Insulin Resistance and the Effect of Insulin on Blood Pressure in Essential Hypertension

Tim Heise, Kai Magnusson, Lutz Heinemann, Peter T. Sawicki

Abstract—The aim of this study was to investigate the effect of 2 weeks of insulin administration on blood pressure and to simultaneously measure insulin sensitivity and insulin-induced vasodilatation in obese hypertensive patients. In a prospective, randomized, double-blind, crossover study (study 1), 23 obese, untreated, nondiabetic, hypertensive patients received either neutral protamine Hagedorn (NPH) insulin (0.3 U/kg body wt per day) or placebo subcutaneously for 2 weeks (washout period, 2 weeks). Office and 24-hour blood pressure values were measured at the beginning and end of each treatment period. In an open-label study (study 2), 8 obese hypertensive patients and 10 healthy control subjects underwent a 3-step hyperinsulinemic, euglycemic glucose clamp (step 1, 0.5; step 2, 2.5; step 3, 5.0 mU · kg⁻¹ · min⁻¹ [120 minutes each]). Leg blood flow (LBF) was measured by venous occlusion plethysmography. Insulin administration decreased mean±SD office blood pressure from 131±13 to 128±12 mm Hg (placebo, 132±13 and 132±13 mm Hg; P<0.05 between final examinations) and mean±SD 24-hour blood pressure by −3.3±6.9 mm Hg (placebo, +0.7±4.6 mm Hg; P<0.05). Insulin infusion increased LBF significantly in the healthy controls but not in obese insulin-resistant hypertensive subjects. Obese hypertensive patients are resistant to the effects of insulin with regard to both glucose uptake and vasodilatation. Administration of insulin exerts a small blood pressure–lowering effect in these patients. These data strongly argue against the postulated pressor action of insulin in essential hypertension. (Hypertension. 1998;32:243-248.)

Key Words: insulin ■ insulin resistance ■ hypertension, essential ■ blood flow ■ vasodilation

Multiple epidemiological and clinical studies have linked insulin resistance and hyperinsulinemia to essential hypertension.1–4 Also, hyperinsulinemia has been proposed to be “the missing causal link” between decreased insulin sensitivity and elevated BP values.5,6 However, this causal relationship between hyperinsulinemia and hypertension has remained controversial,7 mostly because (despite the insulin-mediated effects on the sympathetic nervous system,8 proliferation of smooth-muscle cells,9 ion transport alterations,10 and sodium reabsorption11) administration of insulin led to vasodilatation12,13 rather than vasoconstriction. In addition, insulin decreased arterial BP in a dog model of chronic experimental hyperinsulinemia14 and did not lead to BP elevation in insulin-dependent diabetic patients and in patients with insulinoma.15 Recently, Ferrannini et al16 demonstrated that the effect of obesity on BP elevation appeared to be mediated by insulin resistance rather than hyperinsulinemia. Both parameters correlated independently with diastolic BP, but only insulin sensitivity showed a significant (negative) correlation with systolic BP values. Insulin-resistant states such as essential hypertension, obesity, and non–insulin-dependent diabetes mellitus have been found to be associated with a blunted insulin-induced vasodilatation,17–21 indicating that insulin resistance does not only affect insulin-stimulated glucose uptake but also insulin-induced vasodilatation. Therefore, theoretically, insulin administration could result in a decrease of BP in these patients. However, the direct long-term effect of exogenous insulin administration on BP has until now, to our knowledge, not been studied in patients with essential hypertension. To further elucidate the association between insulin resistance, insulin, and hypertension, we performed 2 studies. The aim of the first study was to investigate whether subcutaneous administration of insulin over 2 weeks influences BP values in untreated patients with essential hypertension. The aim of the second study was to describe the effects of insulin on glucose uptake and vasodilatation in obese hypertensive patients compared with healthy control subjects.

Methods
Permission for both studies was obtained from the local ethics committee, and all participants gave informed written consent. The studies were carried out according to the principles of Good Clinical Practice and the Declaration of Helsinki and in accordance with institutional guidelines.

