showed that a sample size of 9 subjects would allow detection of a 50% increase in forearm blood flow after ET-1 antagonism during hyperinsulinemia, with a power of 80% at \( \alpha = 0.05 \). Statistical comparisons were performed by paired Student’s t test and by ANOVAs for repeated measures. Forearm blood flow responses to L-NMMA during ET-1 receptor blockade in the absence and presence of hyperinsulinemia were compared as percent changes given the different baseline values under the 2 experimental conditions. All calculated probability values are 2-tailed, and a probability value <0.05 was considered to indicate statistical significance. All group data are reported as mean±SD except where indicated.

Results
Mean arterial pressure and heart rate did not change significantly after infusion of any of the substances used in those studies, which suggests that the hemodynamic effects of the various drugs were limited to the infused forearm.

Study 1
Insulin administration resulted in a substantial increase in local insulin levels from the basal value of 3±1 mU/mL. Insulin concentrations in the infused forearm venous circulation were 269±211 mU/mL after 2 hours of insulin alone, 290±204 mU/mL after ET-1 blockade, and 327±208 mU/mL after L-NMMA. There was no statistically significant difference among these 3 experimental conditions (P=0.17). Systemic insulin levels, however, were unchanged during insulin administration. Insulin concentrations in the contralateral forearm vein were 4±1 mU/mL at baseline, 4±1 mU/mL at 2 hours, and 6±1 mU/mL at 4 hours of insulin infusion (P=0.22). Forearm blood flow was similar at baseline (2.4±0.7 mL·min⁻¹·dL⁻¹) and after 2 hours of insulin administration (2.4±0.7 mL·min⁻¹·dL⁻¹) (mean difference 0.02 mL·min⁻¹·dL⁻¹; 95% CI −0.27, 0.23; P=0.88).

In the absence of hyperinsulinemia, forearm blood flow was similar at baseline (2.9±0.6 mL·min⁻¹·dL⁻¹) and after ET-1 receptor blockade (2.8±0.8 mL·min⁻¹·dL⁻¹) (mean difference −0.14 mL·min⁻¹·dL⁻¹; 95% CI −0.57, 0.29; P=0.67). In contrast, during hyperinsulinemia, ET-1 receptor blockade resulted in a significant vasodilator response (from 2.5±0.5 to 4.2±1.7 mL·min⁻¹·dL⁻¹; P<0.001). As a result, forearm blood flow changes induced by ET-1 antagonism were higher in the presence than in the absence of hyperinsulinemia (Figure 1).

NO synthesis inhibition by L-NMMA during the concurrent blockade of ET-1 receptors was associated with a slight, nonsignificant decrease in forearm blood flow (Figure 2). However, in the presence of hyperinsulinemia, L-NMMA administration during ET-1 receptor blockade was associated with a significant vasoconstriction, with return of forearm blood flow to values similar to those recorded at baseline (Figure 2). Importantly, the relative fall in forearm blood flow induced by NO synthesis inhibition during blockade of ET-1 receptors was significantly higher in the presence than in the absence of hyperinsulinemia (Figure 3).

Forearm glucose uptake normalized for local insulin concentrations was 0.38±0.42 mg·min⁻¹·dL⁻¹·mU⁻¹ after 2

Study 2
In the 7 subjects who underwent both nonselective ET-1 (BQ-123 and BQ-788) and selective ETA (BQ-123 alone) receptor blockade during hyperinsulinemia, both treatments resulted in a significant increase in forearm blood flow from baseline (both P<0.001). The vasodilator response, however, was not significantly different between the 2 occasions (Figure 4).

Study 3
In the 4 subjects who received insulin infusion for 4 hours without blockade of ET-1 receptors, hyperinsulinemia did not
result in any significant change in forearm blood flow from baseline (Figure 5).

**Discussion**

The results of this study demonstrate that local infusion of insulin into the forearm circulatory bed of healthy humans results in both ET-1– and NO-mediated hemodynamic effects. In our study subjects, specific blockers of ET-1 receptors induced a significant vasodilator response only during the concurrent infusion of insulin. These findings suggest that ET-1–mediated vasoconstrictor tone is increased after insulin administration. However, despite this increase in ET-1–related vasoconstrictor activity, insulin infusion in the absence of ET-1 receptor blockade did not result in a significant hemodynamic change. Therefore, the marked differences observed in the response to ET-1 blockade induced by hyperinsulinemia are consistent with the notion that insulin, in addition to enhancing ET-1 activity, also stimulates the production of vasodilator substances that oppose the vasoconstrictor effects of ET-1. In the present study, we analyzed NO production during hyperinsulinemia by testing the vasoconstrictor response to NO inhibition with or without insulin infusion. We observed that L-NMMA administration during blockade of ET-1 receptors resulted in a vasoconstrictor response that was higher in the presence than in the absence of hyperinsulinemia. This observation supports the concept that NO-dependent vasodilator tone is also increased by insulin.

