Impaired Insulin Sensitivity and Maximal Responsiveness in Older Hypertensive Men

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Abstract

This study examines the relation between blood pressure and insulin resistance in obese, sedentary middle-aged and older men. Eleven hypertensive and 17 normotensive subjects of comparable age (58.6±1.0 years, mean±SEM), percent body fat (27.7±0.7%), and maximal aerobic capacity (30.2±0.9 mL·kg⁻¹·min⁻¹) participated in this study. Glucose disposal (M, milligrams per kilogram of fat-free mass per minute) determined during a three-dose hyperinsulinemic euglycemic clamp was lower in the hypertensive than normotensive subjects at the low (M at 120 pmol/m²·min: 2.3±0.2 versus 3.2±0.3, P=.06), intermediate (M at 600 pmol/m²·min: 8.0±0.6 versus 10.4±0.6, P=.02), and high (M at 3000 pmol/m²·min: 13.5±0.5 versus 15.5±0.7, P=.04) insulin infusion rates. The calculated insulin concentration necessary for a half-maximal effect (EC₅₀) was greater in the hypertensive than normotensive subjects (1164±168 versus 864±66 pmol/L, P=.03). In this population of normotensive and hypertensive men, systolic, diastolic, and mean arterial blood pressures were related to glucose disposal at these insulin infusion rates (r=-.35 to -.46, P<.05) as well as the EC₅₀ (r=.42 to .44, P<.05). Thus, hypertensive obese, sedentary older men have a reduction in both sensitivity and maximal responsiveness to insulin that is directly related to the severity of hypertension independent of obesity and physical fitness. (Hypertension. 1994;23:320-324.)

Key Words • aging • glucose clamp technique • hypertension, essential • insulin resistance

Insulin resistance is defined as a defect in glucose metabolism in which the biologic response to insulin is less than normal.¹ It has been observed in a number of studies that insulin resistance often coexists with hypertension.²⁻⁵ Several confounding variables may affect the relation between blood pressure and insulin resistance. These variables include age, physical fitness, and obesity. Thus, a study examining the relation between blood pressure and insulin sensitivity should control for these differences by selecting normotensive and hypertensive subjects of comparable age, physical fitness, and obesity.

The hyperinsulinemic euglycemic clamp administered at low, intermediate, and high rates of insulin infusion permits measurement of insulin sensitivity at low, more physiological insulin doses and maximal responsiveness at supraphysiological, high insulin doses.⁶ The relation of hypertension to insulin resistance has only been examined in young and middle-aged hypertensive adults using a single, submaximal-dose, hyperinsulinemic euglycemic clamp to measure insulin sensitivity. In addition, the researchers of previous studies did not consider the potential confounding effects of body composition and physical activity levels on the regulation of blood pressure in selecting their hypertensive and normotensive subjects.

We hypothesize that an abnormal or impaired insulin action in some hypertensive older subjects would occur independent of obesity and physical fitness and be related to defects in sensitivity and maximal responsiveness to insulin quantified in vivo using the three-dose hyperinsulinemic euglycemic clamp.⁷ This study was designed to test this hypothesis by measuring tissue sensitivity and maximal responsiveness to insulin during a three-dose hyperinsulinemic euglycemic clamp in hypertensive and normotensive older subjects of comparable age, obesity, and physical fitness.

Methods

Subjects

Twenty-eight (11 hypertensive and 17 normotensive) middle-aged and older obese sedentary men ranging in age from 50 to 71 years volunteered to participate in this study. All subjects provided written informed consent according to the guidelines of the Institutional Review Boards for Human Studies at the University of Maryland at Baltimore and the Francis Scott Key Medical Center.