Study 1
Subjects
The study sample consisted of 23 nondiabetic untreated patients with essential hypertension but without other concomitant diseases. Nine-
teen patients were men aged 40±11 years, with BMI of 31±5 kg/m² and duration of hypertension of 5±3 years. Any antihypertensive medication was discontinued at least 1 month before the study. Before entry into the study, office BP values without antihypertensive treatment had to be persistently >140/90 mm Hg and for ethical reasons <180/105 mm Hg.

Methods
In a double-blind crossover study design, the patients received either 0.3 U/kg body wt neutral protamine Hagedorn (NPH) insulin (long-acting insulin preparation) per day (Protaphan HM U 100, Novo-Nordisk) given by subcutaneous injections before main meals, or placebo consisting of the insulin solution substance (3 mg m-cresol and 16 mg glycerol per milliliter, Novo-Nordisk). Each period of the crossover study consisted of 2 weeks followed by a 2-week washout period. All placebo and insulin cartridges were blinded to maintain the double-blind character of the study. Office and 24-hour BP measurements were taken at the beginning and end of both 2-week study periods. Office BP was measured 3 times in the morning after 5 minutes of rest in the sitting position with a random-zero sphygmomanometer (Hawksley and Sons) according to WHO criteria; the values of the last 2 measurements were included in the evaluation. Twenty-four-hour BP was assessed with an automatic double microphone device (TM-2420, Boso), with measurements taken between 6 AM and 10 PM every 30 minutes and between 10 PM and 6 AM every 60 minutes. Body weight was measured in light clothes by means of an electronic scale (model 770, Secca). At the beginning and end of both study periods, blood samples were drawn in the morning for radioimmunological measurements of serum insulin, C-peptide, and fructosamine. Additionally, a short insulin tolerance test was performed for determination of insulin sensitivity as described previously. After measurement of blood glucose concentrations in an arterialized blood sample, patients received an intravenous injection of regular insulin (Actrapid HM, Novo-Nordisk) in a dose of 0.1 U/kg body wt. Blood glucose concentrations were measured every minute during the following 15 minutes. Insulin sensitivity was calculated from the first-order rate constant for the disappearance of glucose (Keto, i.e., the slope of the regression line of the logarithm of blood glucose against time) over the period of 3 to 15 minutes.

Initially, the patients received detailed instructions about the technique of subcutaneous insulin injections and blood glucose self-monitoring. In addition to dietary instructions to eat 3 meals per day with at least 20 g of carbohydrates in each meal, the patients received information about symptoms and self-treatment of hypoglycemia. A blood glucose meter (One Touch II, Lifescan Inc) was used for initial glucose monitoring. In addition to dietary instructions to eat 3 meals per day with at least 20 g of carbohydrates in each meal, the patients received information about symptoms and self-treatment of hypoglycemia. A blood glucose meter (One Touch II, Lifescan Inc) was used for initial glucose monitoring.

Laboratory Measurements
Plasma glucose was measured by the glucose oxidase method in duplicate (Beckman Glucose Analyzer II). Serum insulin concentrations were measured by radioimmunoassay (Pharmacia RIA). Serum fructosamine levels were determined using a kinetic test with nitroblue-tetrazolium (SYS 1 BM/Hitachi 717, Boehringer Mannheim). Plasma potassium concentrations were measured instantaneously with an ion-selective electrode (Ionometer EF-HK, Fresenius).

Statistical Analysis
The main outcome parameter was the difference between the mean 24-hour BP values during insulin and placebo administration. Before comparison of insulin and placebo treatment, the main efficacy parameter was tested for period and carryover effects with a BASIC program for the analysis of 2-period crossover studies. Because no significant period or carryover effects were observed, mean changes of all parameters during insulin and placebo administration were calculated and compared using the paired t test or the Wilcoxon signed rank test.