Although previous studies have reported increased plasma levels of ET-1 during hyperinsulinemic euglycemic clamp both in normal subjects and in patients with insulin-resistant states, available evidence that ET-1 production is indeed involved in the modulation of the hemodynamic effects of insulin is far from conclusive. Other studies have failed to demonstrate an increase in ET-1 circulating levels in vivo after insulin administration. Also, the highest proportion of ET-1 produced by endothelial cells is secreted toward the underlying smooth muscle; hence, circulating ET-1 results from variable spillover into the bloodstream and might not accurately reflect the activity of the peptide at the receptor level. Two receptor subtypes, \( \text{ET}_\alpha \) and \( \text{ET}_\beta \), are known to mediate the hemodynamic effects of ET-1. In vascular smooth muscle cells, both receptor subtypes mediate vasoconstriction, whereas stimulation of \( \text{ET}_\beta \) receptors on endothelial cells causes vasodilation through the release of vasorelaxing substances. In the present study, nonselective blockade of \( \text{ET}_\alpha \) and \( \text{ET}_\beta \) receptors, achieved by concurrent infusion of BQ-123 and BQ-788, did not result in any significant change in forearm blood flow in the absence of hyperinsulinemia.

![Figure 3](image3.png)

**Figure 3.** Relative changes in forearm blood flow after NO synthesis inhibition (intra-arterial infusion of L-NMMA at 4 mmol/min for 30 minutes) during nonselective blockade of ET-1 receptors in 9 healthy subjects, in absence or presence of hyperinsulinemia. Bars represent mean ± SEM. \( P \) value refers to comparison between the 2 values by paired Student’s \( t \) test.

![Figure 4](image4.png)

**Figure 4.** Forearm blood flow responses to nonselective ET-1 blockade (intra-arterial infusion of BQ-123 at 100 nmol/min and BQ-788 at 50 nmol/min) (○) and to selective \( \text{ET}_\alpha \) blockade (BQ-123 alone at 100 nmol/min) (●) in 7 healthy subjects during concurrent infusion of insulin (at 0.1 mU · kg \(^{-1} \) · min \(^{-1} \)). Values represent mean ± SEM. \( P \) value refers to comparison between the 2 curves in forearm blood flow changes from baseline by ANOVA for repeated measures.

![Figure 5](image5.png)

**Figure 5.** Forearm blood flow values at baseline and during intra-arterial infusion of insulin (0.1 mU · kg \(^{-1} \) · min \(^{-1} \)) in 4 healthy subjects who received insulin infusion for 4 hours. Bars represent mean ± SEM. No significant change in forearm blood flow from baseline was observed during insulin infusion by ANOVA for repeated measures.
observation from our laboratory with a larger sample of normal volunteers. In contrast, a previous study by Verhaar et al reported a vasodilator response to nonselective blockade of ET-1 receptors in the forearm circulation of healthy subjects, even in the absence of hyperinsulinemia. The discrepancies between their findings and those of the present study cannot be accounted for by differences in drugs dosages or infusion times, because we used higher doses of BQ-123 and BQ-788 and infused them for longer periods of time than in the study by Verhaar et al. One possibility to explain these differences might be that basal levels of ET-1 were higher in the subjects included in the study by Verhaar et al, leading to a greater contribution of ET-1 in the maintenance of resting vascular tone compared with the subjects included in the present study. Indeed, our finding of a lack of a hemodynamic effect of nonselective ET-1 receptor blockade in the absence of hyperinsulinemia suggests that under physiological conditions, the concentration of ET-1 within the vessel wall is too low to participate in the regulation of basal tone, or alternatively, that there is a balance between the vasoconstrictor and vasodilator properties of the peptide. During hyperinsulinemia, in contrast, nonselective ET-1 blockade was associated with significant vasodilation. This indicates that under the influence of insulin, the vasoconstrictor effects of ET-1 become apparent, likely in relation to increased production of the peptide.