Subjects were screened before participation with a medical history, physical examination, fasting plasma glucose, and routine blood chemistries. Subjects were excluded from participation if they exceeded 140% of ideal body weight or had a fasting plasma glucose level greater than 7.8 mmol/L, evidence of diabetes determined during an oral glucose tolerance test, or presence of underlying illness based on screening medical history and examination and baseline biochemical analyses. Four hypertensive subjects were being treated with antihypertensive medications and gradually were tapered off their medication and studied after a minimum of 3 weeks of no drug therapy. Subjects were classified as normotensive if they had no history of hypertension and had a seated diastolic blood pressure less than 90 mm Hg and a systolic blood pressure less than 140 mm Hg on four separate occasions. Hypertension was defined as a diastolic pressure of 90 mm Hg or greater and a systolic pressure of 140 mm Hg or greater on four separate occasions. Subjects had a resting supine and upright 12-lead electrocardiogram and blood pressure measured before undergoing a graded exercise treadmill test to a minimum of 85% of age-predicted maximal heart rate. Sub-
jects who were limited by symptoms of cardiovascular decompensation during the graded exercise treadmill test were excluded from the study because of the inability to measure aerobic capacity (V\text{O}_2\text{max}). To eliminate the effect of diet on insulin sensitivity and blood pressure, all subjects were taught the principles of an American Heart Association (AHA) Step I diet\(^a\) over an 8-week period before cardiovascular fitness, body composition, and metabolic testing. This diet consisted of 50% to 55% of calories as carbohydrate, 30% to 35% as fat, 15% to 20% as protein, 900 to 1500 mg of cholesterol, and less than 3 g/d sodium. Subjects were weight stable on this diet for 4 weeks before testing. Registered dietitians monitored diet adherence by reviewing weekly food records and body weight and calculating dietary composition from biweekly 7-day food records (NUTRITIONIST III, N-Squared Computing).

**Measurement of Body Composition**

Body weight was measured (±50 g) with a Homsms beam balance (Western). Body density was determined by hydrostatic weighing\(^a\) and corrected for residual lung volume measured using the helium-dilution\(^b\) or nitrogen-washout method.\(^c\) Percent body fat was calculated using the Siri equation,\(^d\) and fat-free mass (FFM) was calculated as body weight minus fat mass. Body mass index was calculated by dividing weight (kilograms) by height squared (meters). The waist-to-hip circumference ratio (WHR) was measured as the ratio of the minimal circumference of the abdomen to the circumference of the buttocks at the maximal gluteal protuberance.

**Measurement of Maximal Oxygen Consumption**

A treadmill V\text{O}_2\text{max} test was performed in each subject on at least two separate occasions. The initial treadmill speed was set to elicit 75% of each subject's V\text{O}_2\text{max} measured during their screening treadmill test. The elevation of the treadmill was increased every 2 minutes until the subject was exhausted and could not continue. Oxygen consumption (V\text{O}_2) and carbon dioxide production (V\text{CO}_2) were measured every 30 seconds, and blood pressure and a 12-lead electrocardiogram were recorded every minute during the test. Inspired air volume was measured with an REP-9200 gas meter (Rayfield Equipment Corp). Concentrations of oxygen and carbon dioxide in expired air were analyzed from a mixing chamber with S-3A/I and CD-3A analyzers (Ametek), respectively. Both analyzers were calibrated before each test using standard analyzers. Ventilation, V\text{O}_2, V\text{CO}_2, and respiratory exchange ratio were measured continuously during each test by a computerized data-acquisition system (Rayfield) that was interfaced with the gas meter and gas analyzers. A true V\text{O}_2\text{max} was considered to be attained if two of the following three criteria were achieved: (1) respiratory exchange ratio at maximal exercise greater than 1.10, (2) maximal heart rate greater than 90% of age-predicted maximum (220-age), and (3) a plateau in V\text{O}_2 (change in V\text{O}_2 < 2 mL·kg\(^{-1}\)·min\(^{-1}\) or 200 mL·min\(^{-1}\)) during the last stages of exercise. If a true V\text{O}_2\text{max} was not attained on the second test or the V\text{O}_2\text{max} results for the two exercise tests differed by more than 0.2 L·min\(^{-1}\), additional V\text{O}_2\text{max} tests were performed until these criteria were met.