Study 2
Subjects
Eight male obese hypertensive subjects (aged 37.0±11.0 years; body weight, 107.3±20.5 kg; BMI, 33.5±5 kg/m²) and 10 male healthy volunteers (aged 28.0±2.4 years; body weight, 76.0±9.0 kg; BMI, 28±2 kg/m²) were included in this open-label study. Inclusion criteria for the obese hypertensive subjects were BMI ≥27 kg/m², systolic BP >140 mm Hg, diastolic BP >90 mm Hg, and no antihypertensive treatment during the last 4 weeks. Participants were excluded if they had any history of diabetes mellitus, secondary hypertension, or any major medical illness. Inclusion criteria for the healthy subjects were BMI <27 kg/m², systolic BP <140 mm Hg, diastolic BP <90 mm Hg, and no medication or any concurrent medical illness.

Methods
Each subject took part in a euglycemic, 3-step hyperinsulinemic glucose clamp. After an overnight fast, the volunteers were admitted at 8 AM to our metabolic ward and weighed in light clothing without shoes. To establish the glucose clamp, all participants were connected to a Biostator (glucose controlled infusion system, Life Sciences Instruments). After insertion of 3 intravenous cannulas (1 for blood sampling in the left elbow, 1 for continuous blood glucose measurement in the left wrist, and 1 for insulin and glucose infusion in the right forearm), an intravenous insulin infusion was started (step 1, 0.5 mU/kg · min⁻¹). Blood glucose was kept constant at a target level of 5.0 mmol/L. Glucose infusion rates (GIR) necessary to neutralize the blood glucose–lowering effect of the infused insulin were registered throughout the whole study period of 360 minutes. Blood samples were drawn in regular intervals for estimation of plasma glucose, serum insulin, and blood potassium concentrations. Potassium concentrations were maintained throughout the study at the basal level by varying the infusion rate of an intravenous potassium chloride infusion. After 120 minutes, the insulin infusion rate was increased to 2.5 mU/kg · min⁻¹ for the next 120 minutes (step 2) and to the maximum of 5.0 mU/kg · min⁻¹ for an additional 120 minutes (step 3). The last 30 minutes of each of the 3 insulin infusion steps were regarded as steady-state phases. The insulin sensitivity index (S) was calculated by dividing the GIR by the Δs serum insulin levels registered during the steady-state phases of step 1 and step 2.

LBF was measured simultaneously during the clamp procedure in the right and the left leg by means of venous occlusion mercury-in-Silastic strain-gauge plethysmography with automatic electrical calibration (Compactus 700, Gutman). The strain gauges were placed around the widest circumference of the calf. Venous return was occluded by a cuff, fixed 5 cm above the knee, and inflated to 60 mm Hg during the measurements. Every 10 minutes, 2 periods of 3 successive readings each were performed during the whole study duration. Blood flow values are given in milliliters per 100 mL tissue per minute. The mean of the combined readings of the right and the left leg in the last 30 minutes of each of the 3 insulin infusion steps was used for further analysis.

Blood flow values were measured at the beginning and end of each of the 3 insulin infusion steps with a conventional sphygmomanometer (Boso).

Statistical Analysis
Results are expressed as mean±SD. For statistical analysis, an ANOVA procedure was used or the t test if appropriate. Regression analysis was performed by the least-squares method. The correlation coefficient was calculated according to the method of Pearson. A value of P<0.05 was considered statistically significant.

Selected Abbreviations and Acronyms
BMI = body mass index
BP = blood pressure
LBF = leg blood flow
S = insulin sensitivity index
WHO = World Health Organization
Results

Study 1

Office BP values, 24-hour BP values, and concentrations of serum insulin, C-peptide, and fructosamine were comparable at the beginning of the insulin and placebo administration periods (Table 1). After insulin administration, serum insulin concentrations and the insulin/C-peptide ratio were significantly higher, whereas fructosamine and C-peptide serum concentrations were lower when compared with those after placebo (Table 1). No severe hypoglycemic episodes occurred; 1 person reported minor hypoglycemic symptoms during exercise 3 hours after insulin injection.