To ascertain the contribution of each receptor subtype to the increased ET-1–mediated vasoconstrictor tone observed in the presence of hyperinsulinemia, we compared the hemodynamic effect of nonselective ET-1 and selective ET₄ blockade in the same group of subjects. We observed that the vasodilatory response was not different during the combined infusion of BQ-123 and BQ-788 or during administration of BQ-123 alone. These results suggest that the vasoconstrictor effect of ET-1 during hyperinsulinemia is related to stimulation of the ET₄ receptor subtype.

In the present study, NO synthesis inhibition during blockade of ET-1 receptors in the absence of hyperinsulinemia was associated with only a slight decrease (~13%) in forearm blood flow. This finding differs from previous observations in our laboratory showing that in healthy subjects, ~30% of resting forearm blood flow is dependent on basal release of NO. However, because ET-1 contributes to release of NO through its interaction with endothelial ET₄ receptors, it is possible that in the present study, blockade of these receptors by BQ-788 might have resulted in decreased basal production of NO. In contrast, during hyperinsulinemia, in spite of the concurrent blockade of ET₄ receptors, L-NMMA infusion was associated with a marked decrease (~35%) in forearm blood flow. This result is compatible with a direct stimulatory effect of insulin on endothelial production of NO, as previously suggested by in vitro studies in endothelial cell cultures that showed that insulin stimulation of NO synthesis may share a common intracellular signaling pathway with glucose transport. Our observation is also in accordance with previous reports showing increased NO activity during hyperinsulinemic euglycemic clamp in the limb circulation of healthy humans and confirms the importance of an NO contribution in determining the hemodynamic response to insulin.

Because of the delayed onset of insulin-mediated vasodilation reported in previous studies, we also considered the possibility that the vasodilator response to ET-1 receptor blockade during hyperinsulinemia in the present study could simply be due to a prolonged time course of the effect of the hormone on vascular tone. However, in the group of subjects who received insulin alone for 4 hours, we did not observe any significant hemodynamic change. This observation, therefore, enhances the specificity of the vasodilator responses observed during blockade of ET-1 receptors after insulin administration. Our findings of an absent vasodilator response to the infusion of insulin alone at doses resulting in local hormone concentrations in the supraphysiological range, although limited by the relatively small number of subjects included in the present study, is in keeping with several previous investigations (see Reference 8 for review). However, this observation is at odds with others that described a vasodilator response to insulin, even when given at smaller doses and for shorter infusion times than those used in the present study (see Reference 8 for review). Most of the studies that showed a vasodilator response to insulin were performed with systemic administration of the hormone during euglycemic clamp. In fact, in a previous investigation, we demonstrated a differential hemodynamic effect of insulin in the forearm vasculature of healthy subjects according to its administration route, with vasodilation observed in response to systemic but not to local hyperinsulinemia despite similar intravascular concentrations of the hormone during both infusions. On the basis of the results of the present study, it is also possible to hypothesize that different proportions of NO and ET-1 are released in response to insulin and may be involved in the discrepancies observed in the hemodynamic effects of the hormone.

The present demonstration that substances with opposing vasoactive properties interact to determine the hemodynamic effect of insulin may also have some pathophysiological and clinical relevance. Evidence gathered in recent years suggests that a number of insulin-resistant hyperinsulinemic states, such as essential hypertension, obesity, NIDDM, and aging, are associated with decreased NO activity. Conceivably, the resulting endothelial dysfunction may alter the balance between insulin-stimulated production of NO and ET-1 in favor of the latter, as also suggested by a recent observation from our laboratory showing increased ET-1 vasoconstrictor activity in hypertensive patients compared with normotensive controls. Owing to the mitogenic and vasoconstrictive properties of ET-1, this mechanism may ultimately be responsible for the higher prevalence of hypertension and atherosclerosis commonly observed among insulin-resistant patients. A similar phenomenon might be at work in the pathophysiology of renal complications in patients with NIDDM, in whom ET-1 seems to play an important role in the pathophysiology of kidney damage. In this regard, our observation that blockade of ET-1 receptors effectively antagonizes ET-1–mediated vasoconstriction may have important therapeutic implications for the use of ET-1 antagonists to prevent the vasculotoxic effects of insulin in patients with...
insulin resistance or hyperinsulinemia. Moreover, the fact that insulin signaling pathways related to production of NO in endothelium and to glucose uptake in skeletal muscle and adipose tissue show striking parallels is consistent with the notion that insulin resistance may predispose to hypertension.

References


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