**Hyperinsulinemic Euglycemic Clamp Protocol**

Three days before metabolic testing, subjects were provided with a calculated weight-maintaining AHA Step I diet\(^a\) comparable to their home AHA diet. Body weight varied by less than 0.5 kg during metabolic testing. On the morning of the third day subjects reported to the laboratory after a 12-hour overnight fast. A three-dose hyperinsulinemic euglycemic clamp was performed in each subject using the glucose clamp technique\(^a\) as modified by Rizza et al.\(^a\) In brief, a polyethylene catheter was inserted into an antecubital vein for infusion of potassium, insulin, and glucose. Another polyethylene catheter was inserted into a dorsal hand vein for blood sampling. This hand was placed in a heated (70°C) box to arterialize blood for sampling. Both catheters were kept patent by slow saline infusions.

After a 30-minute equilibration period three arterialized venous blood samples were obtained 10 minutes apart for measurement of baseline glucose and insulin levels. After the third baseline blood sample was drawn, a primed constant infusion of regular insulin (Humulin-R, Eli Lilly Inc) was started at a rate of 120 pmol/m\(^2\)·min; this insulin infusion rate was maintained for 90 minutes. At 90 minutes a second primed constant infusion of insulin was administered at a rate of 400 pmol/m\(^2\)·min, which was also maintained for 90 minutes. A final primed infusion of insulin was started at 180 minutes at a rate of 3000 pmol/m\(^2\)·min; this infusion rate was maintained for 120 minutes. These insulin infusion rates were chosen to span the range of physiological insulin levels and to achieve maximal insulin-mediated glucose disposal based on the data of Pratley et al\(^a\) in our laboratory; the kinetics of insulin,\(^a\) and previous published studies in younger individuals.\(^5,7\)

During the hyperinsulinemic euglycemic clamp, blood samples were obtained at 5-minute intervals, and aliquots of plasma were stored at -70°C for subsequent insulin measurement.\(^18\) Plasma glucose was maintained at baseline levels by means of a variable infusion of 20% glucose that began 4 minutes after the start of the clamp infusion. The glucose infusion rate was adjusted at 5-minute intervals according to a computerized algorithm that calculates required glucose infusion rates based on plasma glucose levels. Potassium chloride was infused at a rate of 4 mmol/h concurrently with insulin to prevent hypokalemia. Glucose disposal rates were calculated from 30 to 90 minutes of the first and second doses and 60 to 120 minutes of the third dose and normalized for FFM (milligrams per kilogram of FFM per minute). Steady-state plasma insulin levels were determined from the blood samples drawn every 10 minutes during the last 40 minutes of each of the three insulin infusion rates.

Dose-response curves were constructed using mean insulin concentrations and mean glucose disposal rates determined over the last 60 minutes of each insulin infusion rate. These data were fit with logistic regression using an iterative computer program.\(^19\) Mean insulin levels were log normalized, and the insulin concentration necessary for a half-maximal effect (EC\(_{50}\) was calculated for each individual.

**Data Analyses**

Data were analyzed with standard statistical software packages (STATVIEW, Abacus Concepts). Repeated-measures ANOVA models were used to test whether the plasma glucose concentration and insulin levels differed within and between groups during the three doses used during the hyperinsulinemic euglycemic clamp. Differences in glucose disposal and steady-state plasma insulin levels at each dose and EC\(_{50}\) between hypertensive and normotensive individuals were tested with a Student's nonpaired t test. Pearson correlation coefficients were calculated between selected variables. All data are presented as mean±SEM.