The mean 24-hour BP values are shown in Table 1 and Figure 1. When compared with baseline, mean 24-hour BP values decreased during insulin administration by $-3.3\pm 6.9$ mm Hg and remained unchanged during placebo administration (+0.7±4.6 mm Hg, $P=0.0358$). During the day (6 AM to 10 PM), systolic BP decreased by $-5.5\pm 5.6$ mm Hg (placebo, $-0.6\pm 6.7$ mm Hg; $P=0.0075$) and diastolic BP decreased by $-1.7\pm 3.6$ mm Hg (placebo, $+1.5\pm 4.4$ mm Hg; $P=0.0099$). During the night (10 PM to 6 AM), systolic BP decreased by $-3.7\pm 4.2$ mm Hg in the insulin administration period (placebo, $+1.5\pm 7.2$ mm Hg; $P=0.1394$) and diastolic BP remained unchanged at $-0.4\pm 2.9$ mm Hg (placebo, $+3.7\pm 2.3$ mm Hg; $P=0.0166$). Systolic office BP values decreased during the insulin injection period from $148.9\pm 15.8$ to $145.2\pm 15.2$ mm Hg (placebo, $149.5\pm 16.9$ and $149.0\pm 16.0$ mm Hg; $P=0.0828$ between the final examinations), whereas diastolic office BP values remained unchanged: $94.1\pm 10.0$ and $94.4\pm 8.2$ mm Hg (placebo, $96.4\pm 8.9$ and $97.7\pm 10.6$ mm Hg; $P=0.0488$;
Table 1). The mean office BP values at the end of both treatment periods were significantly different ($P=0.0208$; Table 1).

There were no significant differences in insulin sensitivity within or between both treatment periods. There were only minor changes in body weight during the whole study, although the increase of approximately 0.4 kg during placebo administration was statistically significant ($P=0.0376$ versus baseline examination; Table 1).

**Study 2**

As expected, $S_i$ was lower in the obese hypertensive patients than in the lean normotensive volunteers (Table 2). Although the intravenous insulin infusion resulted in significantly higher serum insulin concentrations in obese hypertensive subjects, glucose consumption (expressed as glucose infusion rate) was lower in all 3 insulin infusion steps when compared with control (Table 2).

At step 1, LBF was similar in the obese hypertensive subjects and the lean normotensive volunteers (Table 2). In the controls, the rise in insulin infusion rates (and consequently in serum insulin concentrations) resulted in a considerable increase in LBF from step 1 to step 2 and a further slight, but still significant, increase during step 3. In contrast, in the obese hypertensive subjects, the increase in LBF from step 1 to step 2 was less pronounced and not significant ($P=0.1202$). The supraphysiological serum insulin concentrations achieved during step 3 did not result in a further increase in LBF in these subjects (Table 2). Insulin sensitivity and maximal insulin-induced LBF showed a significant positive correlation ($r=0.48$, $P<0.05$; Figure 2).

During all insulin infusion steps, BP values of the obese hypertensive subjects were significantly higher when compared to the lean normotensive volunteers (Figure 2).
pared with those of the normotensive control subjects (Table 2). BP values decreased in both groups during infusion step 2 and remained stable or increased slightly during step 3.

Discussion
These results show that there is a linear association between the resistance to the effects of insulin on both glucose uptake and insulin-induced vasodilatation in obese hypertensive patients (Figure 2). Also, 2 weeks of administration of insulin in these patients did not lead to a rise in BP values but rather exerted a small but consistent antihypertensive effect (Figure 1).

Our results are in accordance with the observation of Natali et al.26 who showed that insulin-induced vasodilatation during a hyperinsulinemic glucose clamp was related to insulin-mediated glucose uptake (the observed correlation coefficient of $r=0.44$ in their study is very close to ours of $r=0.48$). Our findings are also in accordance with the reports of several case-control studies that have been entirely consistent in showing that lower insulin sensitivity but not hyperinsulinemia is associated with higher BP in diabetic and nondiabetic patients.3,27,28 This is also supported by the recent results of Ferrannini et al.,16 who found that measures of insulin resistance but not serum insulin concentrations correlate with systolic BP values.

In the present study, similar insulin infusion rates resulted in significantly higher serum insulin concentrations in obese hypertensive patients (Table 2). Hence, insulin uptake or binding may be reduced in these patients, and this may lead directly to a diminished insulin-induced vasodilatory action. Alternatively, the reduced vascular effect of insulin could be caused indirectly at the smooth muscle cell level either by decreased Na$^+$,K$^+$-ATPase activity,29 causing a subsequent cell membrane depolarization; indirectly by an increase of the sympathetic vasoconstriction through the $\alpha_2$-adrenergic pathway10 via an increase in the amount of norepinephrine reaching the adrenergic receptors31; or by an influence on secretion of endothelin.32 Also, a diminished insulin-mediated activation of nitric oxide synthase may result in decreased nitric oxide production and lead to reduced vasodilatation.32–34 However, the backgrounds of the reduced vasodilatory action of insulin in essential hypertension remain obscure, and this study was not designed to elucidate this mechanism.

Previously, the frequently described higher prevalence of hypertension in insulin-resistant patients has been causally linked to a pressor effect of hyperinsulinemia on the vasculature, which implies a reduced effect of insulin on the glucose uptake but an unrestricted effect on smooth muscle cells in the vasculature.1,56 However, the findings of our study suggest that in patients with reduced insulin sensitivity to glucose uptake, insulin resistance is also present in the vasculature, resulting in a blunted response to insulin. In addition, in these patients, 2 weeks of administration of insulin did not increase but rather lowered BP. Therefore, it seems very unlikely that hyperinsulinemia is the “missing link” between insulin resistance and hypertension. However, the strong association between insulin-resistant states and elevated BP calls for a pathophysiologic explanation. Either insulin resistance and hypertension are both caused by a common yet unknown underlying mechanism, or insulin resistance causes a rise in BP via an unknown factor other than hyperinsulinemia. Alternatively, it may be speculated that in patients predisposed to essential hypertension, the vasculature is resistant to insulin-induced vasodilatation.30,33,34 This reduced vasodilatory effect of insulin may thereby lead to a small increase in both peripheral resistance and decreased vascular distensibility.35 Following the original proposal from Folkow,36 this minor change in the pressor mechanism could theoretically initiate a slight rise in BP and thereby start a positive feedback loop that induces vessel remodeling and, in the long-term, hypertension. Clearly, the present studies cannot clarify these hypotheses, and the elucidation of the mechanisms underlying the striking association between insulin resistance and hypertension must be left to future research.

In summary, our results underline the association between insulin resistance to glucose uptake and its vasodilatory action, and they argue against the hypothesis of a causal pressor effect of insulin as the “missing link” between insulin resistance and essential hypertension.

Acknowledgments
We thank Hoechst AG, Frankfurt, Germany, for financial support of the study and Novo-Nordisk, Mainz, Germany, for the supply of insulin and placebo solutions. We are indebted to Michael Stoffels and Urs Schaden for their invaluable help in performing the first study and to Hendrik Siebecke for his skilful assistance during the second study. We would like to thank Professors Michael Berger and Achim A.R. Starke for the most helpful discussions during planning of the study and manuscript preparation. We thank Dr Manfred Falck and his colleagues of the central laboratory of the Heinrich-Heine-University for their supportive cooperation with the determination of the fructosamine concentrations. We are most grateful to Andrea BroddeIer, Claudia Gottschalk, and Martina Schreier for their exceptional performance of the glucose clamps and to Dr Bernd Richter for labeling of the study medication. The excellent laboratory assistance of Brigitte Senger and Annette Stuhlweissenburg is gratefully acknowledged.

References


Insulin Resistance and the Effect of Insulin on Blood Pressure in Essential Hypertension

Tim Heise, Kai Magnusson, Lutz Heinemann and Peter T. Sawicki

*Hypertension*. 1998;32:243-248
doi: 10.1161/01.HYP.32.2.243

*Hypertension* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1998 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://hyper.ahajournals.org/content/32/2/243

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

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

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