**Results**

**Subject Characteristics**

The hypertensive and normotensive subjects were selected not to differ in age, body weight, percent body fat, WHR, or V\text{O}_2\text{max} (milligrams per kilogram per minute) (Table 1). By design, the hypertensive individuals had significantly higher systolic, diastolic, and mean arterial blood pressures than their normotensive peers (Table 2). Because subjects were of comparable body composition and V\text{O}_2\text{max}, there were no relations between indexes of blood pressure and these variables. The hypertensive
men had higher fasting plasma insulin levels than the normotensive men.

Hyperinsulinemic Euglycemic Clamps
During sequential insulin infusions of 120, 600, and 3000 pmol/m² • min, plasma glucose levels were comparable throughout the 5-hour study in the normotensive (5.1±0.1 mmol/L) and hypertensive (5.2±0.1 mmol/L) subjects. Plasma insulin levels increased during the three-dose hyperinsulinemic euglycemic clamps from fasting levels of 60±9 to 249±18, 164±114, and 24 882±1764 pmol/L in the hypertensive subjects and from fasting levels of 42±6 to 276±12, 1584±84, and 21 468±1050 pmol/L in the normotensive subjects during the insulin infusions of 120, 600, and 3000 pmol/m² • min, respectively. The glucose disposal rate during the hyperinsulinemic euglycemic clamp was reduced in the hypertensive compared with normotensive subjects (Fig 1) at (1) the low-dose insulin infusion by 35% (2.3±0.2 versus 3.2±0.3 mg/kgFFM • min, P=.06), (2) the intermediate insulin infusion by 26% (8.0±1.0 versus 10.1±1.0 mg/kgFFM • min, P=.02), and (3) the high-dose insulin infusion by 15% (13.5±0.5 versus 15.5±0.7 mg/kgFFM • min, P=.04). Because of the comparable levels of percent body fat, WHR, and Vmax in the hypertensive and normotensive subjects, there were no relations between glucose disposal and these variables.

The dose-response curves depicting the relation between insulin-mediated glucose disposal and the steady-state plasma insulin levels achieved at each insulin infusion rate during the three-dose hyperinsulinemic euglycemic clamps were shifted to the right in the subjects with hypertension (Fig 2). The EC₅₀ was greater in the hypertensive than normotensive subjects (1164±168 versus 864±66 pmol/L, P=.03).

Relation of Blood Pressure to Glucose Disposal and EC₅₀
There were no significant relations between measures of blood pressure and glucose disposal and EC₅₀ in either the normotensive or hypertensive subjects (Table 3). However, the ranges of blood pressure and insulin sensitivity were limited in each of these groups of subjects, obviating the possibility of finding a statistically significant correlation coefficient. Recognizing inherent assumptions in pooling data from the two groups for analyses, but when this was done significant associations were found between the measures of blood pressure and insulin sensitivity (Table 3). Diastolic and mean arterial blood pressures were related to glucose disposal at all three insulin infusion rates, whereas systolic blood pressure was related to glucose disposal only at the intermediate insulin infusion rate. Systolic,
Diastolic, and mean arterial blood pressures were related to the calculated EC_{50} (Table 3). These findings suggest that in obese, sedentary normotensive and hypertensive subjects of comparable body composition and VO_{2max} values, 15% to 20% of the variance in blood pressure may be accounted for by differences in insulin sensitivity. There were no relations between EC_{50} and either percent body fat, WHR, or VO_{2max} in these subjects.

**Discussion**

The results of this study show that hypertension in some obese, sedentary older men is related to a decrease in both sensitivity and maximal responsiveness to insulin. This finding occurred independent of the degree of obesity or physical fitness of the subjects. Not only was glucose disposal lower in the hypertensive compared with normotensive individuals, but significant negative correlations were observed between most measures of blood pressure and glucose disposal at all three insulin infusion rates. Regression analyses suggested that glucose disposal at low, intermediate, and high doses of insulin accounted for 11% to 18% of the variance in systolic, diastolic, and mean arterial blood pressure independent of body composition and physical fitness in these obese, sedentary middle-aged and older men.

A number of investigators have reported an inverse relation between blood pressure and insulin sensitivity. The decrease in maximal responsiveness to insulin—20-24 Ferrannini et al.20 measured glucose disposal during a hyperinsulinemic euglycemic glucose clamp at a single submaximal (240 pmol/m^2·min) insulin infusion rate in younger hypertensive and normotensive individuals of similar body composition and age. They observed that the hypertensive individuals had a lower glucose disposal than the normotensive individuals and that the decrease in glucose disposal was directly related to the severity of hypertension. This finding was confirmed in two other studies using hyperinsulinemic euglycemic clamps at low submaximal-dose insulin infusions.24,25 In addition, Pollare et al.25 showed that obesity was not a factor in reducing glucose disposal in hypertensive subjects and that insulin resistance was related to the development of hypertension independent of obesity. The only study examining the relation of blood pressure to insulin resistance using a multiple-dose hyperinsulinemic euglycemic clamp was performed in normotensive young adults. In this study, Saad et al.26 observed that glucose disposal at both low (240 pmol/m^2·min) and high (2400 pmol/m^2·min) insulin infusion rates was directly related to blood pressure in younger male and female white normotensive adults. Thus, the study of Saad et al. did not determine whether defects in sensitivity or maximal responsiveness to insulin were related to elevated blood pressure in hypertensive individuals.

Thus, previous studies have established a close link between hypertension and insulin resistance in young and middle-aged adult hypertensive individuals. However, as Kahn1 pointed out, insulin resistance may be due to a decrease in insulin sensitivity, a decrease in the maximal response to insulin, or a combination of both. To date, research examining the relation between hypertension and insulin resistance in older individuals with hypertension has established a link only between blood pressure and an impairment in glucose metabolism at low levels of infused insulin. Whether an increase in blood pressure is due to a decrease in insulin sensitivity, maximal responsiveness, or both has not been examined in a systematic fashion. The rightward shift in the insulin dose-response curve in the present study suggests a decrease in insulin sensitivity. Kahn1 hypothesized that this reduction in insulin sensitivity may be due to an alteration in the insulin receptor, a change in the affinity of the receptor, or a decrease in the number of insulin receptors. Recently, Baron et al.27 demonstrated that in normotensive individuals insulin-mediated skeletal muscle blood flow is related to insulin sensitivity measured during hyperinsulinemic euglycemic clamp. The relation between skeletal muscle blood flow and insulin sensitivity is not known in older hypertensive individuals, but a reduction in blood flow due to atherosclerotic disease could contribute to the reduction in insulin sensitivity observed in hypertensive patients.

The decrease in maximal responsiveness to insulin-mediated glucose uptake also suggests the presence of an accompanying postreceptor defect in insulin action.28 The distinction between a decrease in sensitivity and maximal responsiveness to insulin is important, because the mechanisms that produce these various forms of insulin resistance may differ. The results of the present study indicate that the relation between blood pressure...
and insulin action is due to a decrease in both insulin sensitivity and maximal responsiveness.

In summary, these findings provide further support for the relation between insulin resistance and blood pressure. The insulin-resistant state observed in this middle-aged and older hypertensive population was a result of a decrease in both insulin sensitivity and maximal responsiveness to insulin. These results suggest that an alteration in insulin responsiveness at muscle and other tissues is associated with the increase in blood pressure observed in older sedentary obese men. We have demonstrated that insulin sensitivity is related to cardiovascular fitness, percent body fat, and an abdominal distribution of body fat in older healthy men and that physical training and weight loss significantly improve glucose utilization. We have planned studies to determine the mechanisms responsible for the decrease in insulin sensitivity and maximal responsiveness associated with the development of hypertension in older individuals as well as the effects of interventions such as aerobic exercise and weight loss on the relation between blood pressure and insulin resistance.